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Description**Sequence Listing**

- 5 [0001] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BiOL0216USL2SEQ.txt created March 12, 2013, which is 124 kb in size.

Field

- 10 [0002] As described in more detail below, methods, compounds, and compositions for treating B-cell lymphoma by inhibiting expression of STAT3 mRNA or protein in an animal are provided herein. Such methods, compounds, and compositions are useful to treat, prevent, or ameliorate B-cell lymphoma.

Background

- 15 [0003] The STAT (signal transducers and activators of transcription) family of proteins are DNA-binding proteins that play a dual role in signal transduction and activation of transcription. Presently, there are six distinct members of the STAT family (STAT1, STAT2, STAT3, STAT4, STAT5, and STAT6) and several isoforms (STAT1 α , STAT1 β , STAT3 α and STAT3 β). The activities of the STATs are modulated by various cytokines and mitogenic stimuli. Binding of a cytokine to its receptor results in the activation of Janus protein tyrosine kinases (JAKs) associated with these receptors. This phosphorylates STAT, resulting in translocation to the nucleus and transcriptional activation of STAT responsive genes. Phosphorylation on a specific tyrosine residue on the STATs results in their activation, resulting in the formation of homodimers and/or heterodimers of STAT which bind to specific gene promoter sequences. Events mediated by cytokines through STAT activation include cell proliferation and differentiation and prevention of apoptosis.
- 20 [0004] The specificity of STAT activation is due to specific cytokines, i.e., each STAT is responsive to a small number of specific cytokines. Other non-cytokine signaling molecules, such as growth factors, have also been found to activate STATs. Binding of these factors to a cell surface receptor associated with protein tyrosine kinase also results in phosphorylation of STAT.
- 25 [0005] STAT3 (also acute phase response factor (APRF)), in particular, has been found to be responsive to interleukin-6 (IL-6) as well as epidermal growth factor (EGF) (Darnell, Jr., J.E., et al., Science, 1994, 264, 1415-1421). In addition, STAT3 has been found to have an important role in signal transduction by interferons (Yang, C.-H., et al., Proc. Natl. Acad. Sci. USA, 1998, 95, 5568-5572). Evidence exists suggesting that STAT3 may be regulated by the MAPK pathway. ERK2 induces serine phosphorylation and also associates with STAT3 (Jain, N., et al., Oncogene, 1998, 17, 3157-3167).
- 30 [0006] STAT3 is expressed in most cell types (Zhong, Z., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 4806-4810). It induces the expression of genes involved in response to tissue injury and inflammation. STAT3 has also been shown to prevent apoptosis through the expression of bcl-2 (Fukada, T., et al., Immunity, 1996, 5, 449-460).
- 35 [0007] Recently, STAT3 was detected in the mitochondria of transformed cells, and was shown to facilitate glycolytic and oxidative phosphorylation activities similar to that of cancer cells (Gough, D.J., et al., Science, 2009, 324, 1713-1716). The inhibition of STAT3 in the mitochondria impaired malignant transformation by activated Ras. The data confirms a Ras-mediated transformation function for STAT3 in the mitochondria in addition to its nuclear roles.
- 40 [0008] Aberrant expression of or constitutive expression of STAT3 is associated with a number of disease processes.

Summary

- 45 [0009] B-cell lymphoma is a B-lymphocyte blood cell cancer that is clinically classified as either Hodgkin's lymphoma or non-Hodgkin's lymphoma. There are several types of non-Hodgkin's lymphoma, of which diffuse large B-cell lymphoma (DLBCL) is the most common type, accounting for approximately 30 percent of all lymphomas. In the United States, DLBCL affects about 7 out of 100,000 people each year.
- 50 [0010] The invention provides an antisense compound complementary to human STAT3 for use in a method of treating B-cell lymphoma in a human subject in need thereof, wherein the method comprises administering to the subject the antisense compound in a first phase and then a second phase, wherein the first phase involves administering a total weekly dose of the compound in the range of 100-750 mg (+/- 12 %) for the first 1-10 weeks, and the second phase involves administering a total weekly dose in the range of 100-250 mg (+/- 12 %) for at least 1 week after the first phase; and wherein the antisense compound is a single-stranded modified oligonucleotide consisting of 16 linked nucleosides
- 55 having a nucleobase sequence consisting of SEQ ID NO: 12, comprising:

a gap segment consisting of ten linked deoxynucleosides;
a 5' wing segment consisting of 3 linked nucleosides; and

a 3' wing segment consisting of 3 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 constrained ethyl nucleoside; wherein each internucleoside linkage
 of the modified oligonucleotide is a phosphorothioate linkage; and wherein each cytosine of the modified oligonu-
 cleotide is a 5-methylcytosine.

Detailed Description

[0011] Several aspects provided herein relate to the discovery that inhibiting the JAK-STAT signaling pathway can be
 useful for treating B-cell lymphoma. As disclosed herein antisense compounds targeting STAT3 are useful for treating
 B-cell lymphoma, such as DLBCL, at unexpectedly low doses for an antisense compound as a cancer therapeutic. In
 several instances, antisense compounds targeting STAT3 provided herein are administered to a subject having B-cell
 lymphoma at a fixed total weekly dose in the range of about 15-750 mg. As disclosed herein, antisense compounds
 targeting STAT3 provided herein are administered to a subject having B-cell lymphoma in the range of about 0.2 to 3.5
 milligrams of the antisense compound per kilogram of the subject's body weight per week (0.2-3.5 mg/kg/wk). Such
 dose ranges are unexpectedly low for treating cancer. By comparison, a Phase 1 study of LY2275796, an antisense
 oligonucleotide targeted to cap-binding protein eukaryotic initiation factor 4E (eIF-4E), concluded that the maximum
 tolerable dose (MTD) and biologically effective dose (BED) of LY2275796 is 1,000 mg under a loading and maintenance
 dose regimen, but even at a 1,000 mg dose, no tumor response was observed. (Hong D.S. et al., Clin Cancer Res. 2011
 17(20):6582-91).

