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Fortsættes ...

DESCRIPTION

Field

[0001] Embodiments described herein disclose methods, compounds, and compositions for reducing expression of apolipoprotein (a) mRNA and protein in an animal. Such methods, compounds, and compositions are useful to treat, prevent, or ameliorate cardiovascular and/or metabolic diseases, disorders or conditions.

Background

[0002] Lipoproteins are globular, micelle-like particles that consist of a non-polar core of acylglycerols and cholesteryl esters surrounded by an amphiphilic coating of protein, phospholipid and cholesterol. Lipoproteins have been classified into five broad categories on the basis of their functional and physical properties: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Chylomicrons transport dietary lipids from intestine to tissues. VLDLs, IDLs and LDLs all transport triacylglycerols and cholesterol from the liver to tissues. HDLs transport endogenous cholesterol from tissues to the liver

[0003] Lipoprotein particles undergo continuous metabolic processing and have variable properties and compositions. Lipoprotein densities increase without increasing particle diameter because the density of their outer coatings is less than that of the inner core. The protein components of lipoproteins are known as apolipoproteins. At least nine apolipoproteins are distributed in significant amounts among the various human lipoproteins.

[0004] The lipoprotein(a) [Lp(a)] particle was identified nearly 50 years ago and is comprised of a highly unique LDL particle in which one apolipoprotein B (apoB) protein is linked via a disulfide bond to a single apolipoprotein(a) [apo(a)] protein. The apo(a) protein shares a high degree of homology with plasminogen particularly within the kringle IV type 2 repetitive domain. Levels of circulating Lp(a) are inversely proportional to the number of kringle IV type 2 variable repeats present in the molecule and, as both alleles are co-expressed within individuals, can display heterozygous plasma isoform profiles (Kraft et al., Eur J Hum Genet, 1996; 4(2): 74-87). It is thought that this kringle repeat domain in apo(a) may be responsible for its pro-thrombotic and anti-fibrinolytic properties, potentially enhancing atherosclerotic progression.

[0005] Apo(a) is transcriptionally regulated by IL-6 and in studies in rheumatoid arthritis patients treated with an IL-6 inhibitor (tocilizumab), plasma levels were reduced by 30% after 3 month treatment (Schultz et al., PLoS One 2010; 5:e14328).

[0006] Apo(a) has been shown to preferentially bind oxidized phospholipids and potentiate vascular inflammation (Bergmark et al., J Lipid Res 2008; 49:2230-2239; Tsimikas et al., Circulation. 2009; 119(13):1711-1719).

[0007] Further, studies suggest that the Lp(a) particle may also stimulate endothelial permeability, induce plasminogen activator inhibitor type-1 expression and activate macrophage interleukin-8 secretion (Koschinsky and Marcovina, Curr Opin Lipidol 2004; 15:167-174). Importantly, recent genetic association studies revealed that Lp(a) was an independent risk factor for myocardial infarction, stroke, peripheral vascular disease and abdominal aortic aneurysm (Rifai et al., Clin Chem 2004; 50:1364-71; Erqou et al., JAMA 2009;302:412-23; Kamstrup et al., Circulation 2008; 117:176-84). Further, in the recent Precocious Coronary Artery Disease (PROCARDIS) study, Clarke *et al.* (Clarke et al., NEJM (2009)361; 2518-2528) described robust and independent associations between coronary heart disease and plasma Lp(a) concentrations. Additionally, Solfrizzi et al., suggested that increased serum Lp(a) may be linked to an increased risk for Alzheimer's Disease (AD) (Solfrizzi et al., J Neurol Neurosurg Psychiatry 2002, 72:732-736). Currently, in the clinic setting, examples of indirect apo(a) inhibitors for treating cardiovascular disease include aspirin, Niaspan, Mipomersen, Anacetrapib, Epirotirome and Lomitapide which reduce plasma Lp(a) levels by 18%, 39%, 32%, 36%, 43% and 17%, respectively. Additionally, Lp(a) apheresis has been used in the clinic to reduce apo(a) containing Lp(a) particles.

[0008] WO 2013/173789 describes antisense oligonucleotide compositions.

[0009] WO 2005/000201 describes modulation of apolipoprotein(a) expression.

[0010] Graham et al. (2012) Circulation 126(21) S20, page A11050 describes antisense inhibition of apolipoprotein(a).

[0011] To date, therapeutic strategies to treat cardiovascular disease by directly targeting apo(a) levels have been limited. Ribozyme oligonucleotides (U.S. Patent 5,877,022) and antisense oligonucleotides (WO 2005/000201; WO 2003/014397; U.S. Patent 8,138,328; Merki et al., J Am Coll Cardiol 2011; 57:1611-1621) have been developed, but none of the compounds directly targeting apo(a) are currently used in the clinic.

[0012] Thus, there remains a clear unmet medical need for novel agents which can potently and selectively reduce apo(a) levels in patients at enhanced risk for cardiovascular events due to chronically elevated plasma Lp(a) levels.

Summary

[0013] The invention provides a compound for decreasing apo(a) expression comprising a modified oligonucleotide consisting of 15 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of at least 15 contiguous nucleobases complementary to an equal length portion of nucleobases 3900 to 3923 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1.

[0014] The invention further provides a compound comprising a modified oligonucleotide consisting of 20 linked nucleosides and having the nucleobase sequence of SEQ ID NO: 58,

wherein the modified oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides;

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5 methylcytosine.

[0015] The invention further provides a composition comprising a compound of the invention, wherein optionally the compound is a salt, and a pharmaceutically acceptable carrier or diluent.

[0016] The invention further provides the compound or composition of the invention for use in therapy.

SUMMARY OF THE DISCLOSURE

[0017] Disclosed herein are compositions and methods for modulating expression of apo(a) mRNA and protein. In certain instances, the apo(a) specific inhibitor decreases expression of apo(a) mRNA and protein.

In certain instances, the composition is an apo(a) specific inhibitor. In certain instances, the apo(a) specific inhibitor is a nucleic acid, protein, or small molecule. In certain instances, the apo(a) specific inhibitor is an antisense oligonucleotide targeting apo(a). In certain instances, the apo(a) specific inhibitor is a modified oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases complementary to an equal length portion of nucleobases 3901 to 3920 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1. In certain instances, the apo(a) specific inhibitor is a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 1-130, 133, 134. In certain instances, the apo(a) specific inhibitor is a modified oligonucleotide consisting of 20 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NO: 58, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0018] Certain instances of the disclosure include a composition comprising a compound described herein, or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0019] In certain instances, the modulation of apo(a) expression occurs in a cell or tissue. In certain instances, the modulations occur in a cell or tissue in an animal. In certain instances, the animal is a human. In certain instances, the modulation is a reduction in apo(a) mRNA level. In certain instances, the modulation is a reduction in apo(a) protein level. In certain instances, both apo(a) mRNA and protein levels are reduced. Such reduction may occur in a time-dependent or in a dose-dependent manner.

[0020] Certain instances of the disclosure include compositions and methods for use in therapy. Certain instances of the disclosure include compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating apo(a) related diseases, disorders, and conditions. Certain instances of the disclosure include compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating Lp(a) related diseases, disorders, and conditions. In certain instances, such diseases, disorders, and conditions are inflammatory, cardiovascular and/or metabolic diseases, disorders, and conditions. In certain instances, the compositions and methods for therapy include administering an apo(a) specific inhibitor to an individual in need thereof. In certain instances, the apo(a) specific inhibitor is a nucleic acid. In certain instances, the nucleic acid is an antisense compound. In certain instances, the antisense compound is a modified oligonucleotide.

Detailed Description

[0021] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or", unless stated otherwise. Additionally, as used herein, the use of "and" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

[0022] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Definitions

[0023] Unless specific definitions are provided, the nomenclature utilized in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the

art. Standard techniques may be used for chemical synthesis, and chemical analysis.

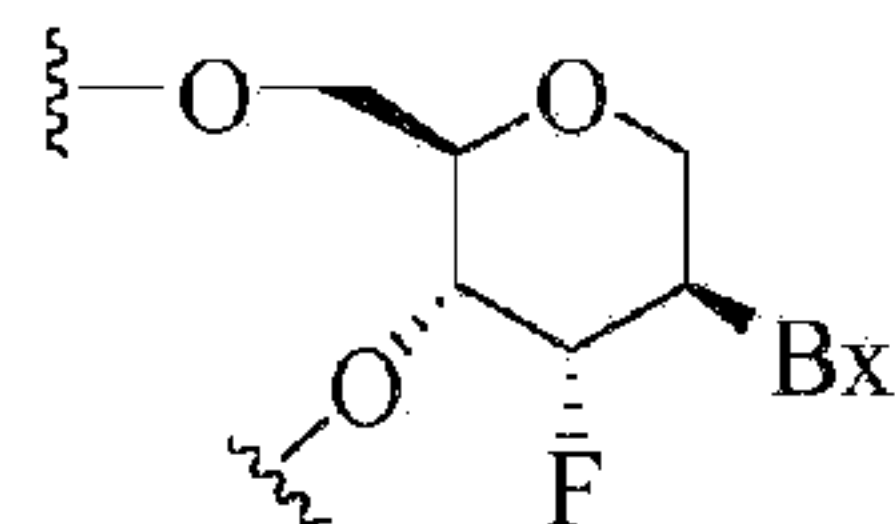
[0024] Unless otherwise indicated, the following terms have the following meanings:

"2'-O-methoxyethyl" (also 2'-MOE, MOE, 2'-O(CH₂)₂-OCH₃ and 2'-O-(2-methoxyethyl)) refers to an O-methoxy-ethyl modification of the 2' position of a furanosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

[0025] "2'-deoxyribonucleoside" means a nucleoside comprising 2'-H furanosyl sugar moiety, as found in naturally occurring deoxyribonucleosides (DNA).

[0026] "2'-MOE nucleoside" (also 2'-O-methoxyethyl nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety. "2'-O-methoxyethyl nucleotide" means a nucleotide comprising a 2'-O-methoxyethyl modified sugar moiety.

[0027] "3'-fluoro-HNA" (also "F-HNA" or "3'-F-HNA") means the sugar moiety of a nucleoside having the following structure:



wherein Bx is a nucleobase.

[0028] "3' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 3'-most nucleotide of a particular antisense compound.

[0029] "5' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 5'-most nucleotide of a particular antisense compound.

[0030] "5-methylcytosine" means a cytosine modified with a methyl group attached to the 5' position. A 5-methylcytosine is a modified nucleobase.

[0031] "About" means within $\pm 10\%$ of a value. For example, if it is stated, "a marker may be increased by about 50%", it is implied that the marker may be increased between 45%-55%.

[0032] "Active pharmaceutical agent" means the substance or substances in a pharmaceutical composition that provide a therapeutic benefit when administered to an individual. For example, in certain instances an antisense oligonucleotide targeted to apo(a) is an active pharmaceutical agent.

[0033] "Active target region" or "target region" means a region to which one or more active antisense compounds is targeted. "Active antisense compounds" means antisense compounds that reduce target nucleic acid levels or protein levels.

[0034] "Administered concomitantly" refers to the co-administration of two agents in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Concomitant administration does not require that both agents be administered in a single

pharmaceutical composition, in the same dosage form, or by the same route of administration. The effects of both agents need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive.

[0035] "Administering" or "administration" means providing a pharmaceutical agent to an individual, and includes, but is not limited to, administering by a medical professional and self-administering. Administration of a pharmaceutical agent to an individual can be continuous, chronic, short or intermittent. Administration can be parenteral or non-parenteral.

[0036] "Agent" means an active substance that can provide a therapeutic benefit when administered to an animal. "First Agent" means a therapeutic compound of the invention. For example, a first agent can be an antisense oligonucleotide targeting apo(a). "Second agent" means a second therapeutic compound of the invention (e.g. a second antisense oligonucleotide targeting apo(a)) and/or a non-apo(a) therapeutic compound.

[0037] "Amelioration" or "ameliorate" or "ameliorating" refers to a lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. The severity of indicators can be determined by subjective or objective measures, which are known to those skilled in the art.

[0038] "Animal" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

[0039] "Antibody" refers to a molecule characterized by reacting specifically with an antigen in some way, where the antibody and the antigen are each defined in terms of the other. Antibody can refer to a complete antibody molecule or any fragment or region thereof, such as the heavy chain, the light chain, Fab region, and Fc region.

[0040] "Antisense activity" means any detectable or measurable activity attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid.

[0041] "Antisense compound" means an oligomeric compound that is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding. Examples of antisense compounds include single-stranded and double-stranded compounds, such as, antisense oligonucleotides, siRNAs, shRNAs, snoRNAs, miRNAs, and satellite repeats. As used herein, the term "antisense compound" encompasses pharmaceutically acceptable derivatives of the compounds described herein.

[0042] "Antisense inhibition" means reduction of target nucleic acid levels or target protein levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound.

[0043] "Antisense oligonucleotide" means a single-stranded oligonucleotide having a nucleobase

sequence that permits hybridization to a corresponding region or segment of a target nucleic acid. As used herein, the term "antisense oligonucleotide" encompasses pharmaceutically acceptable derivatives of the compounds described herein.

[0044] "Apo(a)" means any nucleic acid or protein sequence encoding apo(a). For example, in certain instances, apo(a) includes a DNA sequence encoding apo(a), a RNA sequence transcribed from DNA encoding apo(a) (including genomic DNA comprising introns and exons), a mRNA sequence encoding apo(a), or a peptide sequence encoding apo(a).

[0045] "Apo(a) nucleic acid" means any nucleic acid encoding apo(a). For example, in certain instances, an apo(a) nucleic acid includes a DNA sequence encoding apo(a), a RNA sequence transcribed from DNA encoding apo(a) (including genomic DNA comprising introns and exons), and a mRNA sequence encoding apo(a).

[0046] "Apo(a) mRNA" means a mRNA encoding an apo(a) protein.

[0047] "Apo(a) protein" means any protein sequence encoding Apo(a).

[0048] "Apo(a) specific inhibitor" refers to any agent capable of specifically inhibiting the expression of an apo(a) nucleic acid and/or apo(a) protein. For example, apo(a) specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of apo(a) nucleic acid and/or apo(a) protein. In certain instances, by specifically modulating apo(a) nucleic acid expression and/or apo(a) protein expression, apo(a) specific inhibitors can affect other components of the lipid transport system including downstream components. Similarly, in certain instances, apo(a) specific inhibitors can affect other molecular processes in an animal.

[0049] "Atherosclerosis" means a hardening of the arteries affecting large and medium-sized arteries and is characterized by the presence of fatty deposits. The fatty deposits are called "atheromas" or "plaques," which consist mainly of cholesterol and other fats, calcium and scar tissue, and damage the lining of arteries.

[0050] "Bicyclic sugar" means a furanosyl ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

[0051] "Bicyclic nucleoside" (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

[0052] "Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

[0053] "Cardiovascular disease" or "cardiovascular disorder" refers to a group of conditions related to the heart, blood vessels, or the circulation. Examples of cardiovascular diseases include, but are not limited to, aneurysm, angina, arrhythmia, atherosclerosis, cerebrovascular disease (stroke), coronary heart disease, hypertension, dyslipidemia, hyperlipidemia, hypertriglyceridemia

and hypercholesterolemia.

[0054] "Chemically distinct region" refers to a region of an antisense compound that is in some way chemically different than another region of the same antisense compound. For example, a region having 2'-O-methoxyethyl nucleotides is chemically distinct from a region having nucleotides without 2'-O-methoxyethyl modifications.

[0055] "Chimeric antisense compound" means an antisense compound that has at least two chemically distinct regions.

[0056] "Cholesterol" is a sterol molecule found in the cell membranes of all animal tissues. Cholesterol must be transported in an animal's blood plasma by lipoproteins including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). "Plasma cholesterol" refers to the sum of all lipoproteins (VLDL, IDL, LDL, HDL) esterified and/or non-esterified cholesterol present in the plasma or serum.

[0057] "Cholesterol absorption inhibitor" means an agent that inhibits the absorption of exogenous cholesterol obtained from diet.

[0058] "Co-administration" means administration of two or more agents to an individual. The two or more agents can be in a single pharmaceutical composition, or can be in separate pharmaceutical compositions. Each of the two or more agents can be administered through the same or different routes of administration. Co-administration encompasses parallel or sequential administration.

[0059] "Complementarity" means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid. In certain embodiments, complementarity between the first and second nucleic acid can be between two DNA strands, between two RNA strands, or between a DNA and an RNA strand. In certain embodiments, some of the nucleobases on one strand are matched to a complementary hydrogen bonding base on the other strand. In certain embodiments, all of the nucleobases on one strand are matched to a complementary hydrogen bonding base on the other strand. In certain instances, a first nucleic acid is an antisense compound and a second nucleic acid is a target nucleic acid. In certain such instances, an antisense oligonucleotide is a first nucleic acid and a target nucleic acid is a second nucleic acid.

[0060] "Constrained ethyl" or "cEt" refers to a bicyclic nucleoside having a furanosyl sugar that comprises a methyl(methyleneoxy) (4'-CH(CH₃)-O-2') bridge between the 4' and the 2' carbon atoms.

[0061] "Constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge.

[0062] "Contiguous nucleobases" means nucleobases immediately adjacent to each other.

[0063] "Cross-reactive" means an oligomeric compound targeting one nucleic acid sequence can

hybridize to a different nucleic acid sequence. For example, in some instances an antisense oligonucleotide targeting human apo(a) can cross-react with an apo(a) from another species. Whether an oligomeric compound cross-reacts with a nucleic acid sequence other than its designated target depends on the degree of complementarity the compound has with the non-target nucleic acid sequence. The higher the complementarity between the oligomeric compound and the non-target nucleic acid, the more likely the oligomeric compound will cross-react with the nucleic acid.

[0064] "Cure" means a method that restores health or a prescribed treatment for an illness.

[0065] "Coronary heart disease (CHD)" means a narrowing of the small blood vessels that supply blood and oxygen to the heart, which is often a result of atherosclerosis.

[0066] "Deoxyribonucleotide" means a nucleotide having a hydrogen at the 2' position of the sugar portion of the nucleotide. Deoxyribonucleotides can be modified with any of a variety of substituents.

[0067] "Diabetes mellitus" or "diabetes" is a syndrome characterized by disordered metabolism and abnormally high blood sugar (hyperglycemia) resulting from insufficient levels of insulin or reduced insulin sensitivity. The characteristic symptoms are excessive urine production (polyuria) due to high blood glucose levels, excessive thirst and increased fluid intake (polydipsia) attempting to compensate for increased urination, blurred vision due to high blood glucose effects on the eye's optics, unexplained weight loss, and lethargy.

[0068] "Diabetic dyslipidemia" or "type 2 diabetes with dyslipidemia" means a condition characterized by Type 2 diabetes, reduced HDL-C, elevated triglycerides (TG), and elevated small, dense LDL particles.

[0069] "Diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, the diluent in an injected composition can be a liquid, e.g. saline solution.

[0070] "Dyslipidemia" refers to a disorder of lipid and/or lipoprotein metabolism, including lipid and/or lipoprotein overproduction or deficiency. Dyslipidemias can be manifested by elevation of lipids such as chylomicron, cholesterol and triglycerides as well as lipoproteins such as low-density lipoprotein (LDL) cholesterol.

[0071] "Dosage unit" means a form in which a pharmaceutical agent is provided, e.g. pill, tablet, or other dosage unit known in the art. In certain embodiments, a dosage unit is a vial containing lyophilized antisense oligonucleotide. In certain embodiments, a dosage unit is a vial containing reconstituted antisense oligonucleotide.

[0072] "Dose" means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain instances, a dose can be administered in one, two, or more boluses, tablets, or injections. For example, in certain instances where subcutaneous administration is desired, the desired dose requires a volume not easily

accommodated by a single injection, therefore, two or more injections can be used to achieve the desired dose. In certain instances, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses can be stated as the amount of pharmaceutical agent per hour, day, week, or month. Doses can also be stated as mg/kg or g/kg.

[0073] "Effective amount" or "therapeutically effective amount" means the amount of active pharmaceutical agent sufficient to effectuate a desired physiological outcome in an individual in need of the agent. The effective amount can vary among individuals depending on the health and physical condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual's medical condition, and other relevant factors.

[0074] "Fully complementary" or "100% complementary" means each nucleobase of a nucleobase sequence of a first nucleic acid has a complementary nucleobase in a second nucleobase sequence of a second nucleic acid. In certain instances, a first nucleic acid is an antisense compound and a second nucleic acid is a target nucleic acid.

[0075] "Furanosyl" means a structure comprising a 5-membered ring comprising four carbon atoms and one oxygen atom.

[0076] "Gapmer" means a chimeric antisense compound in which an internal region having a plurality of nucleosides that support RNaseH cleavage is positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising external regions. The internal region may be referred to as a "gap" and the external regions may be referred to as the "wings."

[0077] "Gap-widened" means a chimeric antisense compound having a gap segment of 12 or more contiguous 2'-deoxyribonucleosides positioned between and immediately adjacent to 5' and 3' wing segments having from one to six nucleosides.

[0078] "Glucose" is a monosaccharide used by cells as a source of energy and inflammatory intermediate. "Plasma glucose" refers to glucose present in the plasma.

[0079] "High density lipoprotein-C" or "HDL-C" means cholesterol associated with high density lipoprotein particles. Concentration of HDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum HDL-C" and "plasma HDL-C" mean HDL-C in serum and plasma, respectively.

[0080] "HMG-CoA reductase inhibitor" means an agent that acts through the inhibition of the enzyme HMG-CoA reductase, such as atorvastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

[0081] "Hybridization" means the annealing of complementary nucleic acid molecules. In certain instances, complementary nucleic acid molecules include an antisense compound and a target nucleic acid.

[0082] "Hypercholesterolemia" means a condition characterized by elevated cholesterol or

circulating (plasma) cholesterol, LDL-cholesterol and VLDL-cholesterol, as per the guidelines of the Expert Panel Report of the National Cholesterol Educational Program (NCEP) of Detection, Evaluation of Treatment of high cholesterol in adults (see, Arch. Int. Med. (1988) 148, 36-39).

[0083] "Hyperlipidemia" or "hyperlipemia" is a condition characterized by elevated serum lipids or circulating (plasma) lipids. This condition manifests an abnormally high concentration of fats. The lipid fractions in the circulating blood are cholesterol, low density lipoproteins, very low density lipoproteins, chylomicrons and triglycerides. The Fredrickson classification of hyperlipidemias is based on the pattern of TG and cholesterol-rich lipoprotein particles, as measured by electrophoresis or ultracentrifugation and is commonly used to characterize primary causes of hyperlipidemias such as hypertriglyceridemia (Fredrickson and Lee, Circulation, 1965, 31:321-327; Fredrickson et al., New Eng J Med, 1967, 276 (1): 34-42).

[0084] "Hypertriglyceridemia" means a condition characterized by elevated triglyceride levels. Its etiology includes primary (i.e. genetic causes) and secondary (other underlying causes such as diabetes, metabolic syndrome/insulin resistance, obesity, physical inactivity, cigarette smoking, excess alcohol and a diet very high in carbohydrates) factors or, most often, a combination of both (Yuan et al. CMAJ, 2007, 176: 1113-1120).

[0085] "Identifying" or "selecting an animal with metabolic or cardiovascular disease" means identifying or selecting a subject prone to or having been diagnosed with a metabolic disease, a cardiovascular disease, or a metabolic syndrome; or, identifying or selecting a subject having any symptom of a metabolic disease, cardiovascular disease, or metabolic syndrome including, but not limited to, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypertension increased insulin resistance, decreased insulin sensitivity, above normal body weight, and/or above normal body fat content or any combination thereof. Such identification can be accomplished by any method, including but not limited to, standard clinical tests or assessments, such as measuring serum or circulating (plasma) cholesterol, measuring serum or circulating (plasma) blood-glucose, measuring serum or circulating (plasma) triglycerides, measuring blood-pressure, measuring body fat content, measuring body weight, and the like.

[0086] "Improved cardiovascular outcome" means a reduction in the occurrence of adverse cardiovascular events, or the risk thereof. Examples of adverse cardiovascular events include, without limitation, death, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia.

[0087] "Immediately adjacent" means there are no intervening elements between the immediately adjacent elements, for example, between regions, segments, nucleotides and/or nucleosides.

[0088] "Increasing HDL" or "raising HDL" means increasing the level of HDL in an animal after administration of at least one compound of the invention, compared to the HDL level in an animal not administered any compound.

[0089] "Individual" or "subject" or "animal" means a human or non-human animal selected for treatment or therapy.

[0090] "Individual in need thereof" refers to a human or non-human animal selected for treatment or therapy that is in need of such treatment or therapy.

[0091] "Induce", "inhibit", "potentiate", "elevate", "increase", "decrease", "reduce" or the like denote quantitative differences between two states. For example, "an amount effective to inhibit the activity or expression of apo(a)" means that the level of activity or expression of apo(a) in a treated sample will differ from the level of apo(a) activity or expression in an untreated sample. Such terms are applied to, for example, levels of expression, and levels of activity.

[0092] "Inflammatory condition" refers to a disease, disease state, syndrome, or other condition resulting in inflammation. For example, rheumatoid arthritis and liver fibrosis are inflammatory conditions. Other examples of inflammatory conditions include sepsis, myocardial ischemia/reperfusion injury, adult respiratory distress syndrome, nephritis, graft rejection, inflammatory bowel disease, multiple sclerosis, arteriosclerosis, atherosclerosis and vasculitis.

[0093] "Inhibiting the expression or activity" refers to a reduction or blockade of the expression or activity of a RNA or protein and does not necessarily indicate a total elimination of expression or activity.

[0094] "Insulin resistance" is defined as the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to metabolic syndrome and type 2 diabetes.

[0095] "Insulin sensitivity" is a measure of how effectively an individual processes glucose. An individual having high insulin sensitivity effectively processes glucose whereas an individual with low insulin sensitivity does not effectively process glucose.

[0096] "Internucleoside linkage" refers to the chemical bond between nucleosides.

[0097] "Intravenous administration" means administration into a vein.

[0098] "Linked nucleosides" means adjacent nucleosides which are bonded together.

[0099] "Lipid-lowering" means a reduction in one or more lipids (e.g., LDL, VLDL) in a subject. "Lipid-raising" means an increase in a lipid (e.g., HDL) in a subject. Lipid-lowering or lipid-raising can occur with one or more doses over time.

[0100] "Lipid-lowering therapy" or "lipid lowering agent" means a therapeutic regimen provided to a subject to reduce one or more lipids in a subject. In certain embodiments, a lipid-lowering therapy is provided to reduce one or more of apo(a), CETP, apoB, total cholesterol, LDL-C, VLDL-C, IDL-C, non-HDL-C, triglycerides, small dense LDL particles, and Lp(a) in a subject. Examples of

lipid-lowering therapy include, but are not limited to, apoB inhibitors, statins, fibrates and MTP inhibitors.

[0101] "Lipoprotein", such as VLDL, LDL and HDL, refers to a group of proteins found in the serum, plasma and lymph and are important for lipid transport. The chemical composition of each lipoprotein differs, for example, in that the HDL has a higher proportion of protein versus lipid, whereas the VLDL has a lower proportion of protein versus lipid.

[0102] "Lp(a)" comprises apo(a) and a LDL like particle containing apoB. The apo(a) is linked to the apoB by a disulfide bond.

[0103] "Low density lipoprotein-cholesterol (LDL-C)" means cholesterol carried in low density lipoprotein particles. Concentration of LDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum LDL-C" and "plasma LDL-C" mean LDL-C in the serum and plasma, respectively.

[0104] "Major risk factors" refers to factors that contribute to a high risk for a particular disease or condition. In certain instances, major risk factors for coronary heart disease include, without limitation, cigarette smoking, hypertension, high LDL, low HDL-C, family history of coronary heart disease, age, and other factors disclosed herein.

[0105] "Metabolic disorder" or "metabolic disease" refers to a condition characterized by an alteration or disturbance in metabolic function. "Metabolic" and "metabolism" are terms well known in the art and generally include the whole range of biochemical processes that occur within a living organism. Metabolic disorders include, but are not limited to, hyperglycemia, prediabetes, diabetes (type 1 and type 2), obesity, insulin resistance, metabolic syndrome and dyslipidemia due to type 2 diabetes.