[0012] 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 the term "or" 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.

[0013] The section headings used herein are for organizational purposes only and are not to be construed as limiting
 the subject matter described.

Definitions

[0014] 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.

[0015] Unless otherwise indicated, the following terms have the following meanings:

"2'-deoxynucleoside" means a nucleoside comprising 2'-H furanosyl sugar moiety, as found naturally occurring in de-
 oxyribonucleosides (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may
 comprise an RNA nucleobase (e.g., uracil).

[0016] "2'-O-methoxyethyl" (also 2'-MOE and 2'-O(CH₂)₂OCH₃) 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.

[0017] "2'-MOE nucleoside" (also 2'-O-methoxyethyl nucleoside) means a nucleoside comprising a 2'-MOE modified
 sugar moiety.

[0018] "2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position other than H or OH.
 Unless otherwise indicated, a 2'-substituted nucleoside is not a bicyclic nucleoside.

[0019] "5'-methylcytosine" means a cytosine modified with a methyl group attached to the 5' position. A 5-methylcy-
 tosine is a modified nucleobase.

[0020] "About" as applied to dosing amounts means within $\pm 12\%$ of a value. For example, if it is stated, "the dose is
 an amount in the range of about 15-750 mg," it is implied that the dose is an amount in the range of 13-840 mg. In
 another example, if it is stated that the dose is an amount of "about 50 mg," it is implied that the dose can be from 44
 mg to 56 mg. "About" as applied to activity levels means within $\pm 10\%$ of a value. For example, if it is stated, "the
 compounds affected at least about 70% inhibition of STAT3", it is implied that the STAT3 levels are inhibited within a
 range of 63% and 77%.

[0021] "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 embodiments an antisense oligonu-
 cleotide targeted to STAT3 is an active pharmaceutical agent.

[0022] "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.

[0023] "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.

[0024] "Administering" means providing a pharmaceutical agent to an individual, and includes, but is not limited to administering by a medical professional and self-administering.

[0025] "Amelioration" refers to a lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. The severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

[0026] "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.

[0027] "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.

[0028] "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, and shRNAs.

[0029] "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 as compared to target nucleic acid levels or target protein levels in the absence of the antisense compound.

[0030] "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.

[0031] "Bicyclic sugar" means a furosyl ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

[0032] "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 instances, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

[0033] "Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

[0034] "cEt" or "constrained ethyl" means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-CH(CH₃)-O-2'.

[0035] "Constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge.

[0036] "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.

[0037] "Chimeric antisense compound" means an antisense compound that has at least two chemically distinct regions.

[0038] "Co-administration" means administration of two or more pharmaceutical agents to an individual. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration encompasses parallel or sequential administration.

[0039] "Complementarity" means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

[0040] "Contiguous nucleobases" means nucleobases immediately adjacent to each other.

[0041] "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 may be a liquid, e.g. saline solution.

[0042] "Dose" means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose may be administered in one, two, or more boluses, tablets, or injections. For example, in certain embodiments where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection, therefore, two or more injections may be used to achieve the desired dose. In certain embodiments, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses may be stated as the amount of pharmaceutical agent per hour, day, week, or month. In certain embodiments, single dose means administration of one dose, and only one dose, to a subject.

[0043] "Dosage unit" means a form in which a pharmaceutical agent is provided. In certain embodiments, a dosage unit is a vial containing lyophilized ISIS 481464. In certain embodiments, a dosage unit is a vial containing reconstituted ISIS 481464.

[0044] "Dosing regimen" is a combination of doses designed to achieve one or more desired effects. In certain em-

bodiments, a dose regimen is designed to provide a therapeutic effect quickly.

[0045] "Duration" means the period of time during which an activity or event continues. For example, the duration of a loading phase is the period of time during which loading doses are administered. For example, the duration of the maintenance phase is the period of time during which maintenance doses are administered.

[0046] "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 may 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.

[0047] "First phase" means a dosing phase during which administration is initiated and steady state concentrations of pharmaceutical agents can be, but is not necessarily, achieved in a target tissue. "Second phase" means a dosing phase after the "first phase." In certain embodiments, the dose or total weekly dose of the first phase and the second phase are different.

[0048] "Fully complementary" or "100% complementary" means each nucleobase of a first nucleic acid has a complementary nucleobase in a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a target nucleic acid is a second nucleic acid.

[0049] "Gapmer" means a chimeric antisense compound in which an internal region having a plurality of nucleosides that support RNase H 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 the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings."

[0050] "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.

[0051] "HCC" means hepatocellular carcinoma. It is the most common form of liver cancer and also referred to as malignant hepatoma.

[0052] "Hybridization" means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include an antisense compound and a target nucleic acid.

[0053] "Hyperproliferative disease" means a disease characterized by rapid or excessive growth and reproduction of cells. Examples of hyperproliferative diseases include cancer, e.g., carcinomas, sarcomas, lymphomas, and leukemias as well as associated malignancies and metastases.

[0054] "Identifying an animal at risk for hyperproliferative disease" means identifying an animal having been diagnosed with a hyperproliferative disease or identifying an animal predisposed to develop a hyperproliferative disease. Individuals predisposed to develop a hyperproliferative disease include those having one or more risk factors for hyperproliferative disease including older age; history of other hyperproliferative diseases; history of tobacco use; history of exposure to sunlight and/or ionizing radiation; prior contact with certain chemicals, especially continuous contact; past or current infection with certain viruses and bacteria; prior or current use of certain hormone therapies; genetic predisposition; alcohol use; and certain lifestyle choices including poor diet, lack of physical activity, and/or being overweight. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments.

[0055] "Immediately adjacent" means there are no intervening elements between the immediately adjacent elements.

[0056] "Inhibiting STAT3" means reducing expression of STAT3 mRNA and/or protein levels in the presence of a STAT3 antisense compound, including a STAT3 antisense oligonucleotide, as compared to expression of STAT3 mRNA and/or protein levels in the absence of a STAT3 antisense compound, such as an antisense oligonucleotide.

[0057] "Individual" means a human or non-human animal selected for treatment or therapy.

[0058] "Internucleoside linkage" refers to the chemical bond between nucleosides.

[0059] "ISIS 481464" means a STAT3 antisense oligonucleotide having the nucleobase sequence "CTATTTGGAT-GTCAGC", incorporated herein as SEQ ID NO: 12, where each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methylcytosine, and each of nucleosides 1-3 and 14-16 comprise a cEt moiety. ISIS 481464 is complementary to nucleobases 3016-3031 of the sequence of GENBANK Accession No. NM_139276.2, incorporated herein as SEQ ID NO:1.

[0060] "Linked nucleosides" means adjacent nucleosides which are bonded together.

[0061] "Loading phase" means a dosing phase during which administration is initiated and steady state concentrations of pharmaceutical agents are achieved in a target tissue. For example, a loading phase is a dosing phase during which steady state concentrations of antisense oligonucleotide are achieved in liver.

[0062] "Maintenance phase" means a dosing phase after target tissue steady state concentrations of pharmaceutical agents have been achieved. For example, a maintenance phase is a dosing phase after which steady state concentrations of antisense oligonucleotide are achieved in liver.

[0063] "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.

[0064] "Modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside bond (i.e. a phosphodiester internucleoside bond).

[0065] "Modified nucleobase" refers to any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[0066] "Modified nucleotide" means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, or modified nucleobase. A "modified nucleoside" means a nucleoside having, independently, a modified sugar moiety or modified nucleobase.

[0067] "Modified oligonucleotide" means an oligonucleotide comprising a modified internucleoside linkage, a modified sugar, and/or a modified nucleobase.

[0068] "Modified sugar" refers to a substitution or change from a natural sugar.

[0069] "Motif" means the pattern of chemically distinct regions in an antisense compound.

[0070] "Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[0071] "Natural sugar moiety" means a sugar found in DNA (2'-H) or RNA (2'-OH).

[0072] "Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, small interfering ribonucleic acids (siRNA), and microRNAs (miRNA).

[0073] "Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

[0074] "Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, or nucleobase modification.

[0075] "Nucleoside" means a nucleobase linked to a sugar.

[0076] "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 such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo or tricyclo sugar mimetics, e.g., non furanose sugar units. 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). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system.

[0077] "Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[0078] "Off-target effect" refers to an unwanted or deleterious biological effect associated with modulation of RNA or protein expression of a gene other than the intended target nucleic acid.

[0079] "Oligomeric compound" or "oligomer" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

[0080] "Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

[0081] "Parenteral administration" means administration through injection (e.g., bolus 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.

[0082] "Peptide" means a molecule formed by linking at least two amino acids by amide bonds. Peptide refers to polypeptides and proteins.

[0083] "Pharmaceutical composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition may comprise one or more active pharmaceutical agents and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.

[0084] "Pharmaceutically acceptable derivative" encompasses pharmaceutically acceptable salts, conjugates, prodrugs or isomers of the compounds described herein.

[0085] "Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

[0086] "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.

[0087] "Portion" means a defined number of contiguous (i.e., linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a

portion is a defined number of contiguous nucleobases of an antisense compound.

[0088] "Prevent" 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.

[0089] "Prodrug" means a therapeutic agent that is prepared in an inactive form that is converted to an active form within the body or cells thereof by the action of endogenous enzymes or other chemicals or conditions.

[0090] "Side effects" means physiological responses attributable to a treatment other than the desired effects. In certain embodiments, 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.

[0091] "Signal Transducer and Activator of Transcription 3 nucleic acid" or "STAT3 nucleic acid" means any nucleic acid encoding STAT3. For example, in certain embodiments, a STAT3 nucleic acid includes a DNA sequence encoding STAT3, an RNA sequence transcribed from DNA encoding STAT3 (including genomic DNA comprising introns and exons), and an mRNA sequence encoding STAT3. "STAT3 mRNA" means an mRNA encoding a STAT3 protein.

[0092] "Single-stranded oligonucleotide" means an oligonucleotide which is not hybridized to a complementary strand.

[0093] "Specifically hybridizable" refers to an antisense compound having a sufficient degree of complementarity between an antisense oligonucleotide and 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.

[0094] "Subject" means a human selected for treatment or therapy.

[0095] "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.