[0106] "Metabolic syndrome" means a condition characterized by a clustering of lipid and non-lipid cardiovascular risk factors of metabolic origin. In certain embodiments, metabolic syndrome is identified by the presence of any 3 of the following factors: waist circumference of greater than 102 cm in men or greater than 88 cm in women; serum triglyceride of at least 150 mg/dL; HDL-C less than 40 mg/dL in men or less than 50 mg/dL in women; blood pressure of at least 130/85 mmHg; and fasting glucose of at least 110 mg/dL. These determinants can be readily measured in clinical practice (JAMA, 2001, 285: 2486-2497).

[0107] "Mismatch" or "non-complementary nucleobase" refers to the case when a nucleobase of a first nucleic acid is not capable of pairing with the corresponding nucleobase of a second or target nucleic acid.

[0108] "Mixed dyslipidemia" means a condition characterized by elevated cholesterol and elevated triglycerides.

[0109] "Modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside bond (i.e. a phosphodiester internucleoside bond). For example, a phosphorothioate linkage is a modified internucleoside linkage.

[0110] "Modified nucleobase" refers to any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. For example, 5-methylcytosine is a modified nucleobase. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[0111] "Modified nucleoside" means a nucleoside having at least one modified sugar moiety, and/or modified nucleobase.

[0112] "Modified nucleotide" means a nucleotide having at least one modified sugar moiety, modified internucleoside linkage and/or modified nucleobase.

[0113] "Modified oligonucleotide" means an oligonucleotide comprising at least one modified nucleotide.

[0114] "Modified sugar" refers to a substitution or change from a natural sugar. For example, a 2'-O-methoxyethyl modified sugar is a modified sugar.

[0115] "MOE nucleoside" means a nucleoside comprising a 2'-substituted sugar moiety comprising MOE at the 2'-position.

[0116] "Motif" means the pattern of chemically distinct regions in an antisense compound.

[0117] "Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[0118] "Natural sugar moiety" means a sugar found in DNA (2'-H) or RNA (2'-OH).

[0119] "Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids (ssDNA), double-stranded nucleic acids (dsDNA), small interfering ribonucleic acids (siRNA), and microRNAs (miRNA). A nucleic acid may also comprise any combination of these elements in a single molecule.

[0120] "Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

[0121] "Nucleobase complementarity" refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is capable of base pairing with a nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the oligonucleotide and the target nucleic acid are considered to be complementary at that nucleobase pair.

[0122] "Nucleobase sequence" means the order of contiguous nucleobases independent of any

sugar, linkage, or nucleobase modification.

[0123] "Nucleoside" means a nucleobase linked to a sugar.

[0124] "Nucleoside mimetic" includes those structures used to replace the sugar or the sugar and the base, and not necessarily the linkage at one or more positions of an oligomeric compound; for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo or tricyclo sugar mimetics such as non-furanose sugar units.

[0125] "Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[0126] "Nucleotide mimetic" includes those structures used to replace the nucleoside and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by $-N(H)-C(=O)-O-$ or other non-phosphodiester linkage).

[0127] "Oligomeric compound" or "oligomer" means a polymer of linked monomeric subunits which is capable of hybridizing to a region of a nucleic acid molecule. In certain instances, oligomeric compounds are oligonucleosides. In certain instances, oligomeric compounds are oligonucleotides. In certain embodiments, oligomeric compounds are antisense compounds. In certain instances, oligomeric compounds are antisense oligonucleotides. In certain instances, oligomeric compounds are chimeric oligonucleotides.

[0128] "Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

[0129] "Parenteral administration" means administration through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration. Administration can be continuous, chronic, short or intermittent.

[0130] "Peptide" means a molecule formed by linking at least two amino acids by amide bonds. Peptide refers to polypeptides and proteins.

[0131] "Pharmaceutical agent" means a substance that provides a therapeutic benefit when administered to an individual. For example, in certain instances, an antisense oligonucleotide targeted to apo(a) is a pharmaceutical agent.

[0132] "Pharmaceutical composition" or "composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition can comprise one or more active agents and a pharmaceutical carrier e.g., a sterile aqueous solution.

[0133] "Pharmaceutically acceptable carrier" means a medium or diluent that does not interfere

with the structure of the compound. Certain of such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by a subject. Certain of such carriers enable pharmaceutical compositions to be formulated for injection, infusion or topical administration. For example, a pharmaceutically acceptable carrier can be a sterile aqueous solution.

[0134] "Pharmaceutically acceptable derivative" encompasses derivatives of the compounds described herein such as solvates, hydrates, esters, prodrugs, polymorphs, isomers, isotopically labelled variants, pharmaceutically acceptable salts and other derivatives known in the art.

[0135] "Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. The term "pharmaceutically acceptable salt" or "salt" includes a salt prepared from pharmaceutically acceptable non-toxic acids or bases, including inorganic or organic acids and bases. "Pharmaceutically acceptable salts" of the compounds described herein may be prepared by methods well-known in the art. For a review of pharmaceutically acceptable salts, see Stahl and Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection and Use (Wiley-VCH, Weinheim, Germany, 2002). Sodium salts of antisense oligonucleotides are useful and are well accepted for therapeutic administration to humans. Accordingly, in one instance the compounds described herein are in the form of a sodium salt.

[0136] "Phosphorothioate linkage" means a linkage between nucleosides where the phosphodiester bond is modified by replacing one of the non-bridging oxygen atoms with a sulfur atom. A phosphorothioate linkage (P=S) is a modified internucleoside linkage.

[0137] "Portion" means a defined number of contiguous (i.e. linked) nucleobases of a nucleic acid. In certain instances, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain instances, a portion is a defined number of contiguous nucleobases of an antisense compound.

[0138] "Prevent" or "preventing" refers to delaying or forestalling the onset or development of a disease, disorder, or condition for a period of time from minutes to indefinitely. Prevent also means reducing risk of developing a disease, disorder, or condition.

[0139] "Prodrug" means a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., a drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals or conditions.

[0140] "Raise" means to increase in amount. For example, to raise plasma HDL levels means to increase the amount of HDL in the plasma.

[0141] "Reduce" means to bring down to a smaller extent, size, amount, or number. For example, to reduce plasma triglyceride levels means to bring down the amount of triglyceride in the plasma.

[0142] "Region" or "target region" is defined as a portion of the target nucleic acid having at least

one identifiable structure, function, or characteristic. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. The structurally defined regions for apo(a) can be obtained by accession number from sequence databases such as NCBI. In certain instances, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the target region.

[0143] "Ribonucleotide" means a nucleotide having a hydroxy at the 2' position of the sugar portion of the nucleotide. Ribonucleotides can be modified with any of a variety of substituents.

[0144] "Second agent" or "second therapeutic agent" means an agent that can be used in combination with a "first agent". A second therapeutic agent can include, but is not limited to, antisense oligonucleotides targeting apo(a) or apoB. A second agent can also include anti- apo(a) antibodies, apo(a) peptide inhibitors, cholesterol lowering agents, lipid lowering agents, glucose lowering agents and anti-inflammatory agents.

[0145] "Segments" are defined as smaller, sub-portions of regions within a nucleic acid. For example, a "target segment" means the sequence of nucleotides of a target nucleic acid to which one or more antisense compounds is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment. Alternatively, a "start site" can refer to the 5'-most nucleotide of a target segment and a "stop site" refers to the 3'-most nucleotide of a target segment. A target segment can also begin at the "start site" of one sequence and end at the "stop site" of another sequence.

[0146] "Shortened" or "truncated" versions of antisense oligonucleotides or target nucleic acids taught herein have one, two or more nucleosides deleted.

[0147] "Side effects" means physiological responses attributable to a treatment other than the desired effects. In certain instances, side effects include injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, myopathies, and malaise. For example, increased aminotransferase levels in serum may indicate liver toxicity or liver function abnormality. For example, increased bilirubin may indicate liver toxicity or liver function abnormality.

[0148] "Single-stranded oligonucleotide" means an oligonucleotide which is not hybridized to a complementary strand.

[0149] "Specifically hybridizable" refers to an antisense compound having a sufficient degree of complementarity to a target nucleic acid to induce a desired effect while exhibiting minimal or no effects on non-target nucleic acids under conditions in which specific binding is desired, i.e. under physiological conditions in the case of *in vivo* assays and therapeutic treatments.

[0150] "Statin" means an agent that inhibits the activity of HMG-CoA reductase.

[0151] "Subcutaneous administration" means administration just below the skin.

[0152] "Subject" means a human or non-human animal selected for treatment or therapy.

[0153] "Sugar moiety" means a naturally occurring sugar moiety or a modified sugar moiety of a nucleoside.

[0154] "Symptom of cardiovascular disease or disorder" means a phenomenon that arises from and accompanies the cardiovascular disease or disorder and serves as an indication of it. For example, angina; chest pain; shortness of breath; palpitations; weakness; dizziness; nausea; sweating; tachycardia; bradycardia; arrhythmia; atrial fibrillation; swelling in the lower extremities; cyanosis; fatigue; fainting; numbness of the face; numbness of the limbs; claudication or cramping of muscles; bloating of the abdomen; or fever are symptoms of cardiovascular disease or disorder.

[0155] "Targeting" or "targeted" means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

[0156] "Target nucleic acid," "target RNA," and "target RNA transcript" all refer to a nucleic acid capable of being targeted by antisense compounds.

[0157] "Therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

[0158] "Therapeutic lifestyle change" means dietary and lifestyle changes intended to lower fat/adipose tissue mass and/or cholesterol. Such change can reduce the risk of developing heart disease, and may includes recommendations for dietary intake of total daily calories, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, carbohydrate, protein, cholesterol, insoluble fiber, as well as recommendations for physical activity.

[0159] "Treat" or "treating" refers to administering a compound described herein to effect an alteration or improvement of a disease, disorder, or condition.

[0160] "Triglyceride" or "TG" means a lipid or neutral fat consisting of glycerol combined with three fatty acid molecules.

[0161] "Type 2 diabetes," (also known as "type 2 diabetes mellitus", "diabetes mellitus, type 2", "non-insulin-dependent diabetes", "NIDDM", "obesity related diabetes", or "adult-onset diabetes") is a metabolic disorder that is primarily characterized by insulin resistance, relative insulin deficiency, and hyperglycemia.

[0162] "Unmodified nucleotide" means a nucleotide composed of naturally occurring nucleobases, sugar moieties, and internucleoside linkages. In certain instances, an unmodified nucleotide is an RNA nucleotide (i.e. β -D-ribonucleosides) or a DNA nucleotide (i.e. β -D-deoxyribonucleoside).

[0163] "Wing segment" means one or a plurality of nucleosides modified to impart to an oligonucleotide properties such as enhanced inhibitory activity, increased binding affinity for a

target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Certain Aspects

[0164] Certain instances of the disclosure include a compounds and methods for decreasing apo(a) mRNA and protein expression. In certain instances, the compound is an apo(a) specific inhibitor for treating, preventing, or ameliorating an apo(a) associated disease. In certain instances, the compound is an antisense oligonucleotide targeting apo(a).

[0165] Certain instances of the disclosure include a compounds and methods for decreasing Lp(a) levels. In certain instances, the compound is an apo(a) specific inhibitor for treating, preventing, or ameliorating an Lp(a) associated disease. In certain instances, the compound is an antisense oligonucleotide targeting apo(a).

[0166] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides. In certain instances, the modified oligonucleotide consists of 15 to 30, 18 to 24, 19 to 22, 13 to 25, 14 to 25, 15 to 25 linked nucleosides. In certain instances, the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29 or 30 linked nucleosides. In certain instances, the modified oligonucleotide consists of 20 linked nucleosides.

[0167] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to an equal length portion of any of SEQ ID NOs: 1-4. Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting an apo(a) segment comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to an equal length portion of any of the target segments shown in Tables 3-13 and 28-30. In the tables, the "Start Site" refers to the 5'-most nucleotide of a target segment and "Stop Site" refers to the 3'-most nucleotide of a target segment. A target segment can range from the start site to the stop site of each sequence listed in the tables. Alternatively, the target segment can range from the start site of one sequence and end at the stop site of another sequence. For example, as shown in Table 5, a target segment can range from 3901-3920, the start site to the stop site of SEQ ID NO: 58. In another example, as shown in Table 5, a target segment can range from 3900-3923, the start site of SEQ ID NO: 57 to the stop site of SEQ ID NO: 61.

[0168] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the nucleobase sequence of the modified oligonucleotide is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of SEQ ID NOs: 1-4. Certain instances of the disclosure include a compound comprising a modified

oligonucleotide targeting apo(a), wherein the nucleobase sequence of the modified oligonucleotide is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of the target segments shown in Tables 3-13 and 28-30.

[0169] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising a portion of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to an equal length portion of nucleobases 3901 to 3920 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1.

[0170] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and comprising a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29 or 30 contiguous nucleobases complementary to an equal length portion of nucleobases 3900 to 3923 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1.

[0171] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-130, 133, 134. In certain instances, the modified oligonucleotide has a nucleobase sequence comprising at least 8 contiguous nucleobases of any one of the nucleobase sequences of SEQ ID NOs: 12-130, 133, 134.

[0172] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-20, 22-33, 34-43, 46-49, 50, 53, 57-62, 65-66, 68, 70-79, 81, 85-86, 89-90, 92-94, 97, 105-110, 103-104, 133-134.

[0173] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-19, 26-30, 32, 34, 37-43, 45-46, 49, 57-58, 61, 64-66, 68, 72-74, 76-77, 92-94, 103-110.

[0174] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least

15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 111, 114-121, 123-129.

[0175] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 14, 17, 18, 26-28, 38, 71, 106-107.

[0176] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 14, 26-29, 38-39, 82.

[0177] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 14, 16-18.

[0178] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 26-27, 107.

[0179] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 28-29, 38-39, 46.

[0180] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 28, 93, 104, 134.

[0181] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a) consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 58.

[0182] In certain instances, the modified oligonucleotide has a nucleobase sequence comprising

at least 8 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 58.

[0183] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide is single-stranded.

[0184] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein at least one internucleoside linkage is a modified internucleoside linkage. In certain instances, each internucleoside linkage is a phosphorothioate internucleoside linkage.

[0185] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein at least one nucleoside comprises a modified nucleobase. In certain instances, the modified nucleobase is a 5-methylcytosine.

[0186] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide comprises at least one modified sugar. In certain instances, the modified sugar is a bicyclic sugar. In certain instances, the modified sugar comprises a 2'-O-methoxyethyl, a constrained ethyl, a 3'-fluoro-HNA or a 4'-(CH₂)_n-O-2' bridge, wherein n is 1 or 2.

[0187] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises: (a) a gap segment consisting of linked deoxynucleosides; (b) a 5' wing segment consisting of linked nucleosides; (c) a 3' wing segment consisting of linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

[0188] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide consists of 20 linked nucleosides and comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0189] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NOs: 12-130, 133, 134, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-

methylcytosine.

[0190] Certain instances of the disclosure include a compound comprising a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 58, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0191] Certain embodiments provide a modified oligonucleotide targeting apo(a), wherein the modified oligonucleotide consists of 20 linked nucleosides with the nucleobase sequence of SEQ ID NO: 58, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0192] In certain instances, the compound is in a salt form. In further instances, the compound further comprises of a pharmaceutically acceptable carrier or diluent. In certain instances, the compound comprising a modified oligonucleotide targeting apo(a), or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0193] Certain instances of the disclosure include a composition comprising a compound as described herein, wherein the viscosity level of the compound is less than 40 centipoise (cP). In certain instances, the antisense compounds as described herein are efficacious by virtue of having a viscosity of less than 40 cP, less than 35 cP, less than 30 cP, less than 25 cP, less than 20 cP or less than 15 cP when measured by the parameters as described in Example 13.

[0194] Certain instances of the disclosure include compositions and methods for use in therapy to treat an apo(a) related disease, disorder or condition. Certain instances of the disclosure include compositions and methods for use in therapy to treat an Lp(a) related disease, disorder or condition. In certain instances, the composition is a compound comprising an apo(a) specific inhibitor. In certain instances, the apo(a) specific inhibitor is a nucleic acid. In certain instances, the nucleic acid is an antisense compound. In certain instances, the antisense compound is a modified oligonucleotide targeting apo(a). In certain instances, the modified oligonucleotide targeting apo(a), is used in treating, preventing, slowing progression, ameliorating a cardiovascular and/or metabolic disease, disorder or condition. In certain instances, the compositions and methods for therapy include administering an apo(a) specific inhibitor to an individual in need thereof.

[0195] Certain instances of the disclosure include compositions and methods for reducing apo(a) levels. Certain instances of the disclosure include compositions and methods for reducing Lp(a) levels. In certain instances, reducing apo(a) levels in a tissue, organ or subject improves the ratio

of LDL to HDL or the ratio of TG to HDL.

[0196] Certain instances of the disclosure include compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating apo(a) related diseases, disorders, and conditions in a subject in need thereof. Certain instances of the disclosure include compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating Lp(a) related diseases, disorders, and conditions in a subject in need thereof. In certain instances, such diseases, disorders, and conditions include cardiovascular and/or metabolic diseases, disorders, and conditions. Certain such cardiovascular diseases, disorders or conditions include, but are not limited to, aneurysm (e.g., abdominal aortic aneurysm), angina, arrhythmia, atherosclerosis, cerebrovascular disease, coronary artery disease, coronary heart disease, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, myocardial infarction, peripheral vascular disease (e.g., peripheral artery disease, peripheral artery occlusive disease), retinal vascular occlusion, or stroke. Certain such metabolic diseases, disorders or conditions include, but are not limited to, hyperglycemia, prediabetes, diabetes (type I and type II), obesity, insulin resistance, metabolic syndrome and diabetic dyslipidemia. Certain such inflammatory diseases, disorders or conditions include, but are not limited to, coronary artery disease (CAD), Alzheimer's Disease and thromboembolic diseases, disorder or conditions. Certain thromboembolic diseases, disorders or conditions include, but are not limited to, stroke, thrombosis (e.g., venous thromboembolism), myocardial infarction and peripheral vascular disease.

[0197] Certain instances of the disclosure include a method of reducing at least one symptom of a cardiovascular disease, disorder or condition. In certain instances, the symptoms include, but are not limited to, angina, chest pain, shortness of breath, palpitations, weakness, dizziness, nausea, sweating, tachycardia, bradycardia, arrhythmia, atrial fibrillation, swelling in the lower extremities, cyanosis, fatigue, fainting, numbness of the face, numbness of the limbs, claudication or cramping of muscles, bloating of the abdomen, and fever.

[0198] In certain instances, the modulation of apo(a) or Lp(a) expression occurs in a cell, tissue or organ. In certain instances, the modulations occur in a cell, tissue or organ in an animal. In certain instances, the modulation is a reduction in apo(a) mRNA level. In certain instances, the modulation is a reduction in apo(a) protein level. In certain instances, both apo(a) mRNA and protein levels are reduced. In certain instances, the modulation is a reduction in Lp(a) level. Such reduction may occur in a time-dependent or in a dose-dependent manner.

[0199] In certain instances, the subject or animal is human.

[0200] In certain instances, the compound is parenterally administered. In further instances, the parenteral administration is subcutaneous.

[0201] In certain instances, the compound is co-administered with a second agent or therapy. In certain instances, the second agent is a glucose-lowering agent. In certain instances, the second agent is a LDL, TG or cholesterol lowering agent. In certain instances, the second agent is an anti-inflammatory agent. In certain instances, the second agent is an Alzheimer Disease drug. In certain instances, the second agent can be, but is not limited to, a non-steroidal anti-inflammatory

drug (NSAID e.g., aspirin), niacin (e.g., Niaspan), nicotinic acid, an apoB inhibitor (e.g., Mipomersen), a CETP inhibitor (e.g., Anacetrapib), an apo(a) inhibitor, a thyroid hormone analog (e.g., Eprotirome), a HMG-CoA reductase inhibitor (e.g., a statin), a fibrate (e.g., Gemfibrozil) and an microsomal triglyceride transfer protein inhibitor (e.g., Lomitapide). The therapy can be, but is not limited to, Lp(a) apheresis. Agents or therapies can be co-administered or administered concomitantly. Agents or therapies can be sequentially or subsequently administered.

[0202] Certain instances of the disclosure include use of a compound targeted to apo(a) for decreasing apo(a) levels in an animal. Certain instances of the disclosure include use of a compound targeted to apo(a) for decreasing Lp(a) levels in an animal. Certain instances of the disclosure include use of a compounds targeted to apo(a) for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with apo(a). Certain instances of the disclosure include use of a compounds targeted to apo(a) for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with Lp(a).

[0203] Certain instances of the disclosure include use of a compound targeted to apo(a) in the preparation of a medicament for decreasing apo(a) levels in an animal. Certain instances of the disclosure include use of a compound targeted to apo(a) in the preparation of a medicament for decreasing Lp(a) levels in an animal. Certain instances of the disclosure include use of a compound for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with apo(a). Certain instances of the disclosure include use of a compound for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with Lp(a).

[0204] Certain instances of the disclosure include a kit for treating, preventing, or ameliorating a disease, disorder or condition as described herein wherein the kit comprises: (i) an apo(a) specific inhibitor as described herein; and optionally (ii) a second agent or therapy as described herein.

[0205] A kit of the present disclosure can further include instructions for using the kit to treat, prevent, or ameliorate a disease, disorder or condition as described herein by combination therapy as described herein.

Antisense Compounds

[0206] Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, ribozymes, microRNAs and siRNAs. An oligomeric compound may be "antisense" to a target nucleic acid, meaning that it is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

[0207] In certain instances, an antisense compound has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted. In certain such instances, an antisense oligonucleotide has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse

complement of the target segment of a target nucleic acid to which it is targeted.

[0208] In certain instances, an antisense compound targeted to an apo(a) nucleic acid is 12 to 30 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits. In other instances, the antisense compound is 8 to 80, 10 to 80, 12 to 50, 15 to 30, 18 to 24, 19 to 22, 13 to 25, 14 to 25 or 15 to 25 linked subunits. In certain such instances, the antisense compounds are 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 linked subunits in length, or a range defined by any two of the above values. In certain such instances, the antisense compounds are 8 linked subunits in length. In some instances the antisense compound is an antisense oligonucleotide. In some instances, the linked subunits are nucleosides.

[0209] In certain instances, the antisense compound comprises a shortened or truncated modified oligonucleotide. The shortened or truncated modified oligonucleotide can have one or more nucleosides deleted from the 5' end (5' truncation), one or more nucleosides deleted from the 3' end (3' truncation) or one or more nucleosides deleted from the central portion. Alternatively, the deleted nucleosides can be dispersed throughout the modified oligonucleotide, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

[0210] When a single additional nucleoside is present in a lengthened oligonucleotide, the additional nucleoside can be located at the central portion, 5' or 3' end of the oligonucleotide. When two or more additional nucleosides are present, the added nucleosides can be adjacent to each other, for example, in an oligonucleotide having two nucleosides added to the central portion, to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the oligonucleotide. Alternatively, the added nucleosides can be dispersed throughout the antisense compound, for example, in an oligonucleotide having one nucleoside added to the 5' end and one subunit added to the 3' end.

[0211] It is possible to increase or decrease the length of an antisense compound, such as an antisense oligonucleotide, and/or introduce mismatch bases without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of antisense oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Antisense oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the antisense oligonucleotides were able to direct specific cleavage of the target mRNA, albeit to a lesser extent than the antisense oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase antisense oligonucleotides, including those with 1 or 3 mismatches.

[0212] Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL *in vitro* and *in vivo*. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity *in vivo*.

[0213] Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358,1988) tested a series of tandem 14 nucleobase antisense oligonucleotides, and 28 and 42 nucleobase antisense oligonucleotides comprised of the sequence of two or three of the tandem antisense oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase antisense oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase antisense oligonucleotides.

Antisense Compound Motifs

[0214] In certain instances, antisense compounds targeted to an apo(a) nucleic acid have chemically modified subunits arranged in patterns, or motifs, to confer to the antisense compounds properties, such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

[0215] Chimeric antisense compounds typically contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of a chimeric antisense compound may optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of a RNA: DNA duplex.

[0216] Antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal region having a plurality of nucleotides that supports RNase H cleavage is positioned between external regions having a plurality of nucleotides that are chemically distinct from the nucleosides of the internal region. In the case of an antisense oligonucleotide having a gapmer motif, the gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified nucleosides. In certain instances, the regions of a gapmer are differentiated by the types of sugar moieties comprising each distinct region. The types of sugar moieties that are used to differentiate the regions of a gapmer may in some embodiments include β -D-ribonucleosides, β -D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides may include 2'-MOE, and 2'-O-CH₃, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides may include those having a 4'-(CH₂)_n-O-2' bridge, where n=1 or n=2). Preferably, each distinct region comprises uniform sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5' wing region, "Y" represents the length of the gap region, and "Z" represents the length of the 3' wing region. As used herein, a gapmer described as "X-Y-Z" has a configuration such that the gap segment is positioned immediately adjacent to each of the 5' wing segment and the 3' wing segment. Thus, no intervening nucleotides exist between the 5' wing segment and gap segment, or the gap segment and the 3' wing segment. Any of the antisense compounds described herein can have a gapmer motif. In some embodiments, X and Z are the same; in other instances they are different. In a preferred instance, Y is between 8 and 15 nucleotides. X, Y or Z can be any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more nucleotides. Thus, gapmers include, but are not limited to, for example 5-10-5, 4-8-4, 4-12-3, 4-12-4, 3-14-3, 2-13-5, 2-12-2, 2-16-2, 1-18-1, 3-10-3, 2-10-2, 1-10-1, 2-8-2, 6-8-6, 5-8-5, 1-8-1, 2-6-2, 2-13-2, 1-8-2, 2-8-3, 3-10-2, 1-18-2 or 2-18-2.

[0217] In certain instances, the antisense compound as a "wingmer" motif, having a wing-gap or gap-wing configuration, i.e. an X-Y or Y-Z configuration as described above for the gapmer configuration. Thus, wingmer configurations include, but are not limited to, for example 5-10, 8-4, 4-12, 12-4, 3-14, 16-2, 18-1, 10-3, 2-10, 1-10, 8-2, 2-13 or 5-13.

[0218] In certain instances, antisense compounds targeted to an apo(a) nucleic acid possess a 5-10-5 gapmer motif.

[0219] In certain instances, an antisense compound targeted to an apo(a) nucleic acid has a gap-widened motif.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

[0220] Nucleotide sequences that encode the apo(a) target sequence include, without limitation, the following: GENBANK Accession No. NM_005577.2, incorporated herein as SEQ ID NO: 1; GENBANK Accession No. NT_007422.12 truncated from nucleotides 3230000 to 3380000, incorporated herein as SEQ ID NO: 2; GENBANK Accession No. NT_025741.15 truncated from nucleotides 65120000 to 65258000, designated herein as SEQ ID NO: 3; and GENBANK Accession No. NM_005577.1, incorporated herein as SEQ ID NO: 4.

[0221] It is understood that the sequence set forth in each SEQ ID NO in the Examples contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage or a nucleobase. Antisense compounds described by Isis Number (Isis No.) indicate a combination of nucleobase sequence and motif.

[0222] In certain instances, a "target region" is a structurally defined region of the target nucleic acid. For example, a target region can encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, a translation termination region, or other defined nucleic acid region. The structurally defined regions for apo(a) can be obtained by accession number from sequence databases such as NCBI. In certain instances, a target region can encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the same target region.

[0223] In certain instances, a "target segment" is a smaller, sub-portion of a target region within a nucleic acid. For example, a target segment can be the sequence of nucleotides of a target nucleic acid to which one or more antisense compounds are targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment.

[0224] A target region can contain one or more target segments. Multiple target segments within a target region can be overlapping. Alternatively, they can be non-overlapping. In certain instances, target segments within a target region are separated by no more than about 300 nucleotides. In

certain instances, target segments within a target region are separated by a number of nucleotides that is, is about, is no more than, is no more than about, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10 nucleotides on the target nucleic acid, or is a range defined by any two of the preceding values. In certain instances, target segments within a target region are separated by no more than, or no more than about, 5 nucleotides on the target nucleic acid. In certain instances, target segments are contiguous. Contemplated are target regions defined by a range having a starting nucleic acid that is any of the 5' target sites or 3' target sites listed, herein.