[0096] "Target nucleic acid," "target RNA," "target mRNA," and "target RNA transcript" all refer to a nucleic acid capable of being targeted by antisense compounds.

[0097] "Target segment" means the sequence of nucleotides of a target nucleic acid to which an antisense compound 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.

[0098] "Therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

[0099] "Treat" refers to administering a pharmaceutical composition to effect an alteration or improvement of a disease, disorder, or condition.

[0100] "Unmodified nucleotide" means a nucleotide composed of naturally occurring nucleobases, sugar moieties, and internucleoside linkages. In certain embodiments, an unmodified nucleotide is an RNA nucleotide (i.e. β -D-ribonucleosides) or a DNA nucleotide (i.e. β -D-deoxyribonucleoside).

Certain Instances

[0101] Disclosed herein is an inhibitor of the JAK-STAT pathway for use in treating cancer in a subject which comprises administering to the subject an inhibitor of the JAK-STAT pathway. In certain instances the cancer is B-cell lymphoma.

[0102] Disclosed herein is an inhibitor of the JAK-STAT pathway for use in treating B-cell lymphoma in a subject which comprises administering to the subject an inhibitor of the JAK-STAT pathway.

[0103] Disclosed herein is an antisense compound complementary to a nucleic acid encoding human STAT3 for use in of treating cancer, such as B-cell lymphoma, in a subject which comprises administering to the subject a weekly dose of an antisense compound complementary to a nucleic acid encoding human STAT3, wherein the dose comprises about 0.2 to 3.5 milligrams of the antisense compound per kilogram of the subject's body weight per week (0.2-3.5 mg/kg/wk). In certain embodiments, the dose is about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1.0 mg, about 1.1 mg, about 1.2 mg, about 1.3 mg, about 1.4 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2.0 mg, about 2.1 mg, about 2.2 mg, about 2.3 mg, about 2.4 mg, about 2.5 mg, about 2.6 mg, about 2.7 mg, about 2.8 mg, about 2.9 mg, about 3.0 mg, about 3.1 mg, about 3.2 mg, about 3.3 mg, about 3.4 mg, or about 3.5 mg of the antisense compound per kilogram of the subject's body weight. As disclosed herein, the dose comprises about 1.5 to 3.5 milligrams of the antisense compound per kilogram of the subject's body weight (1.5-3.5 mg/kg/wk. As disclosed herein, the dose is 2.0 milligrams of the antisense compound per kilogram of the subject's body weight per week (2.0 mg/kg/wk). As disclosed herein, the dose is effective to treat cancer and acceptably tolerable. The dose can be administered for at least 1-52 weeks, at least 1-10 weeks, at least 1-7 weeks, at least 1-5 weeks, at least 5 weeks, at least 6 weeks, or at least 7 weeks. As disclosed herein, the dose can be administered to the subject 1, 2, 3, 4, 5, 6, or 7 times per week. As disclosed herein, the dose is administered to the subject 1-6 times per week. As disclosed herein, the dose can be administered 6 times during the first week and 1 time each subsequent week. As disclosed herein, the subject's body weight is calculated as the ideal body weight

using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over 5 feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over 5 feet}$.

[0104] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in a method which comprises administering to a subject having B-cell lymphoma, a single dose of the antisense compound, wherein the single dose comprises an amount of the compound in the range of about 100-250 mg. In certain instances, the single dose is an amount of any of about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, or about 250 mg. In certain instances the dose is effective to treat cancer and acceptably tolerable.

[0105] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in a method which comprises administering to a subject having B-cell lymphoma, a total weekly dose of the antisense compound, wherein the total weekly dose comprises an amount of the compound in the range of about 100-750 mg weekly. In certain instances, the total weekly dose is an amount of any of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, or about 750 mg. In certain instances, the dose is effective to treat cancer and acceptably tolerable. The total weekly dose can be administered in 2, 3, 4, 5, 6, or 7 equal doses within a week, such that the total weekly dose does not exceed about 750 mg. In certain instances, the total weekly dose is administered in 3 equal doses within a week. It will be understood that the aforementioned total weekly dose ranges can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the total weekly dose by the subject's body weight, such as the subject's ideal body weight. For example, dividing the aforementioned total weekly dose by an average adult body weight of 70 kg, in certain instances the total weekly dose can be represented as an amount of about 15 mg/70 kg (0.2 mg/kg/wk) to 750 mg/70 kg (10.7 mg/kg/wk). As disclosed herein, the total weekly dose can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), about 250 mg/70 kg (3.6 mg/kg/wk), about 275 mg/70 kg (3.9 mg/kg/wk), about 300 mg/70 kg (4.3 mg/kg/wk), about 325 mg/70 kg (4.6 mg/kg/wk), about 350 mg/70 kg (5.0 mg/kg/wk), about 375 mg/70 kg (5.4 mg/kg/wk), about 400 mg/70 kg (5.7 mg/kg/wk), about 425 mg/70 kg (6.1 mg/kg/wk), about 450 mg/70 kg (6.4 mg/kg/wk), about 475 mg/70 kg (6.8 mg/kg/wk), about 500 mg/70 kg (7.1 mg/kg/wk), about 525 mg/70 kg (7.5 mg/kg/wk), about 550 mg/70 kg (7.9 mg/kg/wk), about 575 mg/70 kg (8.2 mg/kg/wk), about 600 mg/70 kg (8.6 mg/kg/wk), about 625 mg/70 kg (8.9 mg/kg/wk), about 650 mg/70 kg (9.3 mg/kg/wk), about 675 mg/70 kg (9.6 mg/kg/wk), about 700 mg/70 kg (10.0 mg/kg/wk), about 725 mg/70 kg (10.4 mg/kg/wk), or about 750 mg/70 kg (10.7 mg/kg/wk). As disclosed herein, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over 5 feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over 5 feet}$.

[0106] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in a method of treating B-cell lymphoma which comprises administering the antisense compound to a subject having B-cell lymphoma, wherein administering the antisense compound comprises:

a loading phase comprising a total weekly dose in the range of about 100-750 mg for the first 1-10 weeks, and a maintenance phase comprising a total weekly dose in the range of 100-250 mg for at least 1 week after the loading phase.

[0107] In certain embodiments, the loading phase is 1 week, 2 weeks, 3 weeks, 4 weeks, or 5 weeks. In certain embodiments, the loading phase comprises administering the compound in 2, 3, 4, 5, 6, or 7 equal doses within a week. In certain embodiments, the loading phase comprises administering the compound in 3 equal doses within a week. In several embodiments, the total weekly dose of the antisense compound in the loading phase is an amount of any of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, or about 750 mg. It will be understood that the aforementioned total weekly dose ranges in the loading phase can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the total weekly dose by the subject's body weight, such as the subject's ideal body weight. For example, dividing the aforementioned total weekly dose in the loading phase by an average adult body weight of 70 kg, in certain embodiments the total weekly dose can be represented as an amount

of about 15 mg/70 kg (0.2 mg/kg/wk) to 750 mg/70 kg (10.7 mg/kg/wk). As disclosed herein, the total weekly dose in the loading phase can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), about 250 mg/70 kg (3.6 mg/kg/wk), about 275 mg/70 kg (3.9 mg/kg/wk), about 300 mg/70 kg (4.3 mg/kg/wk), about 325 mg/70 kg (4.6 mg/kg/wk), about 350 mg/70 kg (5.0 mg/kg/wk), about 375 mg/70 kg (5.4 mg/kg/wk), about 400 mg/70 kg (5.7 mg/kg/wk), about 425 mg/70 kg (6.1 mg/kg/wk), about 450 mg/70 kg (6.4 mg/kg/wk), about 475 mg/70 kg (6.8 mg/kg/wk), about 500 mg/70 kg (7.1 mg/kg/wk), about 525 mg/70 kg (7.5 mg/kg/wk), about 550 mg/70 kg (7.9 mg/kg/wk), about 575 mg/70 kg (8.2 mg/kg/wk), about 600 mg/70 kg (8.6 mg/kg/wk), about 625 mg/70 kg (8.9 mg/kg/wk), about 650 mg/70 kg (9.3 mg/kg/wk), about 675 mg/70 kg (9.6 mg/kg/wk), about 700 mg/70 kg (10.0 mg/kg/wk), about 725 mg/70 kg (10.4 mg/kg/wk), or about 750 mg/70 kg (10.7 mg/kg/wk). As disclosed herein, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0108] In certain embodiments, the maintenance phase comprises administering the compound in 2, 3, 4, 5, 6, or 7 equal doses within a week. In several embodiments, the total weekly dose of the antisense compound in the maintenance phase is an amount of any of about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, or about 250 mg. In certain embodiments, the total weekly dose in the maintenance phase is administered as a single dose per week. It will be understood that the aforementioned total weekly dose ranges in the maintenance phase can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the total weekly dose by the subject's body weight, such as the subject's ideal body weight. For example, dividing the aforementioned total weekly dose by an average adult body weight of 70 kg, in certain embodiments the total weekly dose in the maintenance phase can be represented as an amount of about 15 mg/70 kg (0.2 mg/kg/wk) to 250 mg/70 kg (3.6 mg/kg/wk). As disclosed herein, the total weekly dose can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), or about 250 mg/70 kg (3.6 mg/kg/wk). As disclosed herein, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0109] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in treating B-cell lymphoma which comprises administering to a subject having B-cell lymphoma, a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3, wherein administering the antisense compound comprises:

a loading phase about 6, 7, 8, 9, or 10 weeks, and

a maintenance phase comprising a dose of about 2 mg/kg/wk for at least 1 week after the loading phase. In certain embodiments, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0110] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in treating B-cell lymphoma which comprises administering to a subject having B-cell lymphoma, a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3, wherein administering the antisense compound comprises:

a loading phase comprising a dose in the range of about 3 to 4 mg/kg/wk for about 6, 7, 8, 9, or 10 weeks, and

a maintenance phase comprising a dose of about 2 mg/kg/wk for at least 1 week after the loading phase. In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0111] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in treating B-cell lymphoma which comprises administering to a subject having B-cell lymphoma, a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3, wherein administering the antisense compound comprises:

a loading phase comprising a dose of about 3 mg/kg/wk for about 8 weeks, and
 a maintenance phase comprising a dose of about 2 mg/kg/wk for at least 1 week after the loading phase. In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0112] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in a method which comprises administering the antisense compound to a subject having B-cell lymphoma, wherein administering the antisense compound comprises:

a first phase comprising a total weekly dose in the range of about 100-750 mg for the first 1-10 weeks, and

a second phase comprising a total weekly dose in the range of 100-250 mg for at least 1 week after the loading phase.