[0225] Targeting includes determination of at least one target segment to which an antisense compound hybridizes, such that a desired effect occurs. In certain instances, the desired effect is a reduction in mRNA target nucleic acid levels. In certain instances, the desired effect is reduction of levels of protein encoded by the target nucleic acid or a phenotypic change associated with the target nucleic acid.

[0226] Suitable target segments can be found within a 5' UTR, a coding region, a 3' UTR, an intron, an exon, or an exon/intron junction. Target segments containing a start codon or a stop codon are also suitable target segments. A suitable target segment can specifically exclude a certain structurally defined region, such as the start codon or stop codon.

[0227] The determination of suitable target segments can include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm can be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that can hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

[0228] There can be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within an active target region. In certain instances, reductions in apo(a) mRNA levels can be indicative of inhibition of apo(a) expression. Reductions in levels of an apo(a) protein can be indicative of inhibition of target mRNA expression. Further, phenotypic changes can be indicative of inhibition of apo(a) expression. For example, an increase in HDL levels, decrease in LDL levels, decrease in cholesterol levels or decrease in triglyceride levels, are among phenotypic changes that can be assessed for inhibition of apo(a) expression. Other phenotypic indications, e.g., symptoms associated with a cardiovascular disease, may also be assessed; for example, angina; chest pain; shortness of breath; palpitations; weakness; dizziness; nausea; sweating; tachycardia; bradycardia; arrhythmia; atrial fibrillation; swelling in the lower extremities; cyanosis; fatigue; fainting; numbness of the face; numbness of the limbs; claudication or cramping of muscles; bloating of the abdomen; or fever.

Hybridization

[0229] In some instances, hybridization occurs between an antisense compound disclosed herein and an apo(a) nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between

complementary nucleobases of the nucleic acid molecules.

[0230] Hybridization can occur under varying conditions. Stringent conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

[0231] Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art (Sambrooke and Russell, *Molecular Cloning: A Laboratory Manual*, 3rd Ed., 2001). In certain instances, the antisense compounds provided herein are specifically hybridizable with an apo(a) nucleic acid.

Complementarity

[0232] An antisense compound and a target nucleic acid are complementary to each other when a sufficient number of nucleobases of the antisense compound can hydrogen bond with the corresponding nucleobases of the target nucleic acid, such that a desired effect will occur (e.g., antisense inhibition of a target nucleic acid, such as an apo(a) nucleic acid).

[0233] Noncomplementary nucleobases between an antisense compound and an apo(a) nucleic acid can be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound can hybridize over one or more segments of an apo(a) nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

[0234] In certain embodiments, the antisense compounds provided herein, or a specified portion thereof, are, or are at least, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an apo(a) nucleic acid, a target region, target segment, or specified portion thereof. Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods.

[0235] For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases can be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having 4 (four) noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul et al., *J. Mol. Biol.*, 1990, 215, 403 410; Zhang and Madden, *Genome Res.*, 1997, 7, 649 656). Percent homology, sequence identity or complementarity can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park,

Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2,482-489).

[0236] In certain embodiments, the antisense compounds provided herein, or specified portions thereof, are fully complementary (i.e. 100% complementary) to a target nucleic acid, or specified portion thereof. For example, an antisense compound may be fully complementary to an apo(a) nucleic acid, or a target region, or a target segment or target sequence thereof. As used herein, "fully complementary" means each nucleobase of an antisense compound is capable of precise base pairing with the corresponding nucleobases of a target nucleic acid. For example, a 20 nucleobase antisense compound is fully complementary to a target sequence that is 400 nucleobases long, so long as there is a corresponding 20 nucleobase portion of the target nucleic acid that is fully complementary to the antisense compound. Fully complementary can also be used in reference to a specified portion of the first and /or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase antisense compound can be "fully complementary" to a target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase oligonucleotide is fully complementary to the target sequence if the target sequence has a corresponding 20 nucleobase portion wherein each nucleobase is complementary to the 20 nucleobase portion of the antisense compound. At the same time, the entire 30 nucleobase antisense compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the antisense compound are also complementary to the target sequence.

[0237] The location of a non-complementary nucleobase(s) can be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase(s) can be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they can be contiguous (i.e. linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer antisense oligonucleotide.

[0238] In certain instances, antisense compounds that are, or are up to, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as an apo(a) nucleic acid, or specified portion thereof.

[0239] In certain instances, antisense compounds that are, or are up to, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as an apo(a) nucleic acid, or specified portion thereof.

[0240] The antisense compounds provided herein also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an antisense compound. In certain instances, the antisense compounds are complementary to at least an 8 nucleobase portion of a target segment. In certain instances, the antisense compounds are complementary to at least a 12 nucleobase portion of a target segment. In certain instances, the antisense

compounds are complementary to at least a 15 nucleobase portion of a target segment. Also contemplated are antisense compounds that are complementary to at least a 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

[0241] The antisense compounds provided herein can also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific Isis number, or portion thereof. As used herein, an antisense compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the antisense compounds described herein as well as compounds having non-identical bases relative to the antisense compounds provided herein also are contemplated. The non-identical bases can be adjacent to each other or dispersed throughout the antisense compound. Percent identity of an antisense compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

[0242] In certain instances, the antisense compounds, or portions thereof, are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the antisense compounds or SEQ ID NOs, or a portion thereof, disclosed herein.

[0243] In certain instances, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain instances, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleobase portion is compared to an equal length portion of the target nucleic acid.

[0244] In certain instances, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain instances, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Modifications

[0245] A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

[0246] Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

[0247] Chemically modified nucleosides can also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

[0248] The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

[0249] Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

[0250] In certain embodiments, antisense compounds targeted to an apo(a) nucleic acid, as defined in the claims, comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

Modified Sugar Moieties

[0251] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substituent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or

C(R₁)(R₂) (R, R₁ and R₂ are each independently H, C₁-C₁₂ alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (see PCT International Application WO 2008/101157 Published on 8/21/08 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923, published on June 16, 2005) or alternatively 5'-substitution of a BNA (see PCT International Application WO 2007/134181 Published on 11/22/07 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[0252] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (*R* or *S*), 4'-S, 2'-F, 2'-OCH₃, 2'-OCH₂CH₃, 2'-OCH₂CH₂F and 2'-O(CH₂)₂OCH₃ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O-C₁-C₁₀ alkyl, OCF₃, OCH₂F, O(CH₂)₂SCH₃, O(CH₂)₂-O-N(R_m)(R_n), O-CH₂-C(=O)-N(R_m)(R_n), and O-CH₂-C(=O)-N(R₁)-(CH₂)₂-N(R_m)(R_n), where each R₁, R_m and R_n is, independently, H or substituted or unsubstituted C₁-C₁₀ alkyl.

[0253] As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH₂)-O-2' (LNA); 4'-(CH₂)-S-2'; 4'-(CH₂)₂-O-2' (ENA); 4'-CH(CH₃)-O-2' and 4'-CH(CH₂OCH₃)-O-2' (and analogs thereof see U.S. Patent 7,399,845, issued on July 15, 2008); 4'-C(CH₃)(CH₃)-O-2' (and analogs thereof see published International Application WO/2009/006478, published January 8, 2009); 4'-CH₂-N(OCH₃)-2' (and analogs thereof see published International Application WO/2008/150729, published December 11, 2008); 4'-CH₂-O-N(CH₃)-2' (see published U.S. Patent Application US2004-0171570, published September 2, 2004); 4'-CH₂-N(R)-O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see U.S. Patent 7,427,672, issued on September 23, 2008); 4'-CH₂-C(H)(CH₃)-2' (see Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH₂-C(=CH₂)-2' (and analogs thereof see published International Application WO 2008/154401, published on December 8, 2008).

[0254] Further reports related to bicyclic nucleosides can also be found in published literature (see for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U. S. A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129(26) 8362-8379; Elayadi et al., Curr. Opinion Invest. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; and Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Serial Nos. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing

bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α -L-ribofuranose and β -D-ribofuranose (see PCT international application PCT/DK98/00393, published on March 25, 1999 as WO 99/14226).

[0255] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-\text{C}(\text{R}_a)(\text{R}_b)]_n-$, $-\text{C}(\text{R}_a)=\text{C}(\text{R}_b)-$, $-\text{C}(\text{R}_a)=\text{N}-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{NR}_a)-$, $-\text{C}(=\text{S})-$, $-\text{O}-$, $-\text{Si}(\text{R}_a)_2-$, $-\text{S}(=\text{O})_x-$, and $-\text{N}(\text{R}_a)-$;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , COOJ_1 , acyl ($\text{C}(=\text{O})-\text{H}$), substituted acyl, CN, sulfonyl ($\text{S}(=\text{O})_2-\text{J}_1$), or sulfoxyl ($\text{S}(=\text{O})-\text{J}_1$); and

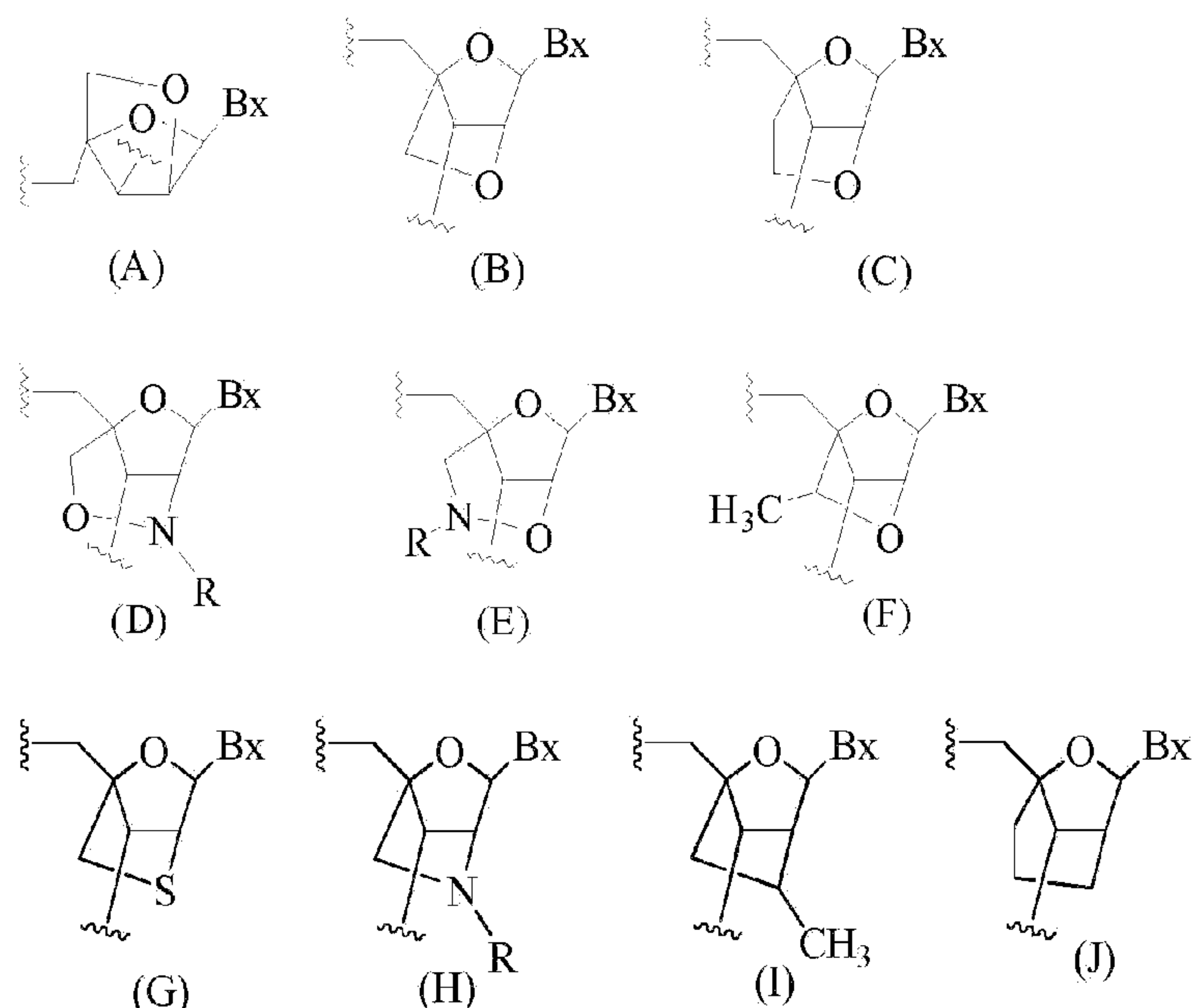
each J_1 and J_2 is, independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($\text{C}(=\text{O})-\text{H}$), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1 - C_{12} aminoalkyl, substituted C_1 - C_{12} aminoalkyl or a protecting group.

[0256] In certain embodiments, the bridge of a bicyclic sugar moiety is $-\text{C}(\text{R}_a)(\text{R}_b)]_n-$, $-\text{C}(\text{R}_a)(\text{R}_b)]_n-\text{O}-$, $-\text{C}(\text{R}_a\text{R}_b)-\text{N}(\text{R})-\text{O}-$ or $-\text{C}(\text{R}_a\text{R}_b)-\text{O}-\text{N}(\text{R})-$. In certain embodiments, the bridge is 4'- CH_2 -2', 4'-(CH_2)₂-2', 4'-(CH_2)₃-2', 4'- CH_2 -O-2', 4'-(CH_2)₂-O-2', 4'- CH_2 -O-N(R)-2' and 4'- CH_2 -N(R)-O-2' wherein each R is, independently, H, a protecting group or C_1 - C_{12} alkyl.

[0257] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α -L configuration or in the β -D configuration. Previously, α -L-methyleneoxy (4'- CH_2 -O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden *et al.*, *Nucleic Acids Research*, 2003, 21, 6365-6372).

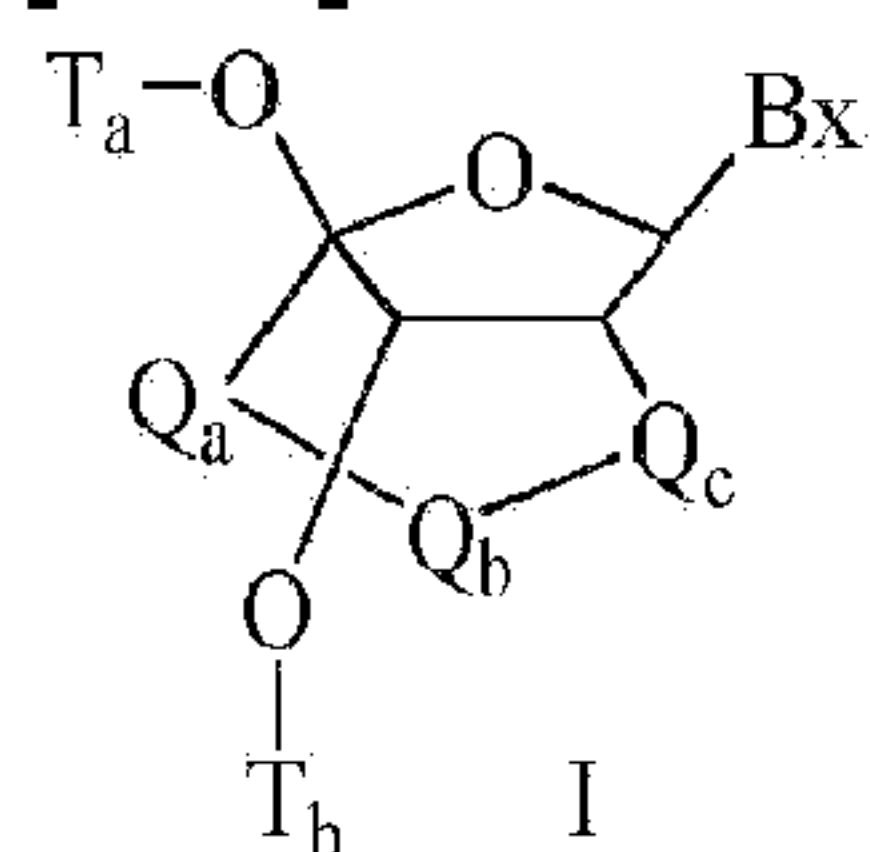
[0258] In certain embodiments, bicyclic nucleosides include, but are not limited to, (A) α -L-methyleneoxy (4'- CH_2 -O-2') BNA, (B) β -D-methyleneoxy (4'- CH_2 -O-2') BNA, (C) ethyleneoxy (4'-(CH_2)₂-O-2') BNA, (D) aminooxy (4'- CH_2 -O-N(R)-2') BNA, (E) oxyamino (4'- CH_2 -N(R)-O-2') BNA, and (F) methyl(methyleneoxy) (4'-CH(CH_3)-O-2') BNA, (G) methylene-thio (4'- CH_2 -S-2') BNA, (H)

methylene-amino (4'-CH₂-N(R)-2') BNA, (I) methyl carbocyclic (4'-CH₂-CH(CH₃)-2') BNA, and (J) propylene carbocyclic (4'-(CH₂)₃-2') BNA as depicted below.



wherein Bx is the base moiety and R is independently H, a protecting group or C₁-C₁₂ alkyl.

[0259] In certain embodiments, bicyclic nucleosides are provided having Formula I:



wherein:

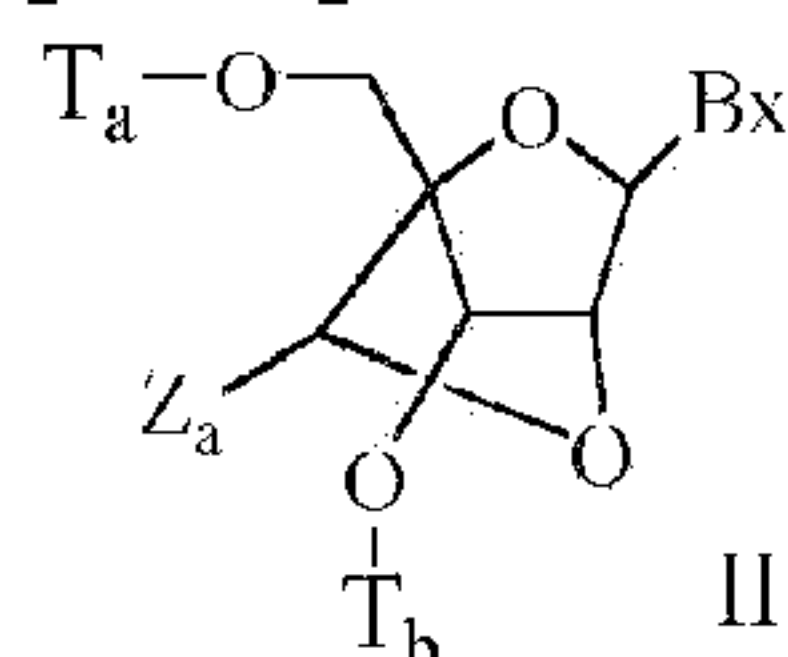
Bx is a heterocyclic base moiety;

-Q_a-Q_b-Q_c- is -CH₂-N(R_c)-CH₂-, -C(=O)-N(R_c)-CH₂-, -CH₂-O-N(R_c)-, -CH₂-N(R_c)-O- or -N(R_c)-O-CH₂;

R_c is C₁-C₁₂ alkyl or an amino protecting group; and

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium.

[0260] In certain embodiments, bicyclic nucleosides are provided having Formula II:



wherein:

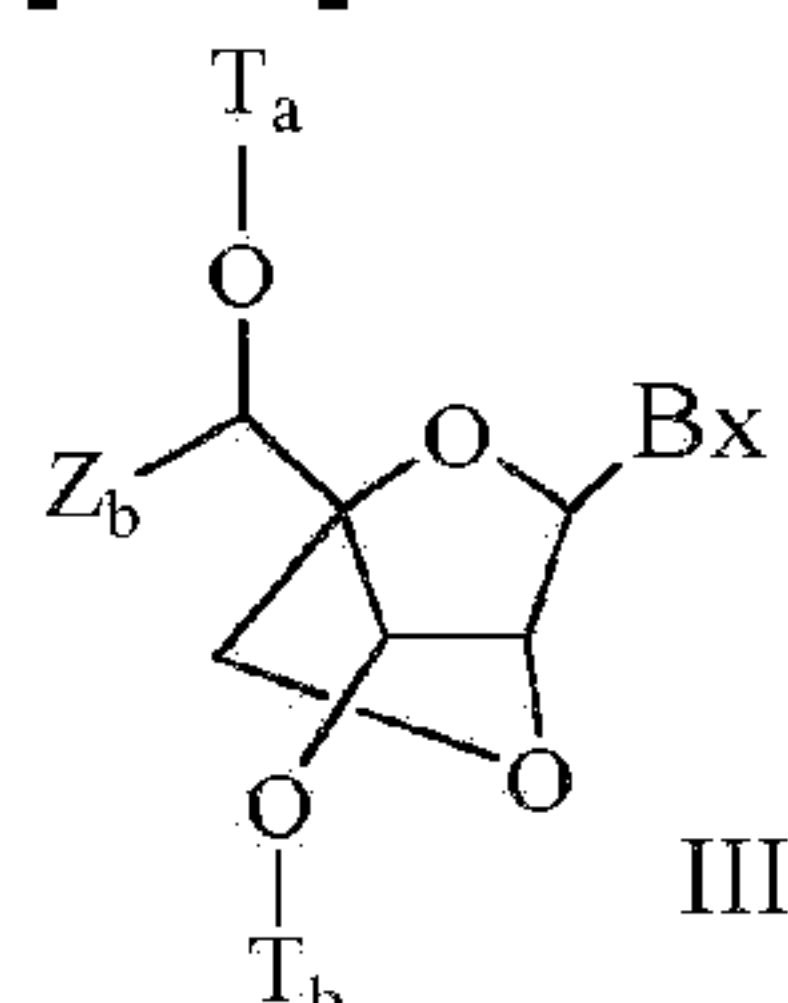
Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

Z_a is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted C_1 - C_6 alkyl, substituted C_2 - C_6 alkenyl, substituted C_2 - C_6 alkynyl, acyl, substituted acyl, substituted amide, thiol or substituted thio.

[0261] In one embodiment, each of the substituted groups is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ_c , NJ_cJ_d , SJ_c , N_3 , $OC(=X)J_c$, and $NJ_eC(=X)NJ_cJ_d$, wherein each J_c , J_d and J_e is, independently, H, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl and X is O or NJ_c .

[0262] In certain embodiments, bicyclic nucleosides are provided having Formula III:



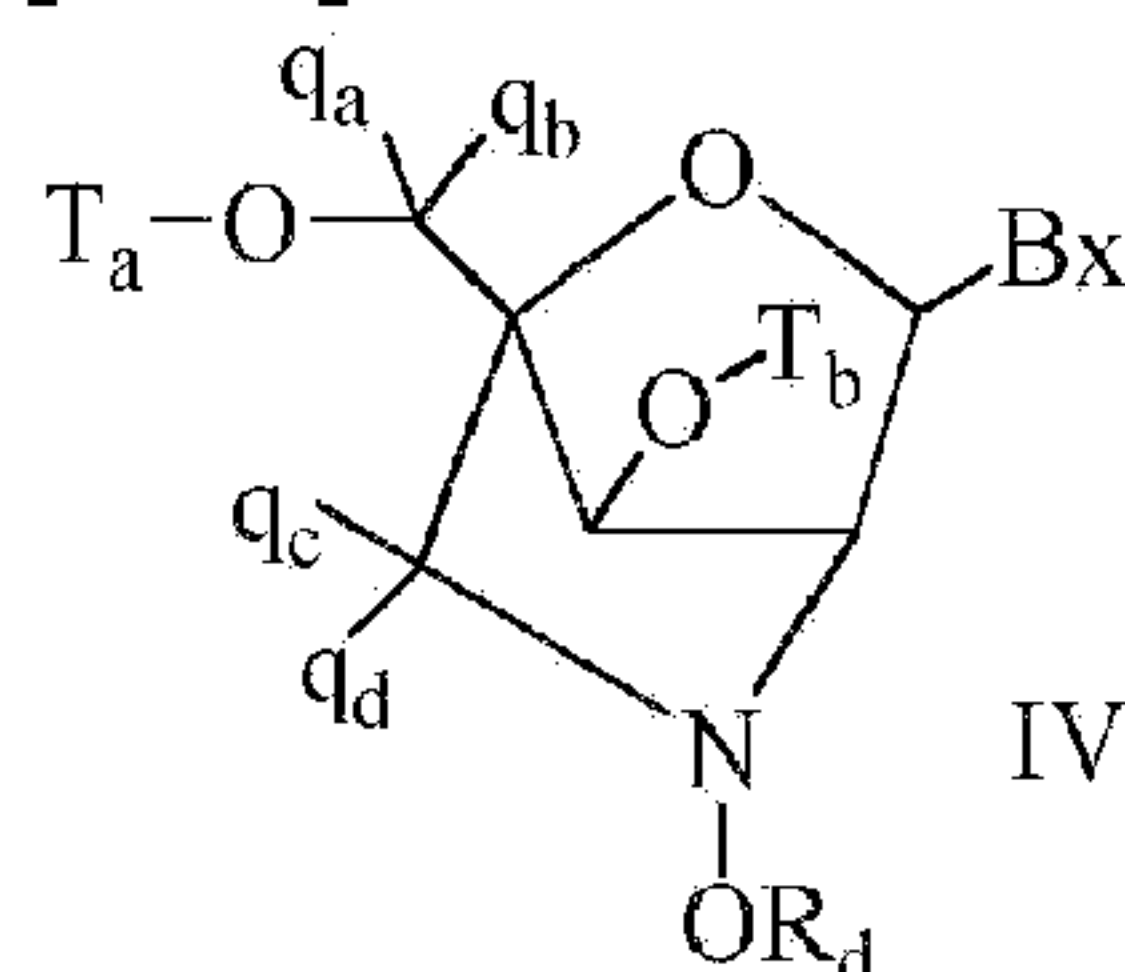
wherein:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

Z_b is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, substituted C_1 - C_6 alkyl, substituted C_2 - C_6 alkenyl, substituted C_2 - C_6 alkynyl or substituted acyl ($C(=O)-$).

[0263] In certain embodiments, bicyclic nucleosides are provided having Formula IV:



wherein:

Bx is a heterocyclic base moiety;

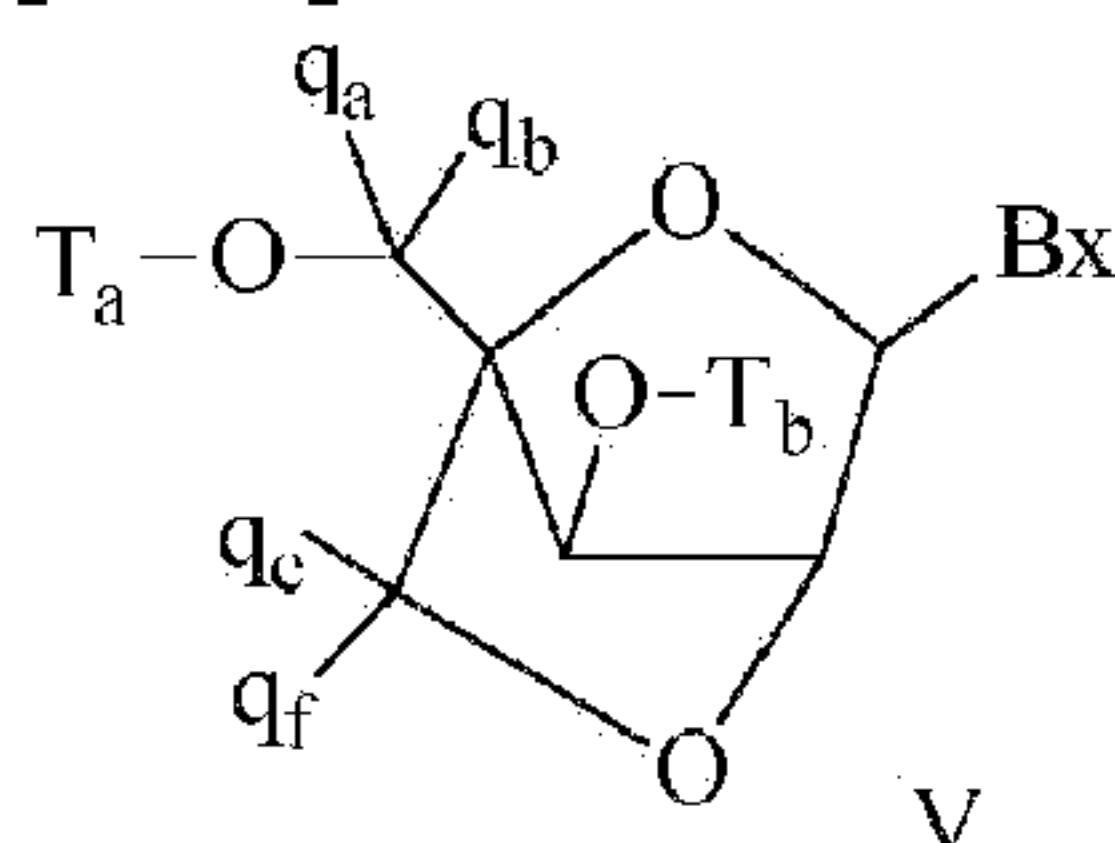
T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

R_d is C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, C_2 - C_6 alkenyl, substituted C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or

substituted C₂-C₆ alkynyl;

each q_a, q_b, q_c and q_d is, independently, H, halogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl or substituted C₂-C₆ alkynyl, C₁-C₆ alkoxyl, substituted C₁-C₆ alkoxyl, acyl, substituted acyl, C₁-C₆ aminoalkyl or substituted C₁-C₆ aminoalkyl;

[0264] In certain embodiments, bicyclic nucleosides are provided having Formula V:



wherein:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently, H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

q_a, q_b, q_e and q_f are each, independently, hydrogen, halogen, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, substituted C₁-C₁₂ alkoxy, OJ_j, SJ_j, SOJ_j, SO₂J_j, NJ_jJ_k, N₃, CN, C(=O)OJ_j, C(=O)NJ_jJ_k, C(=O)J_j, O-C(=O)-NJ_jJ_k, N(H)C(=NH)NJ_jJ_k, N(H)C(=O)NJ_jJ_k or N(H)C(=S)NJ_jJ_k;

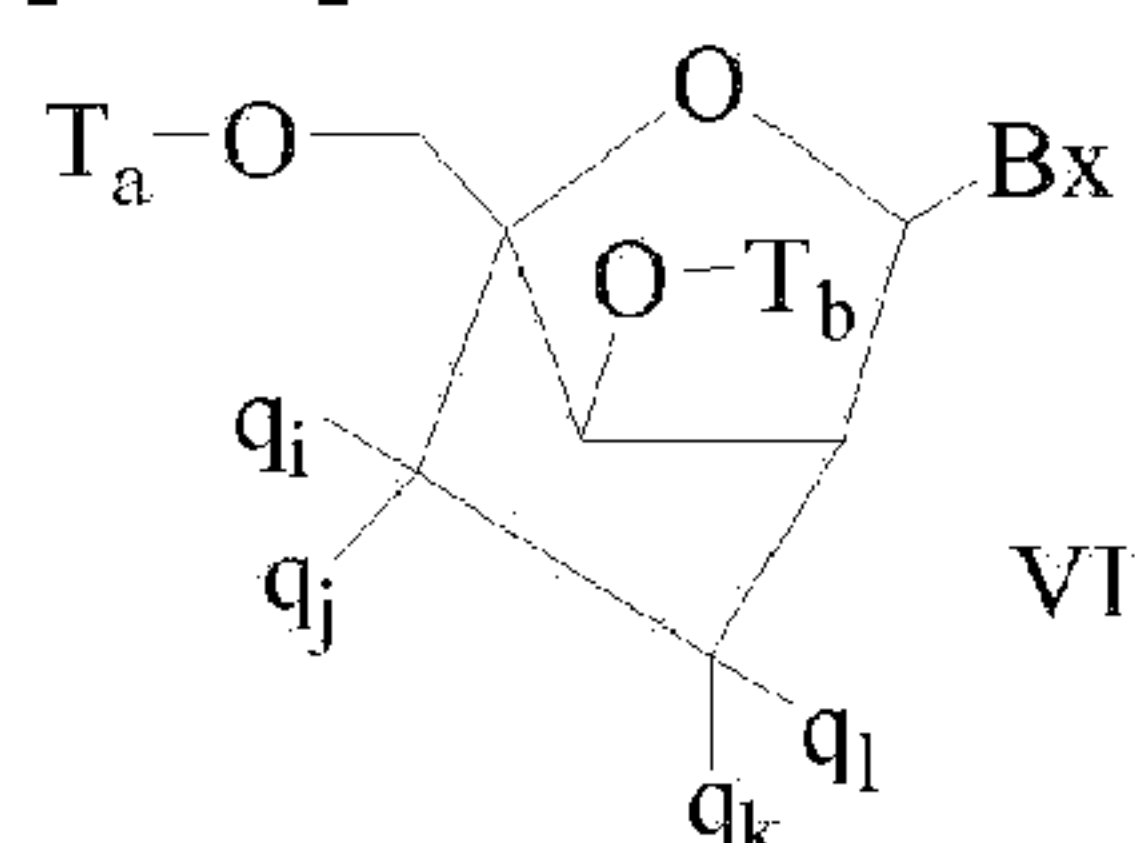
or q_e and q_f together are =C(q_g)(q_h);

q_g and q_h are each, independently, H, halogen, C₁-C₁₂ alkyl or substituted C₁-C₁₂ alkyl.

[0265] The synthesis and preparation of the methyleneoxy (4'-CH₂-O-2') BNA monomers adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin et al., Tetrahedron, 1998, 54, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

[0266] Analogs of methyleneoxy (4'-CH₂-O-2') BNA and 2'-thio-BNAs, have also been prepared (Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222). Preparation of locked nucleoside analogs comprising oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel et al., WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel conformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh et al., J. Org. Chem., 1998, 63, 10035-10039). In addition, 2'-amino- and 2'-methylamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

[0267] In certain embodiments, bicyclic nucleosides are provided having Formula VI:



wherein:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

each q_i, q_j, q_k and q_l is, independently, H, halogen, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, substituted C₁-C₁₂ alkoxy, OJ_j, SJ_j, SOJ_j, SO₂J_j, NJ_jJ_k, N₃, CN, C(=O)OJ_j, C(=O)NJ_jJ_k, C(=O)J_j, O-C(=O)NJ_jJ_k, N(H)C(=NH)NJ_jJ_k, N(H)C(=O)NJ_jJ_k or N(H)C(=S)NJ_jJ_k; and

q_i and q_j or q_l and q_k together are =C(q_g)(q_h), wherein q_g and q_h are each, independently, H, halogen, C₁-C₁₂ alkyl or substituted C₁-C₁₂ alkyl.

[0268] One carbocyclic bicyclic nucleoside having a 4'-(CH₂)₃-2' bridge and the alkenyl analog bridge 4'-CH=CH-CH₂-2' have been described (Freier et al., Nucleic Acids Research, 1997, 25(22), 4429-4443 and Albaek et al., J. Org. Chem., 2006, 71, 7731-7740). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (Srivastava et al., J. Am. Chem. Soc., 2007, 129(26), 8362-8379).

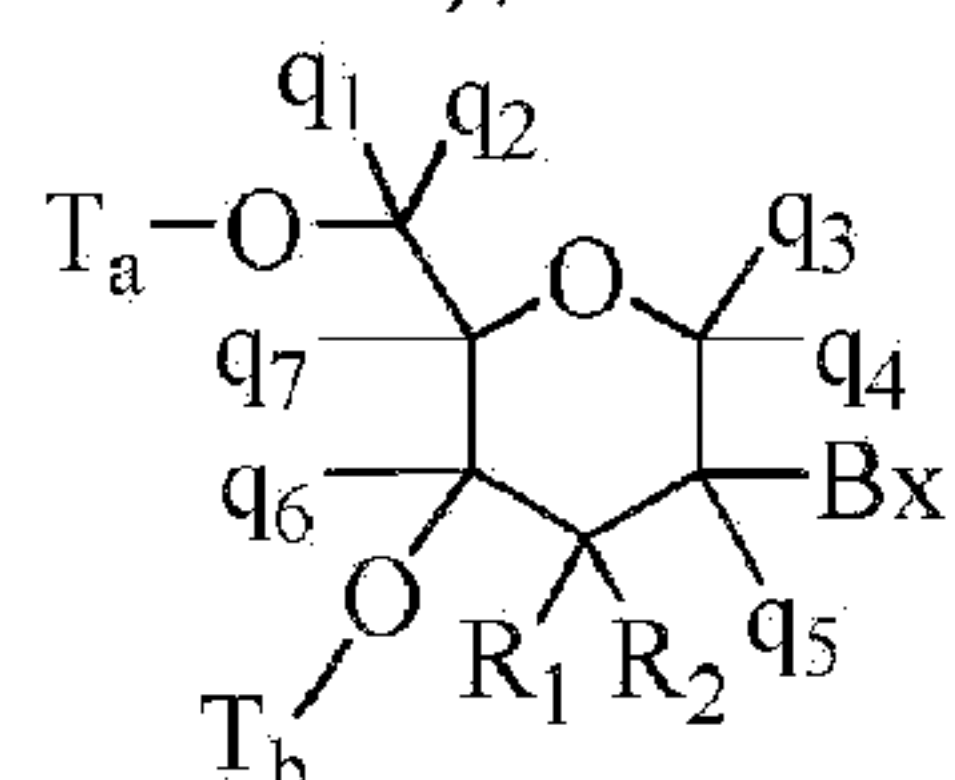
[0269] As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2' carbon atom and the 4' carbon atom of the sugar ring.

[0270] As used herein, "monocyclic nucleosides" refer to nucleosides comprising modified sugar moieties that are not bicyclic sugar moieties. In certain embodiments, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position.

[0271] As used herein, "2'-modified sugar" means a furanosyl sugar modified at the 2' position. In certain embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In certain embodiments, 2' modifications are selected from substituents including, but not limited to: O[(CH₂)_nO]_mCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nF, O(CH₂)_nONH₂, OCH₂C(=O)N(H)CH₃, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. Other 2'- substituent groups can

also be selected from: C₁-C₁₂ alkyl, substituted alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, F, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving pharmacokinetic properties, or a group for improving the pharmacodynamic properties of an antisense compound, and other substituents having similar properties. In certain embodiments, modified nucleosides comprise a 2'-MOE side chain (Baker et al., J. Biol. Chem., 1997, 272, 11944-12000). Such 2'-MOE substitution have been described as having improved binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2'-O-methyl, O-propyl, and O-aminopropyl. Oligonucleotides having the 2'-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for *in vivo* use (Martin, Helv. Chim. Acta, 1995, 78, 486-504; Altmann et al., Chimia, 1996, 50, 168-176; Altmann et al., Biochem. Soc. Trans., 1996, 24, 630-637; and Altmann et al., Nucleosides Nucleotides, 1997, 16, 917-926).

[0272] As used herein, a "modified tetrahydropyran nucleoside" or "modified THP nucleoside" means a nucleoside having a six-membered tetrahydropyran "sugar" substituted in for the pentofuranosyl residue in normal nucleosides (a sugar surrogate). Modified THP nucleosides include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see Leumann, Bioorg. Med. Chem., 2002, 10, 841-854), fluoro HNA (F-HNA) or those compounds having Formula VII:



VII

wherein independently for each of said at least one tetrahydropyran nucleoside analog of Formula VII:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_a and T_b is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_a and T_b is H, a hydroxyl protecting group, a linked conjugate group or a 5' or 3'-terminal group;

q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl or substituted C₂-C₆ alkynyl; and each of R₁ and R₂ is selected from hydrogen, hydroxyl, halogen, substituted or unsubstituted alkoxy, NJ₁J₂, SJ₁, N₃, OC(=X)J₁, OC(=X)NJ₁J₂, NJ₃C(=X)NJ₁J₂ and CN, wherein X is O, S or NJ₁ and each J₁, J₂ and J₃ is, independently, H or C₁-C₆ alkyl.

[0273] In certain embodiments, the modified THP nucleosides of Formula VII are provided wherein q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each H. In certain embodiments, at least one of q₁, q₂, q₃,

q₄, q₅, q₆ and q₇ is other than H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is methyl. In certain embodiments, THP nucleosides of Formula VII are provided wherein one of R₁ and R₂ is fluoro. In certain embodiments, R₁ is fluoro and R₂ is H; R₁ is methoxy and R₂ is H, and R₁ is methoxyethoxy and R₂ is H. In certain embodiments, R₁ is H and R₂ is fluoro; R₁ is H and R₂ is methoxy, and R₁ is H and R₂ is methoxyethoxy.

[0274] As used herein, "2'-modified" or "2'-substituted" refers to a nucleoside comprising a sugar comprising a substituent at the 2' position other than H or OH. 2'-modified nucleosides, include, but are not limited to, bicyclic nucleosides wherein the bridge connecting two carbon atoms of the sugar ring connects the 2' carbon and another carbon of the sugar ring; and nucleosides with non-bridging 2'substituents, such as allyl, amino, azido, thio, O-allyl, O-C₁-C₁₀ alkyl, -OCF₃, O-(CH₂)₂-O-CH₃, 2'-O(CH₂)₂SCH₃, O-(CH₂)₂-O-N(R_m)(R_n), or O-CH₂-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C₁-C₁₀ alkyl. 2'-modified nucleosides may further comprise other modifications, for example at other positions of the sugar and/or at the nucleobase.

[0275] As used herein, "2'-F" refers to a nucleoside comprising a sugar comprising a fluoro group at the 2' position.

[0276] As used herein, "2'-OMe" or "2'-OCH₃" or "2'-O-methyl" each refers to a nucleoside comprising a sugar comprising an -OCH₃ group at the 2' position of the sugar ring.

[0277] As used herein, "MOE" or "2'-MOE" or "2'-OCH₂CH₂OCH₃" or "2'-O-methoxyethyl" each refers to a nucleoside comprising a sugar comprising a -OCH₂CH₂OCH₃ group at the 2' position of the sugar ring.

[0278] As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain embodiments, one or more of the plurality of nucleosides is modified. In certain embodiments, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA).

[0279] Many other bicyclo and tricyclo sugar surrogate ring systems are also known in the art that can be used to modify nucleosides for incorporation into antisense compounds (see for example review article: Leumann, Bioorg. Med. Chem., 2002, 10, 841-854). Such ring systems can undergo various additional substitutions to enhance activity.

[0280] Methods for the preparations of modified sugars are well known to those skilled in the art.

[0281] In nucleotides having modified sugar moieties, the nucleobase moieties (natural, modified or a combination thereof) are maintained for hybridization with an appropriate nucleic acid target.

[0282] In certain embodiments, antisense compounds comprise one or more nucleosides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE. In certain embodiments, the 2'-MOE modified nucleosides are arranged in a gapmer motif. In certain

embodiments, the modified sugar moiety is a bicyclic nucleoside having a (4'-CH(CH₃)-O-2') bridging group. In certain embodiments, the (4'-CH(CH₃)-O-2') modified nucleosides are arranged throughout the wings of a gapmer motif. In certain embodiments, the modified sugar moiety is a cEt. In certain embodiments, the cEt modified nucleotides are arranged throughout the wings of a gapmer motif.

Modified Nucleobases

[0283] Nucleobase (or base) modifications or substitutions are structurally distinguishable from, yet functionally interchangeable with, naturally occurring or synthetic unmodified nucleobases. Both natural and modified nucleobases are capable of participating in hydrogen bonding. Such nucleobase modifications may impart nuclease stability, binding affinity or some other beneficial biological property to antisense compounds. Modified nucleobases include synthetic and natural nucleobases such as, for example, 5-methylcytosine (5-me-C). Certain nucleobase substitutions, including 5-methylcytosine substitutions, are particularly useful for increasing the binding affinity of an antisense compound for a target nucleic acid. For example, 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y.S., Crooke, S.T. and Lebleu, B., eds., *Antisense Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278).

[0284] Additional modified nucleobases include 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH₃) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

[0285] Heterocyclic base moieties may include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Nucleobases that are particularly useful for increasing the binding affinity of antisense compounds include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2 aminopropyladenine, 5-propynyluracil and 5-propynylcytosine.

[0286] In certain embodiments, antisense compounds targeted to an apo(a) nucleic acid, as defined in the claims, comprise one or more modified nucleobases. In certain instances, gap-widened antisense oligonucleotides targeted to an apo(a) nucleic acid, as defined in the claims, comprise one or more modified nucleobases. In certain embodiments, the modified nucleobase is 5-methylcytosine. In certain embodiments, each cytosine is a 5-methylcytosine.

Compositions and Methods for Formulating Pharmaceutical Compositions

[0287] Antisense oligonucleotides may be admixed with pharmaceutically acceptable active or inert substance for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

[0288] Antisense compound targeted to an apo(a) nucleic acid can be utilized in pharmaceutical compositions by combining the antisense compound with a suitable pharmaceutically acceptable diluent or carrier.

[0289] In certain embodiments, the "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and can be selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, etc.); fillers (e.g., lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, etc.); lubricants (e.g., magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, etc.); disintegrants (e.g., starch, sodium starch glycolate, etc.); and wetting agents (e.g., sodium lauryl sulphate, etc.).

[0290] Pharmaceutically acceptable organic or inorganic excipients, which do not deleteriously react with nucleic acids, suitable for parenteral or non-parenteral administration can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

[0291] A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS). PBS is a diluent suitable for use in compositions to be delivered parenterally. Accordingly, in one instance, employed in the methods described herein is a pharmaceutical composition comprising an antisense compound targeted to an apo(a) nucleic acid and a pharmaceutically acceptable diluent. In certain instances, the pharmaceutically acceptable diluent is PBS. In certain instances, the antisense compound is an antisense oligonucleotide.

[0292] Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or an oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of antisense compounds, prodrugs,

pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

[0293] A prodrug can include the incorporation of additional nucleosides at one or both ends of an antisense compound which are cleaved by endogenous nucleases within the body, to form the active antisense compound.

Conjugated Antisense Compounds

[0294] Antisense compounds can be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the resulting antisense oligonucleotides. Typical conjugate groups include cholesterol moieties and lipid moieties. Additional conjugate groups include carbohydrates, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

[0295] Antisense compounds can also be modified to have one or more stabilizing groups that are generally attached to one or both termini of antisense compounds to enhance properties such as, for example, nuclease stability. Included in stabilizing groups are cap structures. These terminal modifications protect the antisense compound having terminal nucleic acid from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap), or at the 3'-terminus (3'-cap), or can be present on both termini. Cap structures are well known in the art and include, for example, inverted deoxy abasic caps. Further 3' and 5'-stabilizing groups that can be used to cap one or both ends of an antisense compound to impart nuclease stability include those disclosed in WO 03/004602, published on January 16, 2003.

Cell culture and antisense compounds treatment

[0296] The effects of antisense compounds on the level, activity or expression of apo(a) nucleic acids can be tested *in vitro* in a variety of cell types. Cell types used for such analyses are available from commercial vendors (e.g. American Type Culture Collection, Manassus, VA; Zen-Bio, Inc., Research Triangle Park, NC; Clonetics Corporation, Walkersville, MD) and are cultured according to the vendor's instructions using commercially available reagents (e.g., Invitrogen Life Technologies, Carlsbad, CA). Illustrative cell types include, but are not limited to, HepG2 cells, Hep3B cells, Huh7 (hepatocellular carcinoma) cells, primary hepatocytes, A549 cells, GM04281 fibroblasts and LLC-MK2 cells.

In Vitro Testing of Antisense Oligonucleotides

[0297] Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

[0298] In general, cells are treated with antisense oligonucleotides when the cells reach approximately 60-80% confluence in culture.

[0299] One reagent commonly used to introduce antisense oligonucleotides into cultured cells includes the cationic lipid transfection reagent LIPOFECTIN® (Invitrogen, Carlsbad, CA). Antisense oligonucleotides are mixed with LIPOFECTIN® in OPTI-MEM® 1 (Invitrogen, Carlsbad, CA) to achieve the desired final concentration of antisense oligonucleotide and a LIPOFECTIN® concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

[0300] Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE 2000® (Invitrogen, Carlsbad, CA). Antisense oligonucleotide is mixed with LIPOFECTAMINE 2000® in OPTI-MEM® 1 reduced serum medium (Invitrogen, Carlsbad, CA) to achieve the desired concentration of antisense oligonucleotide and a LIPOFECTAMINE® concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

[0301] Another reagent used to introduce antisense oligonucleotides into cultured cells includes Cytofectin® (Invitrogen, Carlsbad, CA). Antisense oligonucleotide is mixed with Cytofectin® in OPTI-MEM® 1 reduced serum medium (Invitrogen, Carlsbad, CA) to achieve the desired concentration of antisense oligonucleotide and a Cytofectin® concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

[0302] Another reagent used to introduce antisense oligonucleotides into cultured cells includes Oligofectamine™ (Invitrogen Life Technologies, Carlsbad, CA). Antisense oligonucleotide is mixed with Oligofectamine™ in Opti-MEM™-1 reduced serum medium (Invitrogen Life Technologies, Carlsbad, CA) to achieve the desired concentration of oligonucleotide with an Oligofectamine™ to oligonucleotide ratio of approximately 0.2 to 0.8 µL per 100 nM.

[0303] Another reagent used to introduce antisense oligonucleotides into cultured cells includes FuGENE 6 (Roche Diagnostics Corp., Indianapolis, IN). Antisense oligomeric compound was mixed with FuGENE 6 in 1 mL of serum-free RPMI to achieve the desired concentration of oligonucleotide with a FuGENE 6 to oligomeric compound ratio of 1 to 4 µL of FuGENE 6 per 100 nM.

[0304] Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation (Sambrooke and Russell in Molecular Cloning. A Laboratory Manual. Third Edition. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. 2001).

[0305] Cells are treated with antisense oligonucleotides by routine methods. Cells are typically harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein (Sambrooke and Russell in Molecular Cloning. A Laboratory Manual. Third Edition. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. 2001). In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

[0306] The concentration of antisense oligonucleotide used varies from cell line to cell line.

Methods to determine the optimal antisense oligonucleotide concentration for a particular cell line are well known in the art (Sambrooke and Russell in *Molecular Cloning. A Laboratory Manual*. Third Edition. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. 2001). Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM when transfected with LIPOFECTAMINE2000® (Invitrogen, Carlsbad, CA), Lipofectin® (Invitrogen, Carlsbad, CA) or Cytofectin™ (Genlantis, San Diego, CA). Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using electroporation.

RNA Isolation

[0307] RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art (Sambrooke and Russell in *Molecular Cloning. A Laboratory Manual*. Third Edition. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. 2001). For example, RNA can be prepared using TRIZOL® (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocols.

Analysis of inhibition of target levels or expression

[0308] Inhibition of levels or expression of an apo(a) nucleic acid can be assayed in a variety of ways known in the art (Sambrooke and Russell in *Molecular Cloning. A Laboratory Manual*. Third Edition. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2001). For example, target nucleic acid levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitative real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Quantitative real-time PCR can be conveniently accomplished using the commercially available ABI PRISM 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems (Foster City, CA) and used according to manufacturer's instructions.

Quantitative Real-Time PCR Analysis of Target RNA Levels

[0309] Quantitation of target RNA levels can be accomplished by quantitative real-time PCR using the ABI PRISM® 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

[0310] Prior to real-time PCR, the isolated RNA is subjected to a reverse transcriptase (RT) reaction, which produces complementary DNA (cDNA) that is then used as the substrate for the real-time PCR amplification. The RT and real-time PCR reactions are performed sequentially in the same sample well. RT and real-time PCR reagents are obtained from Invitrogen (Carlsbad, CA). RT and real-time-PCR reactions are carried out by methods well known to those skilled in the

art.

[0311] Gene (or RNA) target quantities obtained by real time PCR can be normalized using either the expression level of a gene whose expression is constant, such as cyclophilin A or GAPDH, or by quantifying total RNA using RIBOGREEN® (Invitrogen, Inc. Carlsbad, CA). Cyclophilin A or GAPDH expression can be quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RIBOGREEN® RNA quantification reagent (Invitrogen, Inc. Carlsbad, CA). Methods of RNA quantification by RIBOGREEN® are taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR® 4000 instrument (PE Applied Biosystems, Foster City, CA) is used to measure RIBOGREEN® fluorescence.

[0312] Probes and primers can be designed to hybridize to an apo(a) nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS® Software (Applied Biosystems, Foster City, CA).

Analysis of Protein Levels

[0313] Antisense inhibition of apo(a) nucleic acids can be assessed by measuring apo(a) protein levels. Protein levels of apo(a) can be evaluated or quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA), quantitative protein assays, protein activity assays (for example, caspase activity assays), immunohistochemistry, immunocytochemistry or fluorescence-activated cell sorting (FACS) (Sambrooke and Russell in Molecular Cloning. A Laboratory Manual. Third Edition. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. 2001). Antibodies directed to a target can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art. Antibodies useful for the detection of apo(a) are commercially available.

In vivo testing of antisense compounds

[0314] Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of apo(a) and produce phenotypic changes. Testing can be performed in normal animals, or in experimental disease models. For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as saline or phosphate-buffered saline. Administration includes parenteral routes of administration. Calculation of antisense oligonucleotide dosage and dosing frequency depends upon factors such as route of administration and animal body weight. Following a period of treatment with antisense oligonucleotides, RNA is isolated from tissue and changes in apo(a) nucleic acid expression are measured. Changes in apo(a) protein levels are also measured.

Certain Indications

[0315] Disclosed herein are methods of treating an individual comprising administering one or more pharmaceutical compositions as described herein. In certain instances, the individual has an apo(a) related disease. In certain instances, the individual has an Lp(a) related disease. In certain instances, the individual has an inflammatory, cardiovascular and/or a metabolic disease, disorder or condition.

[0316] In certain instances, the cardiovascular diseases, disorders or conditions include, but are not limited to, aneurysm (e.g., abdominal aortic aneurysm), angina, arrhythmia, atherosclerosis, cerebrovascular disease, coronary artery disease, coronary heart disease, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, myocardial infarction, peripheral vascular disease (e.g., peripheral artery disease), stroke and the like.

[0317] In certain instances, the compounds targeted to apo(a) described herein modulate physiological markers or phenotypes of the cardiovascular disease, disorder or condition. For example, administration of the compounds to animals can decrease LDL and cholesterol levels in those animals compared to untreated animals. In certain instances, the modulation of the physiological markers or phenotypes can be associated with inhibition of apo(a) by the compounds.

[0318] In certain instances, the physiological markers of the cardiovascular disease, disorder or condition can be quantifiable. For example, LDL or cholesterol levels can be measured and quantified by, for example, standard lipid tests. For such markers, in certain instances, the marker can be decreased by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0319] Also, disclosed herein are methods for preventing, treating or ameliorating a symptom associated with the cardiovascular disease, disorder or condition in a subject in need thereof. In certain instances, disclosed is a method for reducing the rate of onset of a symptom associated with the cardiovascular disease, disorder or condition. In certain instances, disclosed is a method for reducing the severity of a symptom associated with the cardiovascular disease, disorder or condition. In such instances, the methods comprise administering a therapeutically effective amount of a compound targeted to an apo(a) nucleic acid to an individual in need thereof.

[0320] The cardiovascular disease, disorder or condition can be characterized by numerous physical symptoms. Any symptom known to one of skill in the art to be associated with the cardiovascular disease, disorder or condition can be prevented, treated, ameliorated or otherwise modulated with the compounds and methods described herein. In certain instances, the symptom can be any of, but not limited to, angina, chest pain, shortness of breath, palpitations, weakness, dizziness, nausea, sweating, tachycardia, bradycardia, arrhythmia, atrial fibrillation, swelling in the lower extremities, cyanosis, fatigue, fainting, numbness of the face, numbness of the limbs, claudication or cramping of muscles, bloating of the abdomen or fever.