[0113] In certain embodiments, the first phase is 1 week, 2 weeks, 3 weeks, 4 weeks, or 5 weeks. In certain embodiments, the first phase comprises administering the compound in 2, 3, 4, 5, 6, or 7 equal doses within a week. In certain embodiments, the first phase comprises administering the compound in 3 equal doses within a week. In several embodiments, the total weekly dose of the antisense compound in the first phase is an amount of any of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, or about 750 mg. It will be understood that the aforementioned total weekly dose ranges in the first phase can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the total weekly dose by the subject's body weight, such as the subject's ideal body weight. For example, dividing the aforementioned total weekly dose in the first phase by an average adult body weight of 70 kg, as disclosed herein the total weekly dose can be represented as an amount of about 15 mg/70 kg (0.2 mg/kg/wk) to 750 mg/70 kg (10.7 mg/kg/wk). As disclosed herein, the total weekly dose in the first phase can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), about 250 mg/70 kg (3.6 mg/kg/wk), about 275 mg/70 kg (3.9 mg/kg/wk), about 300 mg/70 kg (4.3 mg/kg/wk), about 325 mg/70 kg (4.6 mg/kg/wk), about 350 mg/70 kg (5.0 mg/kg/wk), about 375 mg/70 kg (5.4 mg/kg/wk), about 400 mg/70 kg (5.7 mg/kg/wk), about 425 mg/70 kg (6.1 mg/kg/wk), about 450 mg/70 kg (6.4 mg/kg/wk), about 475 mg/70 kg (6.8 mg/kg/wk), about 500 mg/70 kg (7.1 mg/kg/wk), about 525 mg/70 kg (7.5 mg/kg/wk), about 550 mg/70 kg (7.9 mg/kg/wk), about 575 mg/70 kg (8.2 mg/kg/wk), about 600 mg/70 kg (8.6 mg/kg/wk), about 625 mg/70 kg (8.9 mg/kg/wk), about 650 mg/70 kg (9.3 mg/kg/wk), about 675 mg/70 kg (9.6 mg/kg/wk), about 700 mg/70 kg (10.0 mg/kg/wk), about 725 mg/70 kg (10.4 mg/kg/wk), or about 750 mg/70 kg (10.7 mg/kg/wk). In certain embodiments, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0114] In certain embodiments, the second phase comprises administering the compound in 2, 3, 4, 5, 6, or 7 equal doses within a week. In several embodiments, the total weekly dose of the antisense compound in the second phase is an amount of any of about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, or about 250 mg. In certain embodiments, the total weekly dose in the second phase is administered as a single dose per week. It will be understood that the aforementioned total weekly dose ranges in the second phase can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the total weekly dose by the subject's body weight, such as the subject's ideal body weight. For example, dividing the aforementioned total weekly dose by an average adult body weight of 70 kg, as disclosed herein the total weekly dose in the second phase can be represented as an amount of about 15 mg/70 kg (0.2 mg/kg/wk) to 250 mg/70 kg (3.6 mg/kg/wk). As disclosed herein, the total weekly dose can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), or about 250 mg/70 kg (3.6 mg/kg/wk). In certain embodiments, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0115] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in treating B-cell lymphoma which comprises administering to a subject having B-cell lymphoma, a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3, wherein administering the antisense compound comprises:

a first phase for about 6, 7, 8, 9, or 10 weeks, and
a second phase comprising a dose of about 2 mg/kg/wk for at least 1 week after the loading phase. In certain embodiments, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0116] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in treating B-cell lymphoma which comprises administering to a subject having B-cell lymphoma, a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3, wherein administering the antisense compound comprises:

a first phase comprising a dose in the range of about 3 to 4 mg/kg/wk for about 6, 7, 8, 9, or 10 weeks, and
a second phase comprising a dose of about 2 mg/kg/wk for at least 1 week after the loading phase. In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0117] Disclosed herein is a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3 for use in treating B-cell lymphoma which comprises administering to a subject having B-cell lymphoma, a pharmaceutical composition comprising an antisense compound complementary to a nucleic acid encoding human STAT3, wherein administering the antisense compound comprises:

a first phase comprising a dose of about 3 mg/kg/wk for about 8 weeks, and
a second phase comprising a dose of about 2 mg/kg/wk for at least 1 week after the loading phase. In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0118] In any of the above embodiments, the B-cell lymphoma is a non-Hodgkin's B-cell lymphoma. Examples of non-Hodgkin's B-cell lymphoma of certain aspects include, but are not limited to, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma (MCL), Burkitt lymphoma, mediastinal large B cell lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), intravascular large B-cell lymphoma, primary effusion lymphoma, and lymphomatoid granulomatosis. In certain embodiments, the non-Hodgkin's B-cell lymphoma is diffuse large B cell lymphoma (DLBCL).

[0119] In any of the above embodiments, the B-cell lymphoma is Hodgkin's B-cell lymphoma.

[0120] As disclosed herein, administering the dose of the antisense compound reduces tumor size or tumor volume in the subject. As disclosed herein, administering the dose of the antisense compound prolongs survival of the subject. As disclosed herein, administering the dose of the antisense compound treats cancer, such as B-cell lymphoma, in the subject. As disclosed herein, the method is effective to treat cancer and acceptably tolerable in a subject.

[0121] In certain of the foregoing instances, the subject is identified as having cancer, such as B-cell lymphoma, prior to administering the antisense compound to the subject. In certain instances, the subject identified as having cancer, such as B-cell lymphoma, received or is currently receiving anti-cancer treatment, such as a first-line treatment regimen. For example, in certain instances, the first-line treatment regimen is a combination of cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisone or prednisolone (CHOP). In certain instances, the first-line treatment regimen is a combination of rituximab and CHOP (R-CHOP). In certain instances, the subject is refractory to a first-line treatment regimen such as CHOP and/or R-CHOP.