[0321] In certain instances, the metabolic diseases, disorders or conditions include, but are not limited to, hyperglycemia, prediabetes, diabetes (type I and type II), obesity, insulin resistance,

metabolic syndrome and diabetic dyslipidemia.

[0322] In certain instances, compounds targeted to apo(a) as described herein modulate physiological markers or phenotypes of the metabolic disease, disorder or condition. For example, administration of the compounds to animals can decrease glucose and insulin resistance levels in those animals compared to untreated animals. In certain instances, the modulation of the physiological markers or phenotypes can be associated with inhibition of apo(a) by the compounds.

[0323] In certain instances, physiological markers of the metabolic disease, disorder or condition can be quantifiable. For example, glucose levels or insulin resistance can be measured and quantified by standard tests known in the art. For such markers, in certain instances, the marker can be decreased by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In another example, insulin sensitivity can be measured and quantified by standard tests known in the art. For such markers, in certain instances, the marker can be increased by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0324] Also, disclosed herein are methods for preventing, treating or ameliorating a symptom associated with the metabolic disease, disorder or condition in a subject in need thereof. In certain instances, disclosed is a method for reducing the rate of onset of a symptom associated with the metabolic disease, disorder or condition. In certain instances, disclosed is a method for reducing the severity of a symptom associated with the metabolic disease, disorder or condition. In such instances, the methods comprise administering a therapeutically effective amount of a compound targeted to an apo(a) nucleic acid to an individual in need thereof.

[0325] The metabolic disease, disorder or condition can be characterized by numerous physical symptoms. Any symptom known to one of skill in the art to be associated with the metabolic disease, disorder or condition can be prevented, treated, ameliorated or otherwise modulated with the compounds and methods described herein. In certain instances, the symptom can be any of, but not limited to, excessive urine production (polyuria), excessive thirst and increased fluid intake (polydipsia), blurred vision, unexplained weight loss and lethargy.

[0326] In certain instances, the inflammatory diseases, disorders or conditions include, but are not limited to, coronary artery disease (CAD), Alzheimer's Disease and thromboembolic diseases, disorder or conditions. Certain thromboembolic diseases, disorders or conditions include, but are not limited to, stroke, thrombosis, myocardial infarction and peripheral vascular disease.

[0327] In certain instances, the compounds targeted to apo(a) described herein modulate physiological markers or phenotypes of the inflammatory disease, disorder or condition. For example, administration of the compounds to animals can decrease inflammatory cytokine or other inflammatory markers levels in those animals compared to untreated animals. In certain instances, the modulation of the physiological markers or phenotypes can be associated with inhibition of apo(a) by the compounds.

[0328] In certain instances, the physiological markers of the inflammatory disease, disorder or condition can be quantifiable. For example, cytokine levels can be measured and quantified by standard tests known in the art. For such markers, in certain instances, the marker can be decreased by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0329] Also, disclosed herein are methods for preventing, treating or ameliorating a symptom associated with the inflammatory disease, disorder or condition in a subject in need thereof. In certain instances, disclosed is a method for reducing the rate of onset of a symptom associated with the inflammatory disease, disorder or condition. In certain instances, disclosed is a method for reducing the severity of a symptom associated with the inflammatory disease, disorder or condition. In such instances, the methods comprise administering a therapeutically effective amount of a compound targeted to an apo(a) nucleic acid to an individual in need thereof.

[0330] Also disclosed are methods of treating an individual with an apo(a) related disease, disorder or condition comprising administering a therapeutically effective amount of one or more pharmaceutical compositions as described herein. In certain instances, the individual has elevated apo(a) levels. In certain instances, disclosed are methods of treating an individual with an Lp(a) related disease, disorder or condition comprising administering a therapeutically effective amount of one or more pharmaceutical compositions as described herein. In certain instances, the individual has elevated Lp(a) levels. In certain instances, the individual has an inflammatory, cardiovascular and/or metabolic disease, disorder or condition. In certain instances, administration of a therapeutically effective amount of an antisense compound targeted to an apo(a) nucleic acid is accompanied by monitoring of apo(a) or Lp(a) levels. In certain instances, administration of a therapeutically effective amount of an antisense compound targeted to an apo(a) nucleic acid is accompanied by monitoring of markers of inflammatory, cardiovascular and/or metabolic disease, or other disease process associated with the expression of apo(a), to determine an individual's response to the antisense compound. An individual's response to administration of the antisense compound targeting apo(a) can be used by a physician to determine the amount and duration of therapeutic intervention with the compound.

[0331] In certain instances, administration of an antisense compound targeted to an apo(a) nucleic acid results in reduction of apo(a) expression by at least about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In certain instances, apo(a) expression is reduced to ≤ 100 mg/dL, ≤ 90 mg/dL, ≤ 80 mg/dL, ≤ 70 mg/dL, ≤ 60 mg/dL, ≤ 50 mg/dL, ≤ 40 mg/dL, ≤ 30 mg/dL, ≤ 20 mg/dL or ≤ 10 mg/dL.

[0332] In certain instances, administration of an antisense compound targeted to an apo(a) nucleic acid results in reduction of Lp(a) expression by at least about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0333] In certain instances, pharmaceutical compositions comprising an antisense compound targeted to apo(a) are used for the preparation of a medicament for treating a patient suffering or susceptible to an inflammatory, cardiovascular and/or a metabolic disease, disorder or condition.

Dosing

[0334] In certain instances, pharmaceutical compositions are administered according to a dosing regimen (e.g., dose, dose frequency, and duration) wherein the dosing regimen can be selected to achieve a desired effect. The desired effect can be, for example, reduction of apo(a) or the prevention, reduction, amelioration or slowing the progression of a disease or condition associated with apo(a).

[0335] In certain instances, the variables of the dosing regimen are adjusted to result in a desired concentration of pharmaceutical composition in a subject. "Concentration of pharmaceutical composition" as used with regard to dose regimen can refer to the compound, oligonucleotide, or active ingredient of the pharmaceutical composition. For example, in certain instances, dose and dose frequency are adjusted to provide a tissue concentration or plasma concentration of a pharmaceutical composition at an amount sufficient to achieve a desired effect.

[0336] 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. Dosing is also dependent on drug potency and metabolism. In certain instances, dosage is from 0.01µg to 100mg per kg of body weight, or within a range of 0.001mg - 1000mg dosing, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Following successful treatment, it can 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 0.01µg to 100mg per kg of body weight or ranging from 0.001mg to 1000mg dosing, once or more daily, weekly, monthly, yearly to once every 2 to 20 years.

Certain Combination Therapies

[0337] In certain instances, a first agent comprising the compound described herein is co-administered with one or more secondary agents or therapy. In certain instances, such second agents are designed to treat the same disease, disorder, or condition as the first agent described herein. In certain instances, such second agents are designed to treat a different disease, disorder, or condition as the first agent described herein. In certain instances, a first agent is designed to treat an undesired side effect of a second agent. In certain instances, second agents are co-administered with the first agent to treat an undesired effect of the first agent. In certain instances, such second agents are designed to treat an undesired side effect of one or more pharmaceutical compositions as described herein. In certain instances, second agents are co-administered with the first agent to produce a combinational effect. In certain instances, second agents are co-administered with the first agent to produce a synergistic effect. In certain instances, the coadministration of the first and second agents permits use of lower dosages than would be required to achieve a therapeutic or prophylactic effect if the agents were administered as independent therapy.

[0338] In certain instances, one or more compositions described herein and one or more other

pharmaceutical agents are administered at the same time. In certain instances, one or more compositions of the invention and one or more other pharmaceutical agents are administered at different times. In certain instances, one or more compositions described herein and one or more other pharmaceutical agents are prepared together in a single formulation. In certain instances, one or more compositions described herein and one or more other pharmaceutical agents are prepared separately.

[0339] In certain instances, second agents include, but are not limited to, an apo(a) lowering agent, a Lp(a) lowering agent, an agent for treating Alzheimer's Disease, an agent to reduce thromboembolism formation, a cholesterol lowering agent, a non-HDL lipid lowering (e.g., LDL) agent, a HDL raising agent, fish oil, niacin, nicotinic acid, a fibrate, a statin, DCCR (salt of diazoxide), a glucose-lowering agent, an anti-inflammatory agent and/or an anti-diabetic agent. In certain instances, the first agent is administered in combination with the maximally tolerated dose of the second agent. In certain instances, the first agent is administered to a subject that fails to respond to a maximally tolerated dose of the second agent.

[0340] Examples of apo(a) lowering agents include an apo(a) antisense oligonucleotide different from the first agent, niacin, nicotinic acid, or an apoB antisense oligonucleotide (i.e. Mipomersen). An example of an apo(a) lowering therapy is Lp(a) apheresis.

[0341] Examples of glucose-lowering and/or anti-diabetic agents include, but are not limited to, a therapeutic lifestyle change, PPAR agonist, a dipeptidyl peptidase (IV) inhibitor, a GLP-1 analog, insulin or an insulin analog, an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, metformin, sulfonylurea, rosiglitazone, meglitinide, thiazolidinedione, alpha-glucosidase inhibitor and the like. The sulfonylurea can be acetohexamide, chlorpropamide, tolbutamide, tolazamide, glimepiride, a glipizide, a glyburide, or a gliclazide. The meglitinide can be nateglinide or repaglinide. The thiazolidinedione can be pioglitazone or rosiglitazone. The alpha-glucosidase can be acarbose or miglitol.

[0342] Examples of cholesterol or lipid lowering therapy include, but are not limited to, a therapeutic lifestyle change, statins, bile acids sequestrants, niacin, nicotinic acid, CETP inhibitors and peroxisome proliferation activated receptor agonists such as fibrates. The statins can be atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin and the like. The bile acid sequestrants can be colestevlam, cholestyramine, colestipol and the like. The fibrates can be gemfibrozil, fenofibrate, clofibrate and the like. The CETP inhibitor can be a CETP antisense oligonucleotide or Torcetrapib.

Certain Treatment Populations

[0343] Certain subjects with high Lp(a) levels are at a significant risk of various diseases (Lippi et al., Clinica Chimica Acta, 2011, 412:797-801; Solfrizz et al.). In many subjects with high Lp(a) levels, current treatments cannot reduce their Lp(a) levels to safe levels. Apo(a) plays an important role in the formation of Lp(a), hence reducing apo(a) can reduce Lp(a) and prevent, treat or ameliorate a disease associated with Lp(a).

[0344] In certain instances, treatment with the compounds and methods disclosed herein is indicated for a human animal with elevated apo(a) levels and/or Lp(a) levels. In certain instances, the human has elevated apo(a) levels ≥ 30 mg/dL, ≥ 40 mg/dL, ≥ 50 mg/dL, ≥ 60 mg/dL, ≥ 70 mg/dL, ≥ 80 mg/dL, ≥ 90 mg/dL or ≥ 100 mg/dL.

Certain Compounds

[0345] Selected gapmer antisense oligonucleotides from PCT application WO2005/000201 were assessed (Example 1) and the most potent compound, ISIS 144367, was used as a benchmark comparison for the newly designed antisense oligonucleotides described herein.

[0346] About 90 of the newly designed antisense oligonucleotides were found to be more potent than the benchmark, ISIS 144367, as assessed by single dose *in vitro* studies (Examples 2-3, 5). Of the about 90 antisense oligonucleotides, about 83 were selected for *in vitro* multi-dose response studies and 64 antisense oligonucleotides were found to be more potent than the benchmark (Examples 4, 6).

[0347] About 32 antisense oligonucleotides were further selected for *in vivo* studies in human apo(a) transgenic mice (Example 7). Multiple antisense oligonucleotides were identified that were more potent than the benchmark *in vivo*.

[0348] About 24 antisense oligonucleotides were further selected for viscosity testing *in vitro* (Example 13). Antisense oligonucleotides that were viscous were not carried forward in further studies.

[0349] About 14 antisense oligonucleotides were further selected for *in vivo* studies in rodent tolerability and pharmacokinetics (Examples 8-10). The studies indicated that ISIS 494372 was the best tolerated antisense oligonucleotide.

[0350] ISIS 494283, 494284, 494286, 494301, 494302 and 494372 were tested in cynomolgus monkeys (Examples 11-12). The studies indicated that ISIS 494372 was well tolerated and potent in monkeys.

EXAMPLES

Non-limiting disclosure

[0351] While certain compounds, compositions, and methods described herein have been described with specificity in accordance with certain aspects, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same.

Example 1: Dose-dependent antisense inhibition of human apolipoprotein (a) (apo(a)) in

human primary hepatocytes

[0352] Selected gapmer antisense oligonucleotides from a previous publication (WO2005/000201) were tested in a single dose assay in human primary hepatocytes. Cells were obtained from Tissue Transformation Technologies (BD Biosciences, Franklin Lakes, NJ) and treated with 150 nM of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Human apo(a) primer probe set hAPO(a)3' (forward sequence ACAGCAATCAAACGAAGACACTG, designated herein as SEQ ID NO: 5; reverse sequence AGCTTATACACAAAAATACCAAAAATGC, designated herein as SEQ ID NO: 6; probe sequence TCCCAGCTACCAGCTATGCCAAACCTT, designated herein as SEQ ID NO: 7) was used to measure mRNA levels. Additionally, mRNA levels were also measured using human apo(a) primer probe set hAPO(a)12kB (forward sequence CCACAGTGGCCCCCGGT, designated herein as SEQ ID NO: 8; reverse sequence ACAGGGCTTTTCTCAGGTGGT, designated herein as SEQ ID NO: 9; probe sequence CCAAGCACAGAGGCTCCTTCTGAACAAG, designated herein as SEQ ID NO: 10). Apo(a) mRNA levels were normalized to GAPDH mRNA expression. Results are presented in Table 1 as percent inhibition of apo(a), relative to untreated control cells.

Table 1

Antisense inhibition of human apo(a) in human primary hepatocytes		
ISIS No	% inhibition (hAPO(a)3' PPset)	% inhibition (hAPO(a)12kB PPset)
144367	68	77
144368	42	59
144369	43	69
144370	80	75
144371	42	57
144372	87	54
144373	63	49
144374	45	80
144375	33	11
144376	62	82
144377	42	72
144378	0	72
144379	73	46
144380	75	78
144381	63	64
144382	0	58
144383	63	79
144384	38	0

Antisense inhibition of human apo(a) in human primary hepatocytes		
ISIS No	% inhibition (hAPO(a)3' PPset)	% inhibition (hAPO(a)12kB PPset)
144367	68	77
144385	40	94
144386	47	61
144387	38	60
144388	0	57
144389	52	39
144390	12	0
144391	73	57
144392	43	50
144393	83	82
144394	40	76
144395	80	84
144396	53	72
144397	23	64
144398	7	33
144399	43	44
144400	70	75
144401	87	72

[0353] Several antisense oligonucleotides were selected for further testing in a dose response assay.

[0354] The selected antisense oligonucleotides were tested in human primary hepatocytes with 25 nM, 50 nM, 150 nM, or 300 nM concentrations of antisense oligonucleotide, as specified in Table 2 below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Human apo(a) primer probe set hAPO(a)3' was used to measure mRNA levels. Apo(a) mRNA levels were normalized to GAPDH mRNA expression. Results are presented as percent inhibition of apo(a), relative to untreated control cells.

Table 2

Dose-dependent antisense inhibition of human apo(a) in human primary hepatocytes, as measured with hAPO(a)3'				
ISIS No	25 nM	50 nM	150 nM	300 nM
144367	52	78	76	74
144370	64	74	68	66
144385	0	15	43	5

Dose-dependent antisense inhibition of human apo(a) in human primary hepatocytes, as measured with hAPO(a)3'				
ISIS No	25 nM	50 nM	150 nM	300 nM
144393	0	9	39	25
144395	17	9	8	32

[0355] ISIS 144367 demonstrated better efficacy and dose-dependency than the other antisense oligonucleotides. Hence, ISIS 144367 was considered the benchmark antisense oligonucleotide to compare the potency of newly designed antisense oligonucleotides disclosed herein.

Example 2: Antisense inhibition of human apo(a) in transgenic mouse primary hepatocytes

[0356] Antisense oligonucleotides were newly designed targeting an apo(a) nucleic acid and were tested for their effects on apo(a) mRNA *in vitro*. The antisense oligonucleotides were tested for potency in a series of parallel experiments that had similar culture conditions. Primary hepatocytes from human apo(a) transgenic mice (Frazer, K.A. et al., Nat. Genet. 1995. 9: 424-431) were used in this study. Hepatocytes at a density of 35,000 cells per well were transfected using electroporation with 1,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Human primer probe set hAPO(a)12kB was used to measure mRNA levels. Apo(a) mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. The results for each experiment are presented in separate tables shown below. ISIS 144367 from was used as a benchmark for the new antisense oligonucleotides and also included in the studies. Results are presented as percent inhibition of apo(a), relative to untreated control cells. A total of 1,511 gapmers were tested under these culture conditions. Only those antisense oligonucleotides that were selected for further study are presented in the table below with each table representing a separate experiment.

[0357] The newly designed chimeric antisense oligonucleotides were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

[0358] The apo(a) target sequence contains multiple Kringle repeat sequences, therefore, an antisense oligonucleotide may target one or more regions of apo(a) depending whether on the oligonucleotide targets a Kringle sequence or not. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human sequence. An apo(a) antisense oligonucleotide may have more than one "Start site" or "Stop site" depending on whether or not it targets a Kringle repeat.

[0359] Most gapmers listed in the Tables are targeted with 100% complementarity to one or more regions of either the human apo(a) mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_005577.2) or the human apo(a) genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007422.12 truncated from nucleotides 3230000 to 3380000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular sequence with 100% complementarity.

Table 3

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	90	21210	21229	11
494157	238	257	CCTGTGACAGTGGTGGAGTA	95	21199	21218	12
	580	599			26690	26709	
	922	941			32237	32256	
	1606	1625			43330	43349	
	1948	1967			48874	48893	
	2290	2309			54420	54439	
	3316	3335			72037	72056	
494158	239	258	TCCTGTGACAGTGGTGGAGT	95	21200	21219	13
	581	600			26691	26710	
	923	942			32238	32257	
	1607	1626			43331	43350	
	1949	1968			48875	48894	
	2291	2310			54421	54440	
	3317	3336			72038	72057	
494159	241	260	CTTCCTGTGACAGTGGTGGGA	97	21202	21221	14
	583	602			26693	26712	
	925	944			32240	32259	
	1609	1628			43333	43352	
	1951	1970			48877	48896	
	2293	2312			54423	54442	
	3319	3338			72040	72059	
	4663	4682			94404	94423	
	5005	5024			115515	115534	
494160	242	261	CCTTCCTGTGACAGTGGTGG	97	21203	21222	15
	4664	4683			94405	94424	
	5006	5025			115516	115535	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
494161	243	262	TCCTTCCTGTGACAGTGGTG	96	21204	21223	16
	4665	4684			94406	94425	
	5007	5026			115517	115536	
494162	244	263	GTCCTTCCTGTGACAGTGGT	95	21205	21224	17
	3664	3683			77585	77604	
	4666	4685			94407	94426	
	5008	5027			115518	115537	
494163	245	264	GGTCCTTCCTGTGACAGTGG	96	21206	21225	18
	4667	4686			94408	94427	
494164	246	265	AGGTCCTTCCTGTGACAGTG	93	21207	21226	19
	4668	4687			94409	94428	
494165	247	266	CAGGTCCTTCCTGTGACAGT	91	21208	21227	20
	4669	4688			94410	94429	
494166	248	267	GCAGGTCCTTCCTGTGACAG	89	21209	21228	21
494167	250	269	TGGCAGGTCCTTCCTGTGAC	92	21211	21230	22
494168	251	270	TTGGCAGGTCCTTCCTGTGA	89	21212	21231	23
494169	252	271	CTTGGCAGGTCCTTCCTGTG	92	21213	21232	24
494170	253	272	GCTTGGCAGGTCCTTCCTGT	88	21214	21233	25

Table 4

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	91 84	21210	21229	11
494283	584	603	TCTTCCTGTGACAGTGGTGG	93	26694	26713	26
	926	945			32241	32260	
	1610	1629			43334	43353	
	1952	1971			48878	48897	
	2294	2313			54424	54443	
	3320	3339			72041	72060	
	585	604			26695	26714	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
494284	927	946	TTCTTCCTGTGACAGTGGTG	95	32242	32261	27
	1611	1630			43335	43354	
	1953	1972			48879	48898	
	2295	2314			54425	54444	
	3321	3340			72042	72061	
494285	586	605	GTTCTTCCTGTGACAGTGGT	95	26696	26715	28
	928	947			32243	32262	
	1612	1631			43336	43355	
	1954	1973			48880	48899	
	2296	2315			54426	54445	
494286	587	606	GGTTCTTCCTGTGACAGTGG	95	26697	26716	29
	929	948			32244	32263	
	1613	1632			43337	43356	
	1955	1974			48881	48900	
	2297	2316			54427	54446	
494287	588	607	AGGTTCTTCCTGTGACAGTG	95	26698	26717	30
	930	949			32245	32264	
	1614	1633			43338	43357	
	1956	1975			48882	48901	
	2298	2317			54428	54447	
494288	589	608	CAGGTTCTTCCTGTGACAGT	91	26699	26718	31
	931	950			32246	32265	
	1615	1634			43339	43358	
	1957	1976			48883	48902	
	2299	2318			54429	54448	
	2983	3002			66500	66519	
494290	592	611	TGGCAGGTTCTTCCTGTGAC	90	26702	26721	32
	934	953			32249	32268	
	1618	1637			43342	43361	
	1960	1979			48886	48905	
	2302	2321			54432	54451	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
	2986	3005			66503	66522	
494291	593	612	TTGGCAGGTTCTTCCTGTGA	89	26703	26722	33
	935	954			32250	32269	
	1619	1638			43343	43362	
	1961	1980			48887	48906	
	2303	2322			54433	54452	
	2987	3006			66504	66523	
494292	594	613	CTTGGCAGGTTCTTCCTGTG	94	26704	26723	34
	936	955			32251	32270	
	1620	1639			43344	43363	
	1962	1981			48888	48907	
	2304	2323			54434	54453	
	2988	3007			66505	66524	
494294	596	615	AGCTTGGCAGGTTCTTCCTG	90	26706	26725	35
	938	957			32253	32272	
	1622	1641			43346	43365	
	1964	1983			48890	48909	
	2306	2325			54436	54455	
	2990	3009			66507	66526	
494299	626	645	ACTATGCGAGTGTGGTGTCA	91	26736	26755	36
	968	987			32283	32302	
	1310	1329			37830	37849	
	1652	1671			43376	43395	
	1994	2013			48920	48939	
	2336	2355			54466	54485	
	2678	2697			60021	60040	
	3020	3039			66537	66556	
494300	627	646	GACTATGCGAGTGTGGTGTGTC	93	26737	26756	37
	969	988			32284	32303	
	1311	1330			37831	37850	
	1653	1672			43377	43396	
	1995	2014			48921	48940	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
	2337	2356			54467	54486	
	2679	2698			60022	60041	
	3021	3040			66538	66557	
494301	628	647	CGACTATGCGAGTGTGGTGT	93	26738	26757	38
	970	989			32285	32304	
	1312	1331			37832	37851	
	1654	1673			43378	43397	
	1996	2015			48922	48941	
	2338	2357			54468	54487	
	2680	2699			60023	60042	
	3022	3041			66539	66558	
494302	629	648	CCGACTATGCGAGTGTGGTG	94	26739	26758	39
	971	990			32286	32305	
	1313	1332			37833	37852	
	1655	1674			43379	43398	
	1997	2016			48923	48942	
	2339	2358			54469	54488	
	2681	2700			60024	60043	
	3023	3042			66540	66559	
494303	630	649	TCCGACTATGCGAGTGTGGT	93	26740	26759	40
	972	991			32287	32306	
	1314	1333			37834	37853	
	1656	1675			43380	43399	
	1998	2017			48924	48943	
	2340	2359			54470	54489	
	2682	2701			60025	60044	
	3024	3043			66541	66560	
494304	631	650	GTCCGACTATGCGAGTGTGG	94	26741	26760	41
	973	992			32288	32307	
	1315	1334			37835	37854	
	1657	1676			43381	43400	
	1999	2018			48925	48944	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
	2341	2360			54471	54490	
	2683	2702			60026	60045	
	3025	3044			66542	66561	
494305	632	651	GGTCCGACTATGCGAGTGTG	93	26742	26761	42
	974	993			32289	32308	
	1316	1335			37836	37855	
	1658	1677			43382	43401	
	2000	2019			48926	48945	
	2342	2361			54472	54491	
	2684	2703			60027	60046	
	3026	3045			66543	66562	
494306	633	652	GGGTCCGACTATGCGAGTGT	92	26743	26762	43
	975	994			32290	32309	
	1317	1336			37837	37856	
	1659	1678			43383	43402	
	2001	2020			48927	48946	
	2343	2362			54473	54492	
	2685	2704			60028	60047	
	3027	3046			66544	66563	
494307	1190	1209	CTGCTCAGTCGGTGCTTGTT	91	n/a	n/a	44
	2558	2577					
494310	1193	1212	CCTCTGCTCAGTCGGTGCTT	90	n/a	n/a	45
	2561	2580					
494311	1194	1213	GCCTCTGCTCAGTCGGTGCT	88	37714	37733	46
	2562	2581			59905	59924	
494334	1267	1286	CTTCCAGTGACAGTGGTGGA	90	37787	37806	47
	2635	2654			59978	59997	
494336	1269	1288	TTCTTCCAGTGACAGTGGTG	90	37789	37808	48
	2637	2656			59980	59999	
494337	1270	1289	GTTCTTCCAGTGACAGTGGT	95	37790	37809	49
	2638	2657			59981	60000	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
494338	1271	1290	GGTTCTTCCAGTGACAGTGG	91	37791	37810	50
	2639	2658			59982	60001	
494521	6393	6412	GACCTTAAAAGCTTATACAC	82	140049	140068	51
494525	6397	6416	GTCAGACCTTAAAAGCTTAT	84	140053	140072	52
494530	6402	6421	TGTCAGTCAGACCTTAAAAG	82	140058	140077	53
494535	6407	6426	GAATTTGTCAGTCAGACCTT	85	140063	140082	54
494536	6408	6427	AGAATTTGTCAGTCAGACCT	83	140064	140083	55
494544	6417	6436	CCTTAATACAGAATTTGTCA	82	140073	140092	56

Table 5

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	84	21210	21229	11
494371	3900	3919	GCTCCGTTGGTGCTTGTTCA	93	n/a	n/a	57
494372	3901	3920	TGCTCCGTTGGTGCTTGTTT	93	n/a	n/a	58
494373	3902	3921	TTGCTCCGTTGGTGCTTGTT	83	n/a	n/a	59
494374	3903	3922	TTTGCTCCGTTGGTGCTTGT	89	n/a	n/a	60
494375	3904	3923	CTTTGCTCCGTTGGTGCTTG	85	n/a	n/a	61
494386	3977	3996	TCCTGTAACAGTGGTGGAGA	86	81985	82004	62
494387	3978	3997	TTCCTGTAACAGTGGTGGAG	82	81986	82005	63
494388	3979	3998	CTTCCTGTAACAGTGGTGGA	86	81987	82006	64
494389	3980	3999	CCTTCCTGTAACAGTGGTGG	92	81988	82007	65
494390	3981	4000	TCCTTCCTGTAACAGTGGTG	92	81989	82008	66
494391	3982	4001	GTCCTTCCTGTAACAGTGGT	84	81990	82009	67
494392	3983	4002	TGTCCTTCCTGTAACAGTGG	81	81991	82010	68

Table 6

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	86	21210	21229	11

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
498369	3203	3222	TGGAGCCAGAATAACATTCG	91	70667	70686	69
498379	3213	3232	CCTCTAGGCTTGGAGCCAGA	85	70677	70696	70
498408	3323	3342	AGTTCTTCCTGTGACAGTGG	86	72044	72063	71
498433	3367	3386	GTCCGACTATGCTGGTGTGG	87	72088	72107	72
498434	3368	3387	GGTCCGACTATGCTGGTGTG	86	72089	72108	73
498435	3369	3388	GGGTCCGACTATGCTGGTGT	83	72090	72109	74

Table 7

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	90	21210	21229	11
498229	2871	2890	CCTCTAGGCTTGGAAATCGGG	90	65117	65136	75
498238	2883	2902	G TTCAGAAGGAGCCTCTAGG	93	65129	65148	76
498239	2884	2903	TG TTCAGAAGGAGCCTCTAG	94	65130	65149	77
498240	2887	2906	GCTTG TTCAGAAGGAGCCTC	98	n/a	n/a	78
	4573	4592					
498241	2888	2907	TGCTTG TTCAGAAGGAGCCT	94	n/a	n/a	79
	4574	4593					
498242	2889	2908	GTGCTTG TTCAGAAGGAGCC	96	n/a	n/a	80
	4575	4594					
498243	2890	2909	GGTGCTTG TTCAGAAGGAGC	97	n/a	n/a	81
	4576	4595					
498244	2891	2910	TGGTGCTTG TTCAGAAGGAG	92	n/a	n/a	82
	4577	4596					
498251	2898	2917	GCTCAGTTGGTGCTTGTTCA	90	n/a	n/a	83
498252	2899	2918	TGCTCAGTTGGTGCTTG TTC	90	n/a	n/a	84

Table 8

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	91	21210	21229	11
498517	3548	3567	GCTTGGATCTGGGACCACCG	89	76233	76252	85

Table 9

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	94	21210	21229	11
498833	4900	4919	GCCTCCATGCTTGGAAGTGG	94	114205	114224	86
498859	4926	4945	GCTCAGTTGGTGCTGCTTCA	92	n/a	n/a	87
498868	4978	4997	CCTCGATAACTCTGGCCATT	94	115488	115507	88
498875	5003	5022	TCCTGTGACAGTGGTGGAGA	94	115513	115532	89

Table 10

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	92	21210	21229	11
499020	6257	6276	GTAGGTTGATGCTTCACTCT	91	139913	139932	90
499041	6318	6337	CGTTTGATTGCTGTCTATTA	90	139974	139993	91

Table 11

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	91	21210	21229	11
498523	3554	3573	CTCTGTGCTTGGATCTGGGA	94	76239	76258	92
498524	3555	3574	CCTCTGTGCTTGGATCTGGG	96	76240	76259	93
498525	3556	3575	GCCTCTGTGCTTGGATCTGG	94	76241	76260	94
498529	3560	3579	AGAAGCCTCTGTGCTTGGAT	89	76245	76264	95
498535	3566	3585	TTCAGAAGAAGCCTCTGTGC	89	76251	76270	96

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
498550	3582	3601	GCTCCGTTGGTGCTTCTTCA	90	n/a	n/a	97
498553	3585	3604	TTTGCTCCGTTGGTGCTTCT	87	n/a	n/a	98
498555	3587	3606	GCTTTGCTCCGTTGGTGCTT	90	n/a	n/a	99
	3905	3924					
498556	3588	3607	GGCTTTGCTCCGTTGGTGCT	89	77509	77528	100
	3906	3925			81914	81933	
498557	3589	3608	GGGCTTTGCTCCGTTGGTGC	89	77510	77529	101
	3907	3926			81915	81934	
498579	3662	3681	CCTTCCTGTGACAGTGGTAG	87	77583	77602	102
498580	3663	3682	TCCTTCCTGTGACAGTGGTA	92	77584	77603	103
498581	3665	3684	TGTCCTTCCTGTGACAGTGG	94	77586	77605	104
	5009	5028			115519	115538	

Table 12

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	100	21210	21229	11
494230	477	496	CCTCTAGGCTTGGAACCGGG	95	25380	25399	105
	819	838			30927	30946	
	1161	1180			36471	36490	
	1503	1522			42020	42039	
	1845	1864			47564	47583	
	2187	2206			53110	53129	
	2529	2548			58662	58681	
494243	494	513	TGCTTGTTGCGGAAGGAGCCT	93	n/a	n/a	106
	836	855					
	1178	1197					
	1520	1539					
	1862	1881					
	2204	2223					
	2546	2565					

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
494244	495	514	GTGCTTGTTTCGGAAGGAGCC	95	n/a	n/a	107
	837	856					
	1179	1198					
	1521	1540					
	1863	1882					
	2205	2224					
	2547	2566					

Table 13

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	96	21210	21229	11
494466	4208	4227	GCTTGGAACCTGGGACCACCG	95	85138	85157	108
494470	4212	4231	CTGTGCTTGGAACCTGGGACC	94	85142	85161	109
494472	4214	4233	CTCTGTGCTTGGAACCTGGGA	92	85144	85163	110

Example 3: Dose-dependent antisense inhibition of apo(a) in transgenic mouse primary hepatocytes

[0360] Gapmers from the studies described above exhibiting significant *in vitro* inhibition of apo(a) mRNA were selected and tested at various doses in transgenic mouse primary hepatocytes in a series of parallel studies with similar culture conditions. Cells were plated at a density of 35,000 per well and transfected using electroporation with 0.0625 μM, 0.125 μM, 0.25 μM, 0.500 μM, or 1.000 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Apo(a) primer probe set hAPO(a)12kB was used to measured mRNA levels. Apo(a) mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of apo(a), relative to untreated control cells.

[0361] The results of each of the studies are depicted in the Tables presented below with each table representing a separate experiment. The half maximal inhibitory concentration (IC₅₀) of each

oligonucleotide is also presented in the Tables. Apo(a) mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells. The potency of the newly designed oligos was compared with the benchmark oligonucleotide ISIS 144367.

Table 14

ISIS No	0.0625 μ M	0.125 μ M	0.250 μ M	0.500 μ M	1.000 μ M	IC ₅₀ (μ M)
144367	11	27	46	62	80	0.31
494157	11	47	53	76	87	0.23
494158	19	57	75	84	88	0.13
494159	41	65	77	84	92	0.07
494160	44	69	76	85	91	0.06
494161	40	64	74	85	91	0.08
494162	36	63	76	87	88	0.09
494163	20	59	75	85	92	0.13
494164	3	45	62	74	90	0.21
494165	25	39	57	71	75	0.19
494166	17	30	47	59	76	0.31
494167	30	43	55	72	80	0.18
494168	25	36	44	59	75	0.28
494169	19	39	51	61	81	0.25

Table 15

ISIS No	0.0625 μ M	0.125 μ M	0.250 μ M	0.500 μ M	1.000 μ M	IC ₅₀ (μ M)
144367	23	40	58	76	88	0.19
494170	38	34	60	76	84	0.13
494230	55	71	89	95	97	0.03
494243	47	73	87	92	97	0.05
494244	58	73	86	92	96	0.03
494283	54	70	84	93	94	0.05
494284	45	62	83	92	95	0.07
494285	56	70	84	92	95	0.04
494286	51	70	87	93	95	0.05
494287	32	60	67	87	91	0.11
494288	26	41	61	79	88	0.17
494290	30	43	64	81	87	0.15
494291	29	40	56	75	85	0.18

Table 16

ISIS No	0.0625 μ M	0.125 μ M	0.250 μ M	0.500 μ M	1.000 μ M	IC ₅₀ (μ M)
144367	10	38	62	68	84	0.23

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
494292	17	36	74	85	90	0.17
494294	10	34	53	80	91	0.22
494299	32	29	56	77	88	0.16
494300	34	46	76	86	90	0.12
494301	44	56	72	86	89	0.09
494302	42	59	78	88	89	0.08
494303	37	58	70	86	89	0.10
494304	46	71	78	89	90	0.05
494305	39	58	62	85	87	0.10
494306	31	52	65	79	88	0.13
494307	23	23	39	65	78	0.34
494310	14	29	62	70	88	0.25

Table 17

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
144367	0	29	45	73	92	0.27
494311	28	53	65	85	95	0.13
494334	20	44	66	86	96	0.16
494336	15	38	54	84	97	0.20
494337	28	50	77	90	98	0.12
494338	21	40	68	91	98	0.15
494371	19	0	71	89	97	0.15
494372	33	44	77	91	97	0.12
494373	15	36	65	83	95	0.19
494374	3	17	51	83	90	0.24
494375	1	34	56	80	93	0.23
494386	13	26	46	73	91	0.25
494387	17	27	45	67	88	0.28

Table 18

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
144367	35	42	62	70	91	0.15
494537	19	34	54	79	90	0.21
494544	10	38	73	86	94	0.17
498229	36	58	80	92	97	0.10
498238	41	57	75	91	97	0.09
498239	56	71	79	90	94	0.03
498240	91	94	98	99	100	<0.06

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
498241	75	84	91	96	98	<0.06
498242	11	27	42	47	63	0.49
498243	91	93	96	98	99	<0.06
498244	4	0	0	13	43	>1.00
498251	30	30	42	73	89	0.26
498252	37	33	58	80	92	0.20
498369	22	22	10	22	34	>1.00

Table 19

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
144367	15	32	54	75	90	0.22
498379	29	48	71	80	95	0.13
498408	38	57	77	88	96	0.09
498433	29	36	70	88	96	0.15
498434	49	43	50	78	90	0.19
498435	27	39	57	78	93	0.18
498517	64	72	82	93	98	<0.06
498721	77	84	88	96	97	<0.06
498833	73	78	91	95	99	<0.06
498859	7	24	37	62	75	0.36
498868	7	14	39	63	81	0.36
498875	16	21	33	55	81	0.39
499020	7	24	23	55	78	0.36
499041	6	16	33	64	83	0.35

Table 20

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
144367	14	47	64	79	91	0.14
498523	36	50	80	87	95	0.11
498524	43	79	87	93	97	0.01
498525	32	49	75	86	96	0.12
498529	21	49	57	78	90	0.17
498535	20	34	55	76	86	0.21
498550	12	50	69	84	96	0.11
498553	8	43	55	77	91	0.21
498555	13	35	68	86	94	0.19
498556	27	37	71	85	91	0.15
498557	18	42	75	89	95	0.16

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
498579	16	38	67	89	95	0.16
498580	36	57	81	91	96	0.10
498581	34	64	75	93	97	0.05

Table 21

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
144367	0	9	26	49	77	0.47
494388	0	0	21	33	55	0.89
494389	0	15	22	50	79	0.46
494390	5	20	37	68	81	0.33
494391	7	20	32	54	68	0.46
494392	18	24	40	57	76	0.35
494466	33	45	58	69	82	0.16
494470	45	58	68	79	87	0.08
494472	37	50	60	69	83	0.13
494521	0	0	0	15	54	0.17
494525	0	0	2	28	65	0.85
494530	0	6	27	51	80	0.46
494535	0	7	24	53	74	0.49
494536	0	2	15	42	67	0.63

Table 22

ISIS No	0.0625 µM	0.125 µM	0.250 µM	0.500 µM	1.000 µM	IC ₅₀ (µM)
144367	0	4	16	26	77	0.65
498379	12	18	27	32	63	0.81
498408	0	11	46	50	77	0.41
498433	22	30	46	60	83	0.27
498434	39	29	25	47	78	0.40
498435	21	28	26	43	73	0.50
498517	44	48	63	70	84	0.11
498721	54	54	66	75	89	<0.06
498833	44	51	58	67	83	0.11
498859	0	29	14	35	66	0.69
498868	0	12	9	26	60	1.07
498875	0	30	31	53	78	0.40
499020	0	27	19	45	74	0.51
499041	0	12	10	37	65	0.77

[0362] As presented in the Tables above, ISIS 494157 (SEQ ID NO: 12), ISIS 494158 (SEQ ID NO:13), ISIS 494159 (SEQ ID NO:14), ISIS 494160 (SEQ ID NO: 15), ISIS 494161 (SEQ ID NO:16), ISIS 494162 (SEQ ID NO: 17), ISIS 494163 (SEQ ID NO: 18), ISIS 494164 (SEQ ID NO: 19), ISIS 494165 (SEQ ID NO: 20), ISIS 494167 (SEQ ID NO: 22), ISIS 494168 (SEQ ID NO: 23), ISIS 494169 (SEQ ID NO: 24), ISIS 494170 (SEQ ID NO: 25), ISIS 494230 (SEQ ID NO: 105), ISIS 494243 (SEQ ID NO: 106), ISIS 494244 (SEQ ID NO: 107), ISIS 494283 (SEQ ID NO: 26), ISIS 494284 (SEQ ID NO: 27), ISIS 494285 (SEQ ID NO: 28), ISIS 494286 (SEQ ID NO: 29), ISIS 494287 (SEQ ID NO: 30), ISIS 494288 (SEQ ID NO: 31), ISIS 494290 (SEQ ID NO: 32), ISIS 494291 (SEQ ID NO: 33), ISIS 494292 (SEQ ID NO: 34), ISIS 494294 (SEQ ID NO: 35), ISIS 494299 (SEQ ID NO: 36), ISIS 494300 (SEQ ID NO: 37), ISIS 494301 (SEQ ID NO: 38), ISIS 494302 (SEQ ID NO: 39), ISIS 494303 (SEQ ID NO: 40), ISIS 494304 (SEQ ID NO: 41), ISIS 494305 (SEQ ID NO:42), ISIS 494306 (SEQ ID NO: 43), ISIS 494311 (SEQ ID NO: 46), ISIS 494334 (SEQ ID NO: 47), ISIS 494336 (SEQ ID NO: 48), ISIS 494337 (SEQ ID NO: 49), ISIS 494338 (SEQ ID NO: 50), ISIS 494371 (SEQ ID NO: 57), ISIS 494372 (SEQ ID NO: 58), ISIS 494373 (SEQ ID NO: 59), ISIS 494374 (SEQ ID NO: 60), ISIS 494375 (SEQ ID NO: 61), ISIS 494386 (SEQ ID NO: 62), ISIS 494389 (SEQ ID NO: 65), ISIS 494390 (SEQ ID NO: 66), ISIS 494392 (SEQ ID NO: 68), ISIS 494466 (SEQ ID NO: 108), ISIS 494470 (SEQ ID NO: 109), ISIS 494472 (SEQ ID NO: 110), ISIS 494521 (SEQ ID NO: 51), ISIS 494530 (SEQ ID NO: 53), ISIS 498229 (SEQ ID NO: 75), ISIS 498238 (SEQ ID NO: 76), ISIS 498239 (SEQ ID NO: 77), ISIS 498240 (SEQ ID NO: 78), ISIS 498241 (SEQ ID NO: 79), ISIS 498243 (SEQ ID NO: 81), ISIS 498379 (SEQ ID NO: 70), ISIS 498408 (SEQ ID NO: 71), ISIS 498433 (SEQ ID NO: 72), ISIS 498434 (SEQ ID NO: 73), ISIS 498435 (SEQ ID NO: 74), ISIS 498517 (SEQ ID NO: 85), ISIS 498523 (SEQ ID NO: 92), ISIS 498524 (SEQ ID NO: 93), ISIS 498525 (SEQ ID NO: 94), ISIS 498550 (SEQ ID NO: 97), ISIS 498580 (SEQ ID NO: 103), ISIS 498581 (SEQ ID NO: 104), ISIS 498721 (ATGCCTCGATAACTCCGTCC; SEQ ID NO: 134), ISIS 498833 (SEQ ID NO: 86), ISIS 498875 (SEQ ID NO: 89), and ISIS 499020 (SEQ ID NO: 90) were more potent than ISIS 144367 (SEQ ID NO: 11).

Example 4: Dose-dependent antisense inhibition of apo(a) in transgenic mouse primary hepatocytes

[0363] Potent gapmers from the studies described above were further selected and tested at various doses in transgenic mouse primary hepatocytes in a series of studies with similar culture conditions. Cells were plated at a density of 35,000 per well and transfected using electroporation with 0.049 μ M, 0.148 μ M, 0.444 μ M, 1.333 μ M, or 4.000 μ M concentrations of antisense oligonucleotide, as specified in Tables below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Apo(a) primer probe set hAPO(a)12kB was used to measured mRNA levels. Apo(a) mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of apo(a), relative to untreated control cells.

[0364] The results of each of the studies are depicted in the Tables presented below with each table representing a separate experiment. The half maximal inhibitory concentration (IC₅₀) of each

oligonucleotide is also presented in the Tables. Apo(a) mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells. The potency of the newly designed oligos was compared with the benchmark oligonucleotide, ISIS 144367. As presented in the Tables below, ISIS 494157 (SEQ ID NO: 12), ISIS 494158 (SEQ ID NO:13), ISIS 494159 (SEQ ID NO:14), ISIS 494160 (SEQ ID NO: 15), ISIS 494161 (SEQ ID NO:16), ISIS 494162 (SEQ ID NO: 17), ISIS 494163 (SEQ ID NO: 18), ISIS 494164 (SEQ ID NO: 19), ISIS 494230 (SEQ ID NO: 105), ISIS 494243 (SEQ ID NO: 106), ISIS 494244 (SEQ ID NO: 107), ISIS 494283 (SEQ ID NO: 26), ISIS 494284 (SEQ ID NO: 27), ISIS 494285 (SEQ ID NO: 28), ISIS 494286 (SEQ ID NO: 29), ISIS 494287 (SEQ ID NO: 30), ISIS 494290 (SEQ ID NO: 32), ISIS 494292 (SEQ ID NO: 34), ISIS 494300 (SEQ ID NO: 37), ISIS 494301 (SEQ ID NO: 38), ISIS 494302 (SEQ ID NO: 39), ISIS 494303 (SEQ ID NO: 40), ISIS 494304 (SEQ ID NO: 41), ISIS 494305 (SEQ ID NO: 42), ISIS 494306 (SEQ ID NO: 43), ISIS 494310 (SEQ ID NO: 45), ISIS 494311 (SEQ ID NO: 46), ISIS 494337 (SEQ ID NO: 49), ISIS 494371 (SEQ ID NO: 57), ISIS 494372 (SEQ ID NO: 58), ISIS 494375 (SEQ ID NO: 61), ISIS 494388 (SEQ ID NO: 64), ISIS 494389 (SEQ ID NO: 65), ISIS 494390 (SEQ ID NO: 66), ISIS 494392 (SEQ ID NO: 68), ISIS 494466 (SEQ ID NO: 108), ISIS 494470 (SEQ ID NO: 109), ISIS 494472 (SEQ ID NO: 110), ISIS 498238 (SEQ ID NO: 76), ISIS 498239 (SEQ ID NO: 77), ISIS 498433 (SEQ ID NO: 72), ISIS 498434 (SEQ ID NO: 73), ISIS 498435 (SEQ ID NO: 74), ISIS 498523 (SEQ ID NO: 92), ISIS 498524 (SEQ ID NO: 93), ISIS 498525 (SEQ ID NO: 94), ISIS 498580 (SEQ ID NO: 103), and ISIS 498581 (SEQ ID NO: 104) were more potent than ISIS 144367 (SEQ ID NO: 11).

Table 23

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
144367	0	26	67	89	92	0.32
494157	23	50	83	96	96	0.15
494158	26	62	85	96	96	0.11
494159	42	65	87	95	94	0.07
494160	51	70	88	94	94	<0.05
494161	36	67	87	95	96	0.08
494162	40	69	89	94	95	0.07
494163	41	57	87	95	94	0.08
494164	15	43	75	93	96	0.20
494230	39	77	94	99	99	0.05
494243	39	76	92	98	99	0.06
494244	58	79	91	97	99	0.02
494283	18	45	80	93	91	0.18
494284	9	53	80	95	94	0.18

Table 24

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
144367	21	40	79	94	93	0.18
494285	53	68	90	97	97	<0.05
494286	46	69	89	96	97	0.05

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
494287	31	38	79	94	95	0.15
494290	22	53	74	93	94	0.16
494292	37	51	81	93	95	0.11
494294	22	40	72	91	94	0.19
494299	15	43	75	93	95	0.20
494300	25	38	79	95	95	0.17
494301	23	48	82	92	95	0.15
494302	26	59	86	93	94	0.12
494303	10	58	84	92	91	0.16
494304	25	62	83	93	93	0.12

Table 25

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
144367	23	40	70	90	94	0.19
494305	20	48	82	93	95	0.16
494306	26	53	78	91	92	0.14
494310	36	50	79	88	92	0.12
494311	38	50	74	93	95	0.12
494334	20	42	73	90	94	0.19
494336	5	39	74	92	95	0.23
494337	23	51	87	96	96	0.14
494338	12	42	82	93	95	0.19
494371	28	49	82	94	94	0.14
494372	28	54	81	93	88	0.13
494373	21	28	67	86	92	0.25
494375	26	40	77	85	92	0.18

Table 26

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
144367	5	33	65	78	81	0.32
494388	30	32	60	82	86	0.25
494389	30	45	69	84	84	0.17
494390	32	47	67	83	87	0.16
494392	23	38	54	79	82	0.31
494466	48	67	86	91	95	0.04
494470	74	87	92	96	98	<0.05
494472	69	84	92	96	97	<0.05
494544	5	18	49	74	79	0.48

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
498238	25	51	76	92	96	0.15
498239	25	62	83	93	97	0.12
498379	5	21	53	71	81	0.55
498408	1	38	63	79	80	0.32
498433	23	43	70	77	79	0.21

Table 27

ISIS No	0.049 μ M	0.148 μ M	0.444 μ M	1.333 μ M	4.000 μ M	IC ₅₀ (μ M)
144367	0	40	76	90	93	0.26
498434	32	44	64	78	84	0.20
498435	24	42	64	77	79	0.23
498517	28	23	53	81	85	0.45
498523	50	64	81	90	93	<0.05
498524	53	70	84	93	96	<0.05
498525	38	55	80	92	96	0.09
498550	12	18	62	81	83	0.33
498557	13	33	67	79	83	0.33
498579	6	42	69	80	85	0.31
498580	6	46	76	82	83	0.23
498581	5	40	78	81	84	0.25
498721	40	31	58	78	83	0.35
498833	21	20	58	80	90	0.44

Example 5: Antisense inhibition of human apo(a) in transgenic mouse primary hepatocytes

[0365] Additional antisense oligonucleotides were newly designed targeting an apo(a) nucleic acid and were tested for their effects on apo(a) mRNA *in vitro*. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. Primary hepatocytes from human apo(a) transgenic mice were used in this study. Hepatocytes at a density of 35,000 cells per well were transfected using electroporation with 1,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Human primer probe set hAPO(a)12kB was used to measure mRNA levels. Apo(a) mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. The results for each experiment are presented in separate tables shown below. ISIS 144367 was also included in the studies for comparison. Results are presented as percent inhibition of apo(a), relative to untreated control cells. A total of 231 antisense oligonucleotides were tested under these culture conditions. Only those antisense oligonucleotides that were selected for further studies are presented below.

[0366] The newly designed chimeric antisense oligonucleotides were designed as 3-10-4 MOE gapmers. The gapmers are 17 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising three nucleosides and four nucleosides respectively. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

[0367] The apo(a) target sequence contains multiple Kringle repeat sequences, therefore, an antisense oligonucleotide may target one or more regions of apo(a) depending whether on the oligonucleotide targets a Kringle sequence or not. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human sequence. An apo(a) antisense oligonucleotide may have more than one "Start site" or "Stop site" depending on whether or not it targets a Kringle repeat.

[0368] Most gapmers listed in the Tables are targeted with 100% complementarity to multiple regions of either the human apo(a) mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_005577.2) or the human apo(a) genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007422.12 truncated from nucleotides 3230000 to 3380000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular sequence with 100% complementarity.

Table 28

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	64	21210	21229	11
510542	241	257	CCTGTGACAGTGGTGGG	79	21202	21218	111
	583	599	CCTGTGACAGTGGTGGG		26693	26709	
	925	941	CCTGTGACAGTGGTGGG		32240	32256	
	1609	1625	CCTGTGACAGTGGTGGG		43333	43349	
	1951	1967	CCTGTGACAGTGGTGGG		48877	48893	
	2293	2309	CCTGTGACAGTGGTGGG		54423	54439	
	3319	3335	CCTGTGACAGTGGTGGG		72040	72056	
	4663	4679	CCTGTGACAGTGGTGGG		94404	94420	
	5005	5021	CCTGTGACAGTGGTGGG		115515	115531	
	242	258	TCCTGTGACAGTGGTGG		21203	21219	
	584	600	TCCTGTGACAGTGGTGG		26694	26710	
	926	942	TCCTGTGACAGTGGTGG		32241	32257	
	1610	1626	TCCTGTGACAGTGGTGG		43334	43350	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
510543	1952	1968	TCCTGTGACAGTGGTGG	75	48878	48894	112
	2294	2310	TCCTGTGACAGTGGTGG		54424	54440	
	3320	3336	TCCTGTGACAGTGGTGG		72041	72057	
	4664	4680	TCCTGTGACAGTGGTGG		94405	94421	
	5006	5022	TCCTGTGACAGTGGTGG		115516	115532	
510544	243	259	TTCCTGTGACAGTGGTG	73	21204	21220	113
	585	601	TTCCTGTGACAGTGGTG		26695	26711	
	927	943	TTCCTGTGACAGTGGTG		32242	32258	
	1611	1627	TTCCTGTGACAGTGGTG		43335	43351	
	1953	1969	TTCCTGTGACAGTGGTG		48879	48895	
	2295	2311	TTCCTGTGACAGTGGTG		54425	54441	
	3321	3337	TTCCTGTGACAGTGGTG		72042	72058	
	4665	4681	TTCCTGTGACAGTGGTG		94406	94422	
510545	5007	5023	TTCCTGTGACAGTGGTG	65	115517	115533	114
	244	260	CTTCCTGTGACAGTGGT		21205	21221	
	586	602	CTTCCTGTGACAGTGGT		26696	26712	
	928	944	CTTCCTGTGACAGTGGT		32243	32259	
	1612	1628	CTTCCTGTGACAGTGGT		43336	43352	
	1954	1970	CTTCCTGTGACAGTGGT		48880	48896	
	2296	2312	CTTCCTGTGACAGTGGT		54426	54442	
	3322	3338	CTTCCTGTGACAGTGGT		72043	72059	
	3664	3680	CTTCCTGTGACAGTGGT		77585	77601	
	4666	4682	CTTCCTGTGACAGTGGT		94407	94423	
510546	5008	5024	CTTCCTGTGACAGTGGT	74	115518	115534	115
	245	261	CCTTCCTGTGACAGTGG		21206	21222	
	3665	3681	CCTTCCTGTGACAGTGG		77586	77602	
	4667	4683	CCTTCCTGTGACAGTGG		94408	94424	
510547	5009	5025	CCTTCCTGTGACAGTGG	77	115519	115535	116
	246	262	TCCTTCCTGTGACAGTG		21207	21223	
	3666	3682	TCCTTCCTGTGACAGTG		77587	77603	
	4668	4684	TCCTTCCTGTGACAGTG		94409	94425	
	5010	5026	TCCTTCCTGTGACAGTG		115520	115536	

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
510548	247	263	GTCCTTCCTGTGACAGT	73	21208	21224	117
	3667	3683	GTCCTTCCTGTGACAGT		77588	77604	
	4669	4685	GTCCTTCCTGTGACAGT		94410	94426	
	5011	5027	GTCCTTCCTGTGACAGT		115521	115537	
510549	248	264	GGTCCTTCCTGTGACAG	67	21209	21225	118
	4670	4686	GGTCCTTCCTGTGACAG		94411	94427	
510595	632	648	CCGACTATGCGAGTGTG	76	26742	26758	119
	974	990	CCGACTATGCGAGTGTG		32289	32305	
	1316	1332	CCGACTATGCGAGTGTG		37836	37852	
	1658	1674	CCGACTATGCGAGTGTG		43382	43398	
	2000	2016	CCGACTATGCGAGTGTG		48926	48942	
	2342	2358	CCGACTATGCGAGTGTG		54472	54488	
	2684	2700	CCGACTATGCGAGTGTG		60027	60043	
	3026	3042	CCGACTATGCGAGTGTG		66543	66559	
510597	634	650	GTCCGACTATGCGAGTG	70	26744	26760	120
	976	992	GTCCGACTATGCGAGTG		32291	32307	
	1318	1334	GTCCGACTATGCGAGTG		37838	37854	
	1660	1676	GTCCGACTATGCGAGTG		43384	43400	
	2002	2018	GTCCGACTATGCGAGTG		48928	48944	
	2344	2360	GTCCGACTATGCGAGTG		54474	54490	
	2686	2702	GTCCGACTATGCGAGTG		60029	60045	
	3028	3044	GTCCGACTATGCGAGTG		66545	66561	
510598	635	651	GGTCCGACTATGCGAGT	70	26745	26761	121
	977	993	GGTCCGACTATGCGAGT		32292	32308	
	1319	1335	GGTCCGACTATGCGAGT		37839	37855	
	1661	1677	GGTCCGACTATGCGAGT		43385	43401	
	2003	2019	GGTCCGACTATGCGAGT		48929	48945	
	2345	2361	GGTCCGACTATGCGAGT		54475	54491	
	2687	2703	GGTCCGACTATGCGAGT		60030	60046	
	3029	3045	GGTCCGACTATGCGAGT		66546	66562	

Table 29

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	83	21210	21229	11
510783	6400	6416	GTCAGACCTTAAAAGCT	75	140056	140072	122
512944	3561	3577	AAGCCTCTGTGCTTGGA	81	76246	76262	123
512947	3560	3576	AGCCTCTGTGCTTGAT	85	76245	76261	124
512958	3559	3575	GCCTCTGTGCTTGATC	82	76244	76260	125
512959	3585	3601	GCTCCGTTGGTGCTTCT	77	n/a	n/a	126

Table 30

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
144367	249	268	GGCAGGTCCTTCCTGTGACA	76	21210	21229	11
510701	4217	4233	CTCTGTGCTTGGAAGT	78	85147	85163	127
510702	219	235	TGCCTCGATAACTCTGT	79	21180	21196	128
	561	577			26671	26687	
	903	919			32218	32234	
	1245	1261			37765	37781	
	1587	1603			43311	43327	
	1929	1945			48855	48871	
	2271	2287			54401	54417	
	2613	2629			59956	59972	
	4299	4315			86472	86488	
510704	563	579	TGTGCCTCGATAACTCT	80	26673	26689	129
	905	921			32220	32236	
	1247	1263			37767	37783	
	1589	1605			43313	43329	
	1931	1947			48857	48873	
	2273	2289			54403	54419	
	2615	2631			59958	59974	
	4301	4317			86474	86490	
	4985	5001			115495	115511	
510757	4929	4945	GCTCAGTTGGTGCTGCT	74	n/a	n/a	130

Example 6: Dose-dependent antisense inhibition of apo(a) in transgenic mouse primary hepatocytes

[0369] Potent gapmers from the studies described above were further selected and tested at various doses in transgenic mouse primary hepatocytes in a series of studies with similar culture conditions. Cells were plated at a density of 35,000 per well and transfected using electroporation with 0.156 μ M, 0.313 μ M, 0.625 μ M, 1.250 μ M, 2.500 μ M, or 5.000 μ M concentrations of antisense oligonucleotide, as specified in the Tables below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and apo(a) mRNA levels were measured by quantitative real-time PCR. Apo(a) primer probe set hAPO(a)12kB was used to measured mRNA levels. Apo(a) mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of apo(a), relative to untreated control cells.