[0122] As disclosed herein, the antisense compound comprises a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of nucleobases 3008 to 3033 of SEQ ID NO: 1, wherein the nucleobase sequence is complementary to SEQ ID NO: 1.

[0123] As disclosed herein, the antisense compound comprises a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary

to an equal length portion of nucleobases 3016 to 3031 of SEQ ID NO: 1, wherein the nucleobase sequence is complementary to SEQ ID NO: 1.

[0124] As disclosed herein, the antisense compound comprises a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of nucleobases 6476 to 6491 of SEQ ID NO: 2, wherein the nucleobase sequence is complementary to SEQ ID NO: 2.

[0125] As disclosed herein, the antisense compound comprises a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of nucleobases 250-286; 250-285; 264-285; 264-282; 728-745; 729-745; 729-744; 787-803; 867-883; 955-978; 1146-1170; 1896-1920; 1899-1920; 1899-1919; 1899-1918; 1899-1916; 1901-1916; 1946-1963; 1947-1963; 2155-2205; 2155-2187; 2156-2179; 2204-2221; 2681-2696; 2699-2716; 3001-3033; 3008-3033; 3010-3033; 3010-3032; 3015-3033; 3015-3032; 3015-3031; 3016-3033; 3016-3032; 3016-3033; 3452-3499; 3460-3476; 3583-3608; 3591-3616; 3595-3615; 3595-3614; 3595-3612; 3675-3706; 3713-3790; 3715-3735; 3833-3878; 3889-3932; 3977-4012; 4067-4100; 4225-4256; 4234-4252; 4235-4252; 4235-4251; 4236-4252; 4306-4341; 4431-4456; 4439-4454; 4471-4510; 4488-4505; 4530-4558; 4539-4572; 4541-4558; 4636-4801; 4782-4796; 4800-4823; 4811-4847; 4813-4859; 4813-4815; 4813-4831; 4827-4859; 4827-4844; or 4842-4859 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is complementary to SEQ ID NO: 1.

[0126] As disclosed herein, the antisense compound comprises a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of nucleobases 2668-2688; 2703-2720; 5000-5021; 5001-5017; 5697-5722; 5699-5716; 6475 - 6490; 6475 - 6491; 6476 - 6491; 7682-7705; 8078-8097; 8079-8095; 9862-9811; 9870-9897; 9875-9893; 9875-9891; 9877-9893; 11699-11719; 12342-12366; 12345-12364; 12346-12364; 12347-12364; 12353-12380; 12357-12376; 12358-12376; 12358-12373; 12360-12376; 14128-14148; 16863-16883; 46091-46111; 50692-50709; 50693-50709; 50693-50708; 61325-61349; 66133-66157; 66136-66157; 66136 - 66155; 66136-66153; 66138-66153; 66184-66200; 67067-67083; 4171-74220; 74199-74220; 74202-74220; 74171-74219; 74199-74219; 74202-74219; 74171-74218; 74199-74218; 74202-74218; 74723-74768; 74764-74803; 74782-74802; 74782-74801; 74782-74800; 74782-74799; 74783-74802; 74783-74801; 74783-74800; 74783-74799; 74862-74893; 74900-74977; 74902-74922; 74902-74920; 75070-75119; 75164-75199; 75254-75287; 75412-75443; 75421-75439; 75422-75439; 75422-75438; 75423-75439; 75423-75438; 75493-75528; 75616-75643; 75626-75641; 75658-75699; 75676-75692; 75717-75745; 75726-75759; 75726-75745; 75727-75745; 75728-75745; 75831-75988; 75852-75969; 75969-75984; 75987-76056; 76000-76046; 76000-76032; 76000-76018; 76014-76046; 76014-76032; 76029-76046; or 76031-76046 of SEQ ID NO: 2, wherein the nucleobase sequence of the modified oligonucleotide is complementary to SEQ ID NO: 2.

[0127] As disclosed herein, the nucleobase sequence of the modified oligonucleotide comprises the sequence of SEQ ID NO: 12 or consists of the sequence of SEQ ID NO: 12. In certain instances, the modified oligonucleotide is 100% complementary to SEQ ID NO: 1 or 2.

[0128] As disclosed herein, the nucleobase sequence of the modified oligonucleotide comprises the sequence of any of the STAT3 antisense oligonucleotides described in WO 2012/135736.

[0129] In certain instances, the modified oligonucleotide is a single-stranded modified oligonucleotide. In certain instances, the modified oligonucleotide comprises at least one modified internucleoside linkage. In several instances, each internucleoside linkage is a phosphorothioate internucleoside linkage. As disclosed herein, at least one nucleoside comprises a modified sugar, such as a bicyclic sugar including, but not limited to, a 4'-CH₂-O-2' bridge or a 4'-CH(CH₃)-O-2' bridge. As disclosed herein, the modified sugar comprises a 2'-O(CH₂)₂-OCH₃ group. In certain instances, at least one nucleoside comprises a modified nucleobase, such as a 5-methylcytosine.

[0130] As disclosed herein, the modified oligonucleotide comprises:

- a 5'-wing consisting of 1 to 5 linked nucleosides;
- a 3'-wing consisting of 1 to 5 linked nucleosides; and
- a gap between the 5'-wing and the 3'-wing consisting of 8 to 12 linked 2'-deoxynucleosides;

wherein at least one of the 5'-wing and the 3'-wing comprises at least one bicyclic nucleoside or one 2'-substituted nucleoside. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-O(CH₂)₂-OCH₃ group or a 2'-O-CH₃ group. In certain instances, the bicyclic nucleoside comprises a 4'-CH₂-O-2' bridge or a 4'-CH(CH₃)-O-2' bridge.

[0131] As disclosed herein, pharmaceutical compositions described herein are administered in the form of a dosage unit (e.g., injection, infusion, etc.). In certain instances, such pharmaceutical compositions comprise an antisense oligonucleotide in an amount of any of about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about

675 mg, about 700 mg, about 725 mg, or about 750 mg. It will be understood that the aforementioned amounts of antisense oligonucleotide can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the amount by the subject's body weight per week. For example, dividing the aforementioned amounts by an average adult body weight of 70 kg, as disclosed herein the dosage unit can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), about 250 mg/70 kg (3.6 mg/kg/wk), about 275 mg/70 kg (3.9 mg/kg/wk), about 300 mg/70 kg (4.3 mg/kg/wk), about 325 mg/70 kg (4.6 mg/kg/wk), about 350 mg/70 kg (5.0 mg/kg/wk), about 375 mg/70 kg (5.4 mg/kg/wk), about 400 mg/70 kg (5.7 mg/kg/wk), about 425 mg/70 kg (6.1 mg/kg/wk), about 450 mg/70 kg (6.4 mg/kg/wk), about 475 mg/70 kg (6.8 mg/kg/wk), about 500 mg/70 kg (7.1 mg/kg/wk), about 525 mg/70 kg (7.5 mg/kg/wk), about 550 mg/70 kg (7.9 mg/kg/wk), about 575 mg/70 kg (8.2 mg/kg/wk), about 600 mg/70 kg (8.6 mg/kg/wk), about 625 mg/70 kg (8.9 mg/kg/wk), about 650 mg/70 kg (9.3 mg/kg/wk), about 675 mg/70 kg (9.6 mg/kg/wk), about 700 mg/70 kg (10.0 mg/kg/wk), about 725 mg/70 kg (10.4 mg/kg/wk), or about 750 mg/70 kg (10.7 mg/kg/wk). In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0132] As disclosed herein, pharmaceutical compositions described herein comprise a dose of antisense oligonucleotide in an amount in the range of about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, or about 750 mg. It will be understood that the aforementioned amounts of antisense oligonucleotide can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the amount by the subject's body weight per week. For example, dividing the aforementioned amounts by an average adult body weight of 70 kg, as disclosed herein the dose of antisense oligonucleotide can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), about 250 mg/70 kg (3.6 mg/kg/wk), about 275 mg/70 kg (3.9 mg/kg/wk), about 300 mg/70 kg (4.3 mg/kg/wk), about 325 mg/70 kg (4.6 mg/kg/wk), about 350 mg/70 kg (5.0 mg/kg/wk), about 375 mg/70 kg (5.4 mg/kg/wk), about 400 mg/70 kg (5.7 mg/kg/wk), about 425 mg/70 kg (6.1 mg/kg/wk), about 450 mg/70 kg (6.4 mg/kg/wk), about 475 mg/70 kg (6.8 mg/kg/wk), about 500 mg/70 kg (7.1 mg/kg/wk), about 525 mg/70 kg (7.5 mg/kg/wk), about 550 mg/70 kg (7.9 mg/kg/wk), about 575 mg/70 kg (8.2 mg/kg/wk), about 600 mg/70 kg (8.6 mg/kg/wk), about 625 mg/70 kg (8.9 mg/kg/wk), about 650 mg/70 kg (9.3 mg/kg/wk), about 675 mg/70 kg (9.6 mg/kg/wk), about 700 mg/70 kg (10.0 mg/kg/wk), about 725 mg/70 kg (10.4 mg/kg/wk), or about 750 mg/70 kg (10.7 mg/kg/wk). As disclosed herein body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0133] The compositions described herein may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions described herein. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, and/or aromatic substances and the like which do not deleteriously interact with the oligonucleotide(s) of the formulation.

[0134] Antisense oligonucleotides may be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the 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.

[0135] Antisense oligonucleotides 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 oligonucleotide 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.

Certain treatments

[0136] Disclosed herein is a method of treating a subject suffering from cancer comprising administering to the subject an antisense compound complementary to human STAT3. In certain embodiments the antisense compound complementary to human STAT3 is as described herein or as disclosed in WO2012/135736.

[0137] In certain instances, the cancer is B-cell lymphoma. Disclosed herein is an antisense compound complementary to human STAT3 for use in treating cancer. As disclosed herein the antisense compound complementary to human STAT3 is as described herein or as disclosed in WO2012/135736. In certain instances, the cancer is selected from B-cell lymphoma.

[0138] In certain aspects there is provided an antisense compound complementary to human STAT3 for use in a method of treating cancer in a subject in need thereof, wherein the method comprises administering to the subject the antisense compound in a loading phase and then a maintenance phase, wherein the loading phase involves administering a total weekly dose of the compound in the range of about 100-750 mg for the first 1-10 weeks, and the maintenance phase involves administering a total weekly dose in the range of 100-250 mg for at least 1 week after the loading phase. As disclosed herein the antisense compound complementary to human STAT3 is as described herein