[0370] The results of each of the studies are depicted in the Tables presented below with each study represented in a separate table. The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented in the Tables.

Table 31

ISIS No	0.156 μ M	0.312 μ M	0.625 μ M	1.250 μ M	2.500 μ M	5.000 μ M	IC_{50} (μ M)
144367	28	55	70	83	90	92	0.31
510542	33	58	75	87	89	90	0.27
510543	33	45	68	78	89	89	0.34
510544	33	50	65	78	88	90	0.33
510545	33	58	76	87	91	90	0.26
510546	39	62	76	87	89	91	0.22
510547	36	66	82	84	86	91	0.22
510548	50	70	82	91	88	90	0.13
510549	32	59	73	85	86	90	0.27
510595	26	57	78	88	90	90	0.29
510597	30	53	76	85	89	89	0.30

Table 32

ISIS No	0.156 μ M	0.312 μ M	0.625 μ M	1.250 μ M	2.500 μ M	5.000 μ M	IC_{50} (μ M)
144367	36	52	78	87	93	94	0.26
510598	48	58	81	88	93	92	0.18
510701	45	59	78	87	95	95	0.18
510702	49	63	75	90	94	95	0.15
510704	55	67	80	93	94	95	<0.16

ISIS No	0.156 μ M	0.312 μ M	0.625 μ M	1.250 μ M	2.500 μ M	5.000 μ M	IC ₅₀ (μ M)
510757	34	48	68	79	90	93	0.33
510783	21	32	51	58	78	84	0.69
512944	57	72	81	91	96	97	<0.16
512947	64	74	86	92	96	97	<0.16
512958	48	69	83	91	96	97	0.13
512959	39	59	76	84	93	93	0.22

Table 33

ISIS No	0.156 μ M	0.312 μ M	0.625 μ M	1.250 μ M	2.500 μ M	5.000 μ M	IC ₅₀ (μ M)
144367	41	58	75	81	88	87	0.22
510542	38	54	69	74	85	83	0.27
510545	21	43	73	77	80	78	0.39
510546	37	58	73	81	83	81	0.24
510547	38	58	72	79	84	86	0.24
510548	40	63	77	79	81	84	0.21
510549	37	47	67	77	81	83	0.31
510595	34	66	73	81	80	75	0.23
510597	39	59	74	83	76	77	0.23

Table 34

ISIS No	0.156 μ M	0.312 μ M	0.625 μ M	1.250 μ M	2.500 μ M	5.000 μ M	IC ₅₀ (μ M)
144367	33	60	72	83	81	81	0.26
510598	47	62	75	75	76	76	0.18
510701	41	67	80	87	92	91	0.19
510702	51	64	77	80	80	83	0.13
510704	54	61	77	84	89	80	0.12
512944	71	74	81	88	92	94	0.02
512947	65	77	86	90	93	95	0.03
512958	63	73	84	92	93	96	0.06
512959	39	62	80	82	86	82	0.22

[0371] Apo(a) mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide-treated cells. The potency of the newly designed oligonucleotides was compared with the benchmark oligonucleotide, ISIS 144367. As presented in the Tables above, ISIS 510542 (SEQ ID NO: 111), ISIS 510545 (SEQ ID NO: 114), ISIS 510546 (SEQ ID NO: 115), ISIS 510547 (SEQ ID NO: 116), ISIS 510548 (SEQ ID NO: 117), ISIS 510549 (SEQ ID NO: 118), ISIS 510595 (SEQ ID NO: 119), ISIS 510597 (SEQ ID NO: 120), ISIS 510598 (SEQ ID NO: 121), ISIS 510701 (SEQ ID NO: 127), ISIS 510702 (SEQ ID NO: 128), ISIS 510704 (SEQ ID NO: 129), ISIS 512944 (SEQ ID NO: 123), ISIS 512947 (SEQ ID NO: 124), ISIS 512958 (SEQ ID NO: 125), and ISIS

512959 (SEQ ID NO: 126) were more potent than ISIS 144367 (SEQ ID NO: 11).

Example 7: Effect of *in vivo* antisense inhibition of human apo(a) in human apo(a) transgenic mice

[0372] Transgenic mice with the human apo(a) gene (Frazer, K.A. et al., Nat. Genet. 1995. 9: 424-431) were utilized in the studies described below. ISIS antisense oligonucleotides that demonstrated statistically significant inhibition of apo(a) mRNA *in vitro* as described above were evaluated further in this model.

Study 1

[0373] Female human apo(a) transgenic mice were maintained on a 12-hour light/dark cycle and fed *ad libitum* normal lab chow. The mice were divided into treatment groups consisting of 4 mice each. The groups received intraperitoneal injections of ISIS 494159, ISIS 494160, ISIS 494161, ISIS 494162, ISIS 494163, ISIS 494230, ISIS 494243, ISIS 494244, ISIS 494283, ISIS 494284, ISIS 494285, ISIS 494286, ISIS 494301, ISIS 494302, ISIS 494304, ISIS 494466, ISIS 494470, ISIS 494472, ISIS 498239, ISIS 498408, ISIS 498517, ISIS 494158, ISIS 494311, ISIS 494337, ISIS 494372, ISIS 498238, ISIS 498523, ISIS 498525, ISIS 510548, ISIS 512944, ISIS 512947, or ISIS 512958 at a dose of 25 mg/kg twice a week for 2 weeks. One group of mice received intraperitoneal injections of PBS twice a week for 2 weeks. The PBS group served as the control group. Two days following the final dose, the mice were euthanized, organs harvested and analyses done.

Inhibition of human apo(a) mRNA

[0374] Total RNA was extracted from the livers of some of the treatment groups, and human apo(a) mRNA was quantitated by RT-PCR. The results are presented in Table 35, expressed as percent inhibition of apo(a) mRNA compared to the PBS control.

Table 35

Percent inhibition of human apo(a) mRNA in transgenic mice	
ISIS No	% inhibition
144367	98
494159	100
494160	95
494161	98
494162	100
494163	100
494230	96

Percent inhibition of human apo(a) mRNA in transgenic mice	
ISIS No	% inhibition
494243	99
494244	99
494283	100
494284	100
494285	100
494286	98
494301	99
494302	96
494304	94
494466	97
494470	93
494472	98
498239	72
498408	100
498517	98

[0375] The data demonstrates significant inhibition of apo(a) mRNA by several ISIS oligonucleotides. ISIS 494159 (SEQ ID NO: 14), ISIS 494162 (SEQ ID NO: 17), ISIS 494163 (SEQ ID NO: 18), ISIS 494243 (SEQ ID NO: 106), ISIS 494244 (SEQ ID NO: 107), ISIS 494283 (SEQ ID NO: 26), ISIS 494284 (SEQ ID NO: 27), ISIS 494285 (SEQ ID NO: 28), ISIS 494301 (SEQ ID NO: 38), and ISIS 498408 (SEQ ID NO: 71) were more potent than the benchmark ISIS 144367 (SEQ ID NO: 11).

Inhibition of human apo(a) protein

[0376] Plasma human apo(a) protein was measured from all treatment groups using an Apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). The results are presented in Table 36, expressed as percent inhibition of apo(a) mRNA compared to the PBS control.

Table 36

Percent inhibition of human apo(a) protein in transgenic mice	
ISIS No	% inhibition
144367	86
494159	86
494160	0
494161	82
494162	84

Percent inhibition of human apo(a) protein in transgenic mice	
ISIS No	% inhibition
494163	82
494230	60
494243	84
494244	87
494283	98
494284	98
494285	89
494286	89
494301	93
494302	88
494304	83
494466	76
494470	73
494472	72
498239	54
498408	84
498517	56
494158	71
494311	83
494337	80
494372	78
498238	58
498523	47
498525	58
510548	74
512944	18
512947	65
512958	72

[0377] The data demonstrates significant inhibition of apo(a) mRNA by several ISIS oligonucleotides. ISIS 494159 (SEQ ID NO: 14), ISIS 494244 (SEQ ID NO: 82), ISIS 494283 (SEQ ID NO: 26), ISIS 494284 (SEQ ID NO: 27), ISIS 494285 (SEQ ID NO: 28), ISIS 494286 (SEQ ID NO: 29), ISIS 494301 (SEQ ID NO: 38), and ISIS 494302 (SEQ ID NO: 39) were as potent as or more potent than the benchmark ISIS 144367 (SEQ ID NO: 11).

Study 2

[0378] ISIS 494159, ISIS 494161, ISIS 494162, ISIS 494163, and ISIS 494243 were further evaluated in this transgenic model. ISIS 144367 was included for comparison.

Treatment

[0379] Female human apo(a) transgenic mice were divided into treatment groups consisting of 4 mice each. The groups received intraperitoneal injections of ISIS 144367, ISIS 494159, ISIS 494161, ISIS 494162, ISIS 494163, or ISIS 494243 at doses of 1.5 mg/kg, 5 mg/kg, 15 mg/kg, or 50 mg/kg twice a week for 2 weeks. One group of mice received intraperitoneal injections of PBS twice a week for 2 weeks. The PBS group served as the control group. Two days following the final dose, the mice were euthanized, organs harvested and analyses done.

Inhibition of human apo(a) mRNA

[0380] Total RNA was extracted from the livers of the treatment groups, and human apo(a) mRNA was quantitated by RT-PCR. The results are presented in Table 37, expressed as percent inhibition of apo(a) mRNA compared to the PBS control.

Table 37

Dose-dependent inhibition of human apo(a) mRNA in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
144367	100	71	31
	30	42	
	10	0	
	3	5	
494159	100	91	5
	30	67	
	10	48	
	3	39	
494161	100	82	6
	30	49	
	10	61	
	3	30	
494162	100	90	5
	30	67	
	10	58	
	3	25	

Dose-dependent inhibition of human apo(a) mRNA in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494163	100	83	5
	30	66	
	10	58	
	3	21	
494243	100	80	32
	30	26	
	10	0	
	3	6	

[0381] The data demonstrates significant inhibition of apo(a) mRNA by several ISIS oligonucleotides. ISIS 494159 (SEQ ID NO: 14), ISIS 494161 (SEQ ID NO: 16), 494162 (SEQ ID NO: 17), and ISIS 94163 (SEQ ID NO: 18) were more efficacious than the benchmark ISIS 144367 (SEQ ID NO: 11). *Reduction of human apo(a) protein levels*

[0382] Blood was collected from the treatment groups, and human apo(a) protein levels were quantitated by an Apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). The results are presented in Table 38, expressed as percent reduction of apo(a) protein levels compared to the PBS control.

Table 38

Dose-dependent inhibition of human apo(a) protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
144367	100	73	71
	30	0	
	10	6	
	3	69	
494159	100	88	2
	30	88	
	10	85	
	3	36	
494161	100	90	2
	30	85	
	10	73	
	3	44	
494162	100	89	3
	30	78	
	10	76	

Dose-dependent inhibition of human apo(a) protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
	3	24	
494163	100	90	3
	30	86	
	10	60	
	3	37	
494243	100	61	174
	30	0	
	10	0	
	3	0	

[0383] The data demonstrates significant reduction of apo(a) plasma protein levels by several ISIS oligonucleotides. ISIS 494159 (SEQ ID NO: 14), ISIS 494161 (SEQ ID NO: 16), ISIS 494162 (SEQ ID NO: 17), and ISIS 494163 (SEQ ID NO: 18) were more efficacious than the benchmark ISIS 144367 (SEQ ID NO: 11).

Study 3

[0384] ISIS 494244, ISIS 494283, and ISIS 494284 were further evaluated in this model. ISIS 144367 was included for comparison.

Treatment

[0385] Female human apo(a) transgenic mice were divided into treatment groups consisting of 4 mice each. The groups received intraperitoneal injections of ISIS 144367, ISIS 494244, ISIS 494283, or ISIS 494284 at doses of 0.75 mg/kg, 2.5 mg/kg, 7.5 mg/kg, or 25 mg/kg twice a week for 2 weeks. One group of mice received intraperitoneal injections of PBS twice a week for 2 weeks. The PBS group served as the control group. Two days following the final dose, the mice were euthanized, organs harvested and analyses done.

Inhibition of human apo(a) mRNA

[0386] Total RNA was extracted from the livers of the treatment groups, and human apo(a) mRNA was quantitated by RT-PCR. The results are presented in Table 39, expressed as percent inhibition of apo(a) mRNA compared to the PBS control.

Table 39

Dose-dependent inhibition of human apo(a) mRNA in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
144367	50	75	22
	15	60	
	5	0	
	1.5	0	
494244	50	73	18
	15	41	
	5	34	
	1.5	0	
494283	50	74	16
	15	52	
	5	24	
	1.5	0	
494284	50	73	16
	15	58	
	5	17	
	1.5	2	

[0387] The data demonstrates significant inhibition of apo(a) mRNA by several ISIS oligonucleotides. ISIS 494244 (SEQ ID NO: 107), ISIS 494283 (SEQ ID NO: 26), and ISIS 494284 (SEQ ID NO: 27) were more efficacious than the benchmark, ISIS 144367 (SEQ ID NO: 11).

Reduction of human apo(a) protein levels

[0388] Blood was collected from the treatment groups, and human apo(a) protein levels were quantitated by an Apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). The results are presented in Table 40, expressed as percent reduction of apo(a) protein levels compared to the PBS control.

Table 40

Dose-dependent inhibition of human apo(a) plasma protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
144367	50	64	16
	15	14	
	5	0	
	1.5	0	
	50	67	

Dose-dependent inhibition of human apo(a) plasma protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494244	15	60	2
	5	58	
	1.5	0	
494283	50	64	4
	15	65	
	5	64	
	1.5	69	
494284	50	66	4
	15	63	
	5	51	
	1.5	54	

[0389] The data demonstrates significant reduction of apo(a) plasma protein levels by several ISIS oligonucleotides. ISIS 494244 (SEQ ID NO: 107), ISIS 494283 (SEQ ID NO: 26), and ISIS 494284 (SEQ ID NO: 27) were more efficacious than the benchmark, ISIS 144367 (SEQ ID NO: 11).

Study 4

[0390] ISIS 494285, ISIS 494286, ISIS 494301, ISIS 494302, and ISIS 494311 were further evaluated in this model.

Treatment

[0391] Male human apo(a) transgenic mice were divided into treatment groups consisting of 4 mice each. Each such group received intraperitoneal injections of ISIS 494285, ISIS 494286, ISIS 494301, ISIS 494302, or ISIS 494311 at doses of 5 mg/kg, 15 mg/kg, or 50 mg/kg once a week for 2 weeks. One group of 3 mice received intraperitoneal injections of PBS once a week for 2 weeks. The PBS group served as the control group. Two days following the final dose, the mice were euthanized, organs harvested and analyses done.

Inhibition of human apo(a) mRNA

[0392] Total RNA was extracted from the livers of the treatment groups, and human apo(a) mRNA was quantitated by RT-PCR. The results are presented in Table 41, expressed as percent inhibition of apo(a) mRNA compared to the PBS control. The data demonstrates significant

inhibition of apo(a) mRNA by ISIS 494285 (SEQ ID NO: 28), ISIS 494286 (SEQ ID NO: 29), ISIS 494301 (SEQ ID NO: 38), ISIS 494302 (SEQ ID NO: 39) and ISIS 494311 (SEQ ID NO: 46).

Table 41

Dose-dependent inhibition of human Apo(a) mRNA in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494285	50	98	1
	15	97	
	5	79	
494286	50	97	1
	15	91	
	5	80	
494301	50	98	3
	15	96	
	5	59	
494302	50	98	2
	15	88	
	5	72	
494311	50	99	1
	15	96	
	5	87	

Reduction of human apo(a) protein levels

[0393] Blood was collected from the treatment groups, and human apo(a) protein levels were quantitated by an Apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). The results are presented in Table 42, expressed as percent reduction of apo(a) protein levels compared to the PBS control. The data demonstrates significant reduction of apo(a) plasma protein levels by ISIS 494285, ISIS 494286, ISIS 494301, ISIS 494302 and ISIS 494311.

Table 42

Dose-dependent inhibition of human apo(a) protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494285	50	88	2
	15	88	
	5	72	
494286	50	90	2
	15	85	
	5	75	

Dose-dependent inhibition of human apo(a) protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494301	50	89	5
	15	86	
	5	38	
494302	50	90	3
	15	82	
	5	61	
494311	50	90	3
	15	82	
	5	69	

Study 5

[0394] ISIS 494372, ISIS 498524, ISIS 498581, ISIS 498721, and ISIS 498833 were further evaluated in this model.

Treatment

[0395] Female human apo(a) transgenic mice were divided into treatment groups consisting of 4 mice each. The groups received intraperitoneal injections of ISIS 494372, ISIS 498524, ISIS 498581, ISIS 498721, or ISIS 498833 at doses of 5 mg/kg, 15 mg/kg, or 50 mg/kg once a week for 2 weeks. One group of 3 mice received intraperitoneal injections of PBS once a week for 2 weeks. The PBS group served as the control group. Two days following the final dose, the mice were euthanized, organs harvested and analyses done.

Inhibition of human apo(a) mRNA

[0396] Total RNA was extracted from the livers of the treatment groups, and human apo(a) mRNA was quantitated by RT-PCR. The results are presented in Table 43, expressed as percent inhibition of apo(a) mRNA compared to the PBS control. The data demonstrates significant inhibition of apo(a) mRNA by ISIS 494372 (SEQ ID NO: 28), ISIS 498524 (SEQ ID NO: 93), ISIS 498581 (SEQ ID NO: 104), and ISIS 498721 (ATGCCTCGATAACTCCGTCC; SEQ ID NO: 134).

Table 43

Dose-dependent inhibition of human Apo(a) mRNA in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
	50	88	

Dose-dependent inhibition of human Apo(a) mRNA in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494372	15	49	18
	5	0	
498524	50	83	8
	15	74	
	5	34	
498581	50	98	7
	15	58	
	5	48	
498721	50	97	14
	15	68	
	5	0	
498833	50	61	155
	15	0	
	5	17	

Reduction of human apo(a) protein levels

[0397] Blood was collected from the treatment groups, and human apo(a) protein levels were quantitated by an Apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). The results are presented in Table 44, expressed as percent reduction of apo(a) protein levels compared to the PBS control. The data demonstrates significant reduction of apo(a) plasma protein levels by ISIS 494372 (SEQ ID NO: 28), ISIS 498581 (SEQ ID NO: 104), and ISIS 498721 (ATGCCTCGATAACTCCGTCC; SEQ ID NO: 134).

Table 44

Dose-dependent inhibition of human apo(a) protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
494372	50	68	32
	15	25	
	5	12	
498524	50	38	118
	15	0	
	5	0	
498581	50	79	9
	15	52	
	5	49	

Dose-dependent inhibition of human apo(a) protein in transgenic mice			
ISIS No	Dose (mg/kg/wk)	% inhibition	ED ₅₀
498721	50	81	10
	15	63	
	5	29	
498833	50	15	738
	15	0	
	5	67	

Example 8: Tolerability of antisense oligonucleotides targeting human apo(a) in rodent models

[0398] Gapmer antisense oligonucleotides targeting human apo(a) were selected from the studies described above for tolerability studies in CD1 mice and in Sprague Dawley rats. Rodents do not express endogenous apo(a), hence these studies tested the tolerability of each human antisense oligonucleotide in an animal rather than any phenotypic changes that may be caused by inhibiting apo(a) in the animal.

Tolerability in CD1 mice: Study 1

[0399] CD1® mice (Charles River, MA) are a multipurpose mice model, frequently utilized for safety and efficacy testing. The mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

[0400] Groups of male CD1 mice were injected subcutaneously twice a week for 6 weeks with 50 mg/kg of ISIS 494159, ISIS 494161, ISIS 494162, ISIS 494244, ISIS 494283, ISIS 494284, ISIS 494285, ISIS 494286, ISIS 494301, ISIS 494302, ISIS 494311, ISIS 494337, ISIS 494372, and ISIS 510548. One group of six-week old male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

[0401] To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of

transaminases, bilirubin, albumin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 45. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 45

Plasma chemistry markers of CD1 mice						
	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Bilirubin (mg/dL)
PBS	38	71	2.9	25.2	0.16	0.15
ISIS 494159	615	525	2.7	23.9	0.11	0.20
ISIS 494161	961	670	2.6	23.7	0.15	0.14
ISIS 494162	1373	1213	2.7	23.7	0.14	0.18
ISIS 494283	237	242	2.5	26.2	0.14	0.13
ISIS 494284	192	307	2.3	27.1	0.14	0.10
ISIS 494285	582	436	2.3	25.4	0.16	0.11
ISIS 494286	191	227	2.5	21.1	0.12	0.15
ISIS 494301	119	130	2.7	26.4	0.15	0.12
ISIS 494302	74	96	2.8	24.8	0.14	0.15
ISIS 494311	817	799	2.7	28.7	0.12	0.17
ISIS 494337	722	397	2.5	20.0	0.13	0.11
ISIS 494372	73	164	2.6	28.5	0.16	0.11
ISIS 510548	2819	2245	3.1	26.0	0.15	0.15

Organ weights

[0402] Liver, spleen and kidney weights were measured at the end of the study, and are presented in Table 46. ISIS oligonucleotides that caused any changes in organ weights outside the

expected range for antisense oligonucleotides were excluded from further studies.

Table 46

Organ weights of CD1 mice (g)			
	Kidney	Liver	Spleen
PBS	0.68	2.0	0.13
ISIS 494159	0.68	3.0	0.21
ISIS 494161	0.62	3.5	0.20
ISIS 494162	0.60	3.3	0.20
ISIS 494283	0.65	2.8	0.24
ISIS 494284	0.69	2.7	0.29
ISIS 494285	0.59	3.2	0.21
ISIS 494286	0.64	2.8	0.25
ISIS 494301	0.72	3.0	0.43
ISIS 494302	0.63	2.3	0.23
ISIS 494311	0.61	3.2	0.19
ISIS 494337	0.56	2.3	0.17
ISIS 494372	0.60	2.5	0.27
ISIS 510548	0.55	3.7	0.20

Tolerability in Sprague Dawley rats

[0403] Sprague-Dawley rats are a multipurpose model used for safety and efficacy evaluations. The rats were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

[0404] Groups of male Sprague Dawley rats were injected subcutaneously twice a week for 8 weeks with 30 mg/kg of ISIS 494159, ISIS 494161, ISIS 494162, ISIS 494244, ISIS 494283, ISIS 494284, ISIS 494285, ISIS 494286, ISIS 494301, ISIS 494302, ISIS 494311, ISIS 494337, ISIS 494372, and ISIS 510548. One group of six male Sprague Dawley rats was injected subcutaneously twice a week for 8 weeks with PBS. Rats were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

[0405] To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of

transaminases, bilirubin, albumin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 47. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 47

Plasma chemistry markers of Sprague Dawley rats						
	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Albumin (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)
PBS	30	82	0.09	3.2	19	0.28
ISIS 494159	182	208	0.14	3.4	22	0.35
ISIS 494161	36	86	0.13	3.4	23	0.35
ISIS 494162	102	158	0.17	2.6	28	0.32
ISIS 494283	53	156	0.13	2.9	24	0.32
ISIS 494284	34	113	0.08	2.0	28	0.32
ISIS 494285	110	294	0.10	1.4	110	0.52
ISIS 494286	40	83	0.07	1.6	48	0.44
ISIS 494301	38	132	0.08	3.0	18	0.33
ISIS 494302	47	105	0.09	3.2	19	0.34
ISIS 494311	93	185	0.51	2.7	23	0.30
ISIS 494372	54	119	0.12	3.0	19	0.33
ISIS 510548	116	181	0.11	1.7	65	0.66

Kidney function

[0406] To evaluate the effect of ISIS oligonucleotides on kidney function, urine levels of total protein and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in Table 48, expressed in mg/dL.

Table 48

Kidney function markers (mg/dL) in S pague-Dawley rats		
	Creatinine	Total protein
PBS	103	118
ISIS 494159	70	279
ISIS 494161	105	315
ISIS 494162	58	925
ISIS 494283	114	1091
ISIS 494284	97	2519
ISIS 494285	38	2170
ISIS 494286	51	625
ISIS 494301	62	280
ISIS 494302	101	428
ISIS 494311	48	1160
ISIS 494372	46	154
ISIS 510548	55	2119

Organ weights

[0407] Liver, spleen and kidney weights were measured at the end of the study, and are presented in Table 49. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 49

Organ weights of Sprague Dawley rats (g)			
	Kidney	liver	Spleen
PBS	3.5	13.1	0.9
ISIS 494159	3.1	11.7	1.6
ISIS 494161	2.8	12.5	2
ISIS 494162	3.1	14.2	1.6
ISIS 494283	3.3	12.9	2.3
ISIS 494284	4.1	15.8	2.7
ISIS 494285	3.8	13.4	0.8
ISIS 494286	4.2	16.7	2.5
ISIS 494301	3.2	12.1	2.3
ISIS 494302	3.4	13.3	2.4
ISIS 494311	3.5	17.4	3.2
ISIS 494372	3.6	12.9	3.2

Organ weights of Sprague Dawley rats (g)			
	Kidney	liver	Spleen
ISIS 510548	6.4	21.2	1.5

[0408] The finding from the rodent tolerability studies showed that in general, taking into consideration all the tolerability markers screened, ISIS 494372 was the best tolerated antisense compound in both the CD1 mouse model and the Sprague Dawley rat model.

Example 9: Pharmacokinetics of antisense oligonucleotide in CD1 mice

[0409] CD1 mice were treated with ISIS oligonucleotides and the oligonucleotide concentrations in the liver and kidney were evaluated.

Treatment

[0410] Groups of four CD1 mice each were injected subcutaneously twice per week for 6 weeks with 50 mg/kg of ISIS 494283, ISIS 494284, ISIS 494286, ISIS 494301, ISIS 494302, or ISIS 494372. The mice were sacrificed 2 days following the final dose. Livers were harvested for analysis.

Measurement of oligonucleotide concentration

[0411] The concentration of the total oligonucleotide concentration was measured. The method used is a modification of previously published methods (Leeds et al., 1996; Geary et al., 1999) which consist of a phenol-chloroform (liquid-liquid) extraction followed by a solid phase extraction. An internal standard (ISIS 355868, a 27-mer 2'-O-methoxyethyl modified phosphorothioate oligonucleotide, GCGTTTGCTCTTCTTCTTGCGTTTTTT, designated herein as SEQ ID NO: 131) was added prior to extraction. Tissue sample concentrations were calculated using calibration curves, with a lower limit of quantitation (LLOQ) of approximately 1.14 µg/g. Half-lives were then calculated using WinNonlin software (PHARSIGHT).

[0412] The results are presented in Table 50, expressed as µg/g liver or kidney tissue. The data indicates that ISIS 494372 was at an acceptable concentration in the liver and kidneys.

Table 50

Oligonucleotide concentration (µg/g tissue) of ISIS oligonucleotides in CD1 mice		
ISIS No	Liver	Kidney
494283	581	549
494284	511	678
494286	368	445

Oligonucleotide concentration (µg/g tissue) of ISIS oligonucleotides in CD1 mice		
ISIS No	Liver	Kidney
494301	812	347
494302	617	263
494372	875	516

Example 10: Pharmacokinetics of antisense oligonucleotide in Sprague Dawley rats

[0413] Male Sprague Dawley rats were treated with ISIS oligonucleotides and the oligonucleotide concentrations in the liver and kidney were evaluated.

Treatment

[0414] Groups of four rats each were injected subcutaneously twice per week for 3 weeks with 10 mg/kg of ISIS 494283, ISIS 494284, ISIS 494286, ISIS 494301, ISIS 494302, or ISIS 494372. The rats were sacrificed 2 days following the final dose. Livers were harvested for analysis.

Measurement of oligonucleotide concentration

[0415] The concentration of the total oligonucleotide concentration was measured. The method used is a modification of previously published methods (Leeds et al., 1996; Geary et al., 1999) which consist of a phenol-chloroform (liquid-liquid) extraction followed by a solid phase extraction. An internal standard (ISIS 355868, a 27-mer 2'-O-methoxyethyl modified phosphorothioate oligonucleotide, GCGTTTGCTCTTCTTCTTGCGTTTTTT, designated herein as SEQ ID NO: 131) was added prior to extraction. Tissue sample concentrations were calculated using calibration curves, with a lower limit of quantitation (LLOQ) of approximately 1.14 µg/g. Half-lives were then calculated using WinNonlin software (PHARSIGHT).

[0416] The results are presented in Table 51, expressed as µg/g liver or kidney tissue. The data indicates that ISIS 494372 was at an acceptable concentration in the liver and kidneys.

Table 51

Oligonucleotide concentration (µg/g tissue) of ISIS oligonucleotides in Sprague Dawley rats		
ISIS No	Liver	Kidney
494283	220	434
494284	178	573
494286	234	448
494301	279	540

Oligonucleotide concentration (µg/g tissue) of ISIS oligonucleotides in Sprague Dawley rats		
ISIS No	Liver	Kidney
494302	205	387
494372	288	663

Example 11: Effect of ISIS antisense oligonucleotides targeting human apo(a) in cynomolgus monkeys

[0417] Cynomolgus monkeys were treated with ISIS antisense oligonucleotides selected from studies described above. At the time this study was undertaken, the cynomolgus monkey genomic sequence was not available in the National Center for Biotechnology Information (NCBI) database; therefore, cross-reactivity with the cynomolgus monkey gene sequence could not be confirmed. Instead, the sequences of the ISIS antisense oligonucleotides used in the cynomolgus monkeys was compared to a rhesus monkey sequence for homology. It is expected that ISIS oligonucleotides with homology to the rhesus monkey sequence are fully cross-reactive with the cynomolgus monkey sequence as well.

[0418] The human antisense oligonucleotides tested are also cross-reactive with the rhesus mRNA sequence (XM_001098061.1; designated herein as SEQ ID NO: 132). The greater the complementarity between the human oligonucleotide and the rhesus monkey sequence, the more likely the human oligonucleotide can cross-react with the rhesus monkey sequence. The start and stop sites of each oligonucleotide to SEQ ID NO: 132 is presented in Table 52. Each antisense oligonucleotide targets more than one region in SEQ ID NO:132 and has multiple start sites. "Start site" indicates the 5'-most nucleotide to which the gapmer is targeted in the rhesus monkey sequence. 'Mismatches' indicates the number of nucleotides mismatched between the human oligonucleotide sequence and the rhesus sequence.

[0419] Antisense oligonucleotide tolerability, as well as their pharmacokinetic profile in the liver and kidney, was evaluated.

Table 52

Antisense oligonucleotides complementary to SEQ ID NO: 132		
ISIS No	Start Site	Mismatches
494283	278	2
	620	2
	923	2
	1265	2
	1607	1
	1949	1
	2267	1

Antisense oligonucleotides complementary to SEQ ID NO: 132		
ISIS No	Start Site	Mismatches
	2609	1
	2951	1
	3293	1
494284	279	1
	621	1
	924	1
	1266	1
	1608	1
	1950	1
	2268	1
	2610	1
	2952	1
	3294	1
494286	281	1
	623	1
	926	1
	1268	1
	1610	2
	1952	2
	2270	2
	2612	2
	2954	2
	3296	2
494301	322	2
	664	2
	967	2
	1309	1
	1651	2
494302	323	2
	968	2
	1310	1
	1652	2
494372	1186	2
	1870	1
	2188	1

Treatment

[0420] Prior to the study, the monkeys were kept in quarantine for at least a 30-day period, during which the animals were observed daily for general health. The monkeys were 2-4 years old and weighed between 2 and 4 kg. Seven groups of four randomly assigned male cynomolgus monkeys each were injected subcutaneously with ISIS oligonucleotide or PBS using a stainless steel dosing needle and syringe of appropriate size into the one of four sites on the back of the monkeys. The injections were given in clockwise rotation; one site per dosing. The monkeys were dosed four times a week for the first week (days 1, 3, 5, and 7) as loading doses, and subsequently once a week for weeks 2-12, with 40 mg/kg of ISIS 494283, ISIS 494284, ISIS 494286, ISIS 494301, ISIS 494302, or ISIS 494372. A control group of 8 cynomolgus monkeys was injected with PBS subcutaneously thrice four times a week for the first week (days 1, 3, 5, and 7), and subsequently once a week for weeks 2-12.

[0421] During the study period, the monkeys were observed at least once daily for signs of illness or distress. Any animal experiencing more than momentary or slight pain or distress due to the treatment, injury or illness was treated by the veterinary staff with approved analgesics or agents to relieve the pain after consultation with the Study Director. Any animal in poor health or in a possible moribund condition was identified for further monitoring and possible euthanasia. For instance, one animal in the treatment group of ISIS 494302 was found moribund on day 56 and was euthanized. Scheduled euthanasia of the animals was conducted on days 86 and 87 by exsanguination under deep anesthesia. The protocols described in the Example were approved by the Institutional Animal Care and Use Committee (IACUC).

Target Reduction

RNA analysis

[0422] On day 86, RNA was extracted from liver tissue for real-time PCR analysis of apo(a) using human primer probe set ABI Hs00916691_ml (Applied Biosystems, Carlsbad CA). Results are presented as percent inhibition of apo(a) mRNA, relative to PBS control. As shown in Table 53, treatment with ISIS antisense oligonucleotides resulted in significant reduction of apo(a) mRNA in comparison to the PBS control.

[0423] The mRNA levels of plasminogen, another kringle-containing protein, were also measured. Treatment with ISIS 494372 did not alter the mRNA levels of plasminogen.

Table 53

Percent Inhibition of apo(a) mRNA in the cynomolgus monkey liver relative to the PBS control	
ISIS No	% inhibition
494283	91
494284	99
494286	96
494301	88
494302	89
494372	93

Protein analysis

[0424] On different days, one mL of blood was collected from the cephalic, saphenous, or femoral vein of all study monkeys. The blood samples were put into tubes containing K2-EDTA for plasma separation. The tubes were centrifuged at 3,000 rpm for 10 min at room temperature to obtain plasma. Apo(a) protein levels were analyzed by an Apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). Results are presented as percentage change of levels from the baseline. As shown in Table 54, treatment with several ISIS antisense oligonucleotides resulted in significant reduction of apo(a) protein levels in comparison to the PBS control. Specifically, treatment with ISIS 494372 reduced cynomolgous plasma protein levels of apo(a).

[0425] The protein levels of apoB were also measured in the study groups. Antisense inhibition of apo(a) had no effect on apoB levels.

Table 54

Apo(a) plasma protein levels (% inhibition over baseline values) in the cynomolgus monkey						
	Day 16	Day 30	Day 44	Day 56	Day 72	Day 86
PBS	0	0	10	0	0	0
ISIS 494283	78	79	81	66	66	70
ISIS 494284	92	95	95	93	93	94
ISIS 494286	92	95	96	94	94	94
ISIS 494301	41	45	52	20	17	29
ISIS 494302	17	0	2	0	0	20
ISIS 494372	67	80	83	79	78	81

Tolerability studies

Body and organ weight measurements

[0426] To evaluate the effect of ISIS oligonucleotides on the overall health of the animals, body and organ weights were measured at day 86. Body weights were measured and are presented in Table 55. Organ weights were measured and the data is presented in Table 56. The results indicate that treatment with ISIS 494372 was well tolerated in terms of the body and organ weights of the monkeys.

Table 55

Body weights (g) in the cynomolgus monkey						
	Day 14	Day 35	Day 49	Day 56	Day 70	Day 84
PBS	2637	2691	2748	2733	2739	2779
ISIS 494283	2591	2670	2698	2656	2704	2701
ISIS 494284	2559	2661	2676	2675	2662	2646
ISIS 494286	2693	2770	2838	2800	2796	2816
ISIS 494301	2587	2604	2627	2591	2596	2604
ISIS 494302	2759	2760	2839	2825	3113	3122
ISIS 494372	2719	2877	2985	2997	3037	3036

Table 56

Organ weights (% body weight) in the cynomolgus monkey					
	Spleen	Kidneys	Liver	Heart	Lungs
PBS	0.14	0.38	2.2	0.33	0.51
ISIS 494283	0.24	0.95	2.8	0.33	0.49
ISIS 494284	0.19	0.60	2.6	0.36	0.55
ISIS 494286	0.22	0.63	2.7	0.38	0.55
ISIS 494301	0.38	0.81	3.0	0.36	0.61
ISIS 494302	0.17	0.95	2.5	0.39	0.57
ISIS 494372	0.18	1.16	2.6	0.36	0.56

Liver function

[0427] To evaluate the effect of ISIS oligonucleotides on hepatic function, monkeys were fasted overnight prior to blood collection. Approximately 1.5 mL of blood was collected from each animal and put into tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 min and then centrifuged at 3,000 rpm for 10 min at room temperature to obtain serum. Levels of various liver function markers were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan). Plasma levels of ALT and AST were measured and the results are presented in Table 57, expressed in IU/L. Bilirubin, a liver

function marker, was similarly measured and is presented in Table 57, expressed in mg/dL. The results indicate that treatment with ISIS 494372 was well tolerated in terms of the liver function in monkeys.

Table 57

Liver function markers in cynomolgus monkey plasma			
	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)
PBS	33	43	0.20
ISIS 494283	75	73	0.12
ISIS 494284	115	79	0.17
ISIS 494286	67	73	0.13
ISIS 494301	129	90	0.15
ISIS 494302	141	75	0.15
ISIS 494372	46	75	0.17

C-reactive protein level analysis

[0428] To evaluate any inflammatory effect of ISIS oligonucleotides in cynomolgus monkeys, blood samples were taken for analysis. The monkeys were fasted overnight prior to blood collection. Approximately 1.5 mL of blood was collected from each animal and put into tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 min and then centrifuged at 3,000 rpm for 10 min at room temperature to obtain serum. C-reactive protein (CRP), which is synthesized in the liver and which serves as a marker of inflammation, was measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan). The results indicate that treatment with ISIS 494372 did not cause any inflammation in monkeys.

Table 58

C-reactive protein levels (mg/L) in cynomolgus monkey plasma	
	CRP
PBS	1.4
ISIS 494283	14.7
ISIS 494284	7.7
ISIS 494286	4.4
ISIS 494301	3.5
ISIS 494302	2.4
ISIS 494372	10.2

Complement C3 analysis

[0429] To evaluate any effect of ISIS oligonucleotides on the complement pathway in cynomolgus monkeys, blood samples were taken for analysis on day 84 (pre-dose) and day 85 (24 hours post-dose). Approximately 0.5 mL of blood was collected from each animal and put into tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 min and then centrifuged at 3,000 rpm for 10 min at room temperature to obtain serum. C3 was measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan). The results indicate that treatment with ISIS 494372 did not cause any effect on the complement pathway in monkeys.

Table 59

Complement C3 levels (mg/dL) in cynomolgus monkey plasma		
	Pre-dose	Post-dose
PBS	140	139
ISIS 494283	127	101
ISIS 494284	105	75
ISIS 494286	84	38
ISIS 494301	118	76
ISIS 494302	98	58
ISIS 494372	123	109

Hematology

[0430] To evaluate any effect of ISIS oligonucleotides in cynomolgus monkeys on hematologic parameters, blood samples of approximately 0.5 mL of blood was collected on day 87 from each of the available study animals in tubes containing K₂-EDTA. Samples were analyzed for red blood cell (RBC) count, white blood cells (WBC) count, as well as for platelet count, using an ADVIA120 hematology analyzer (Bayer, USA). The data is presented in Table 60.

[0431] The data indicate that treatment with ISIS 494372 was well tolerated in terms of the hematologic parameters of the monkeys.

Table 60

Blood cell counts in cynomolgus monkeys			
	WBC (x 10 ³ /μL)	RBC (x 10 ⁶ /μL)	Platelet (x 10 ³ /μL)
PBS	15	6.3	329
ISIS 494283	16	5.3	456
ISIS 494284	13	6.3	330
ISIS 494286	14	5.5	304
ISIS 494301	15	6.0	392
ISIS 494302	12	6.3	305

Blood cell counts in cynomolgus monkeys			
	WBC (x 10 ³ /μL)	RBC (x 10 ⁶ /μL)	Platelet (x 10 ³ /μL)
ISIS 494372	11	6.1	447

Example 12: Characterization of the pharmacological activity of ISIS 494372 in cynomolgus monkeys

[0432] The pharmacological activity of ISIS 494372 was characterized by measuring liver apo(a) mRNA and plasma apo(a) levels in monkeys administered the compound over 13 weeks and allowed to recover for another 13 weeks.

Treatment

[0433] Five groups of 14 randomly assigned male and female cynomolgus monkeys each were injected subcutaneously with ISIS oligonucleotide or PBS using a stainless steel dosing needle and syringe of appropriate size into the one of four sites on the back (scapular region) of the monkeys. The monkeys were dosed four times a week for the first week (days 1, 3, 5, and 7) as loading doses, and subsequently once a week for weeks 2-13 as maintenance doses, as shown in the table below. The loading dose during the first week is expressed as mg/kg/dose, while the maintenance doses on weeks 2-13 are expressed as mg/kg/week.

Table 61

Dosing groups in cynomolgus monkeys					
Group	Test Article	Dose	Number of animals for necropsy		
			Interim	Terminal	Recovery
1	PBS	-	4	6	4
2	ISIS 494372	4	-	6	-
3		8	-	6	-
4		12	4	6	4
5		40	4	6	4

[0434] Liver samples from animals were taken at the interim, terminal and recovery phases of the study for the analyses of apo(a) mRNA. In addition, plasma samples were collected on different days to measure apo(a) protein levels. This non-clinical study was conducted in accordance with the United States Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations, 21 CFR Part 58.

RNA analysis

[0435] Liver samples were collected from monkeys on days 30, 93, and 182, and frozen. Briefly, a piece (0.2 g) of frozen liver was homogenized in 2 mL of RLT solution (Qiagen). The resulting lysate was applied to Qiagen RNeasy mini columns. After purification and quantification, the tissues were subjected to RT-PCR analysis. The Perkin-Elmer ABI Prism 7700 Sequence Detection System, which uses real-time fluorescent RT-PCR detection, was used to quantify apo(a) mRNA. The assay is based on a target-specific probe labeled with fluorescent reporter and quencher dyes at opposite ends. The probe was hydrolyzed through the 5'-exonuclease activity of Taq DNA polymerase, leading to an increasing fluorescence emission of the reporter dye that can be detected during the reaction. A probe set (ABI Rhesus LPA probe set ID Rh02789275_ml, Applied Biosystems, Carlsbad CA) targeting position 1512 of the rhesus monkey apo(a) mRNA transcript GENBANK Accession No XM_001098061.2 (SEQ ID NO: XXX) sequence was used to measure cynomolgus monkey liver apo(a) mRNA expression levels. Apo(a) expression was normalized using RIBOGREEN®. Results are presented as percent inhibition of apo(a) mRNA, relative to PBS control.

[0436] As shown in Table 62, treatment with ISIS 494372 resulted in a dose-dependent reduction of apo(a) mRNA in comparison to the PBS control. At day 30, hepatic apo(a) mRNA expression was reduced in a dose-dependent manner by 74% and 99% in the 12 mg/kg/week and 40 mg/kg/week dosing cohorts, respectively. These reductions are statistically significant by one-way ANOVA (Dunnett's multiple comparison test, $P < 0.05$).

[0437] Apo(a) mRNA levels were also measured during the recovery phase. Liver expression levels at day 88 after the last dose were still reduced 49% and 69% in the 12 mg/kg/week and 40 mg/kg/week dosing cohorts, respectively.

Table 62

Percent inhibition levels of liver apo(a) mRNA in the dosing phase in cynomolgus monkeys treated with ISIS 494372		
Day	Dose (mg/kg/wk)	% inhibition
30	12	73
	40	99
93	4	44
	8	43
	12	53
	40	93

Protein analysis

[0438] Approximately 20 µl of plasma was analyzed using a commercially available apo(a) ELISA kit (Mercodia 10-1106-01, Uppsala, Sweden). The assay protocol was performed as described by the manufacturer. The results are presented in Tables 63 and 64 as percentage change from Day

1 pre-dose apo(a) plasma protein concentrations. Statistically significant differences from Day 1 baseline plasma apo(a) using the Dunnett's multicomparison test are marked with an asterisk.

[0439] Maximal reduction in plasma apo(a) protein was observed in all dosing cohorts by Day 93. In the recovery phase, apo(a) plasma protein levels in the 40 mg/kg/week dosing cohort were at 22% and 93% of the baseline after 4 and 13 weeks (Days 121 and 182) of recovery, respectively. The rate of recovery in the 12 mg/kg/week cohort was similar to that seen in the 40 mg/kg/week cohort.

Table 63

Apo(a) plasma protein levels as a percent of Day 1 levels in the dosing phase in cynomolgus monkeys treated with ISIS 494372		
Day	Dose (mg/kg/wk)	%
30	4	93
	8	70
	12	49
	40	15*
93	4	73
	8	56
	12	32*
	40	11*

Table 64

Apo(a) plasma protein levels as a percent of Day 1 levels in the recovery phase in cynomolgus monkeys treated with ISIS 494372		
Day	Dose (mg/kg/wk)	%
121	12	38*
	40	22*
182	12	84
	40	93

Example 13: Measurement of viscosity of ISIS antisense oligonucleotides targeting human Apo(a)

[0440] The viscosity of select antisense oligonucleotides from the studies described above was measured with the aim of screening out antisense oligonucleotides which have a viscosity more than 40 cP. Oligonucleotides having a viscosity greater than 40 cP would have less than optimal viscosity.

[0441] ISIS oligonucleotides (32-35 mg) were weighed into a glass vial, 120 µL of water was added and the antisense oligonucleotide was dissolved into solution by heating the vial at 50°C. Part (75 µL) of the pre-heated sample was pipetted to a micro-viscometer (Cambridge). The

temperature of the micro-viscometer was set to 25 °C and the viscosity of the sample was measured. Another part (20 µL) of the pre-heated sample was pipetted into 10 mL of water for UV reading at 260 nM at 85 °C (Cary UV instrument). The results are presented in Table 65 and indicate that most of the antisense oligonucleotides solutions are optimal in their viscosity under the criterion stated above. Those that were not optimal are marked as 'viscous'. Specifically, ISIS 494372 was optimal in its viscosity under the criterion stated above.

Table 65

Viscosity and concentration of ISIS antisense oligonucleotides targeting human Apo(a)			
ISIS No	Motif	Viscosity (cP)	Concentration (mg/mL)
494158	5-10-5 MOE	9.0	350
494159	5-10-5 MOE	11.7	325
494161	5-10-5 MOE	12.0	350
494162	5-10-5 MOE	25.8	350
494163	5-10-5 MOE	Viscous	275
494243	5-10-5 MOE	28.4	325
494244	5-10-5 MOE	19.2	300
494283	3-10-4 MOE	13.4	300
494284	5-10-5 MOE	13.4	350
494285	5-10-5 MOE	23.1	350
494286	5-10-5 MOE	16.5	275
494301	5-10-5 MOE	17.1	325
494302	5-10-5 MOE	24.3	350
494304	5-10-5 MOE	49.3	275
494311	5-10-5 MOE	10.8	325
494337	5-10-5 MOE	29.5	325
494372	5-10-5 MOE	12.5	350
494466	5-10-5 MOE	Viscous	275
494470	5-10-5 MOE	16.7	350
494472	5-10-5 MOE	23.6	350
498408	5-10-5 MOE	31.5	300
510548	5-10-5 MOE	9.0	350
512947	3-10-4 MOE	6.8	350
512958	5-10-5 MOE	26.0	350

SEQUENCE LISTING**[0442]**

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<120> METHODS AND COMPOSITIONS FOR MODULATING
APOLIPOPROTEIN (a) EXPRESSION

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gccttgctaa agctaagcag gtactaa 3987

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Patentkrav

1. Forbindelse til reducere af apo(a)-ekspresion, som omfatter et modificeret oligonukleotid, der består af 15 til 30 koblede nukleosider og har en nukleobasesekvens, 5 der omfatter en del på mindst 15 sammenhængende nukleobaser, der er komplementære til en del med tilsvarende længde af nukleobaserne 3900 til 3923 af SEQ ID NO: 1, og hvor nukleobasesekvensen af det modificerede oligonukleotid er mindst 80 % komplementær til SEQ ID NO: 1.
- 10 2. Forbindelse ifølge krav 1, hvor det modificerede oligonukleotid består af 18 til 24, 19 til 22, 15 til 25, 16 eller 20 koblede nukleosider.
3. Forbindelse ifølge krav 1, hvor det modificerede oligonukleotid omfatter en nukleobasesekvens, der omfatter en del på mindst 16, mindst 18, mindst 19 eller mindst 15 20 sammenhængende nukleobaser, der er komplementær til en del af tilsvarende længde af SEQ ID NO: 1.
4. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor nukleobasesekvensen af det modificerede oligonukleotid er mindst 85 %, mindst 90 %, mindst 95 % eller 20 100 % komplementær til SEQ ID NO: 1.
5. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor nukleobasesekvensen af det modificerede oligonukleotid omfatter mindst 15, mindst 16, mindst 17, mindst 18, mindst 19 eller 20 sammenhængende nukleobaser af nukleobasesekvensen ifølge SEQ 25 ID NO: 58.
6. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor det modificerede oligonukleotid består af 18 til 24 koblede nukleosider, og hvor nukleobasesekvensen omfatter mindst 18 sammenhængende nukleobaser af nukleobasesekvensen ifølge SEQ 30 ID NO: 58.
7. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor:
(i) det modificerede oligonukleotid er enkeltstrenget,

- (ii) mindst én internukleosidkobling af en modificeret internukleosidkobling, eventuelt hvor mindst én internukleosidkobling af en phosphorothioat-internukleosidkobling,
- (iii) det modificerede oligonukleotid omfatter mindst ét modificeret sukker, eventuelt hvor: (a) mindst ét modificeret sukker er et bicyklisk sukker, eventuelt et begrænset ethyl
 5 eller et sukker, der omfatter en 4'-(CH₂)_n-O-2'-bro, hvor n er 1 eller 2, eller (b) mindst ét modificeret sukker omfatter et 2'-O-methoxyethyl eller er et 3'-fluor-HNA, og/eller
- (iv) mindst ét nukleosid omfatter en modificeret nukleobase, eventuelt hvor den modificerede nukleobase er en 5-methylcytosin.
- 10 8. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor det modificerede oligonukleotid omfatter:
- et gapsegment, der består af koblede deoxynukleosider;
- et 5'-vingesegment, der består af koblede nukleosider;
- et 3'-vingesegment, der består af koblede nukleosider;
- 15 hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, og hvor hvert nukleosid af hvert vingesegment omfatter et modificeret sukker.
9. Forbindelse ifølge krav 8, hvor det modificerede oligonukleotid består af 20 koblede nukleosider og omfatter:
- 20 et gapsegment, der består af 10 koblede deoxynukleosider;
- et 5'-vingesegment, der består af 5 koblede nukleosider;
- et 3'-vingesegment, der består af 5 koblede nukleosider;
- hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, hvor hvert nukleosid af hvert vingesegment omfatter et 2'-O-methoxyethylsukker, hvor hver
 25 internukleosidkobling er en phosphorothioatkobling, og hvor hver cytosinrest er en 5-methylcytosin.
10. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor det modificerede oligonukleotid består af 20 koblede nukleosider og har en nukleobasesekvens, der
 30 omfatter mindst 15 sammenhængende nukleobaser af nukleobasesekvensen ifølge SEQ ID NO: 58, hvor det modificerede oligonukleotid omfatter:
- et gapsegment, der består af 10 koblede deoxynukleosider;
- et 5'-vingesegment, der består af 5 koblede nukleosider;

et 3'-vingesegment, der består af 5 koblede nukleosider;

hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, hvor hvert nukleosid af hvert vingesegment omfatter et 2'-O-methoxyethylsukker, hvor hver internukleosidkobling er en phosphorothioatkobling, og hvor hver cytosinrest er en 5-methylcytosin.

11. Forbindelse, der omfatter et modificeret oligonukleotid, der består af 20 koblede nukleosider og har nukleobasesekvensen ifølge SEQ ID NO: 58, hvor det modificerede oligonukleotid omfatter:

10 et gapsegment, der består af 10 koblede deoxynukleosider;

et 5'-vingesegment, der består af 5 koblede nukleosider;

et 3'-vingesegment, der består af 5 koblede nukleosider;

hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, hvor hvert nukleosid af hvert vingesegment omfatter et 2'-O-methoxyethylsukker, hvor hver internukleosidkobling er en phosphorothioatkobling, og hvor hver cytosinrest er en 5-methylcytosin.

12. Forbindelse ifølge et hvilket som helst af kravene 8-11, hvor det modificerede oligonukleotid er enkeltstrenget.

20

13. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor forbindelsen er en konjugeret antisenseforbindelse.

14. Sammensætning, der omfatter en forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor eventuelt forbindelsen er et salt, og et farmaceutisk acceptabelt bæremateriale eller fortyndingsmiddel.

25

15. Forbindelse ifølge et hvilket som helst af kravene 1-13 eller sammensætning ifølge krav 14 til anvendelse til terapi.

30

16. Forbindelse eller sammensætning til anvendelse ifølge krav 15, hvor terapien er behandling, forebyggelse eller forsinkelse af progression af en sygdom forbundet med

forhøjet apo(a) og/eller forhøjet Lp(a), eventuelt hvor sygdommen er en inflammatorisk, kardiovaskulær eller metabolisk sygdom, forstyrrelse eller tilstand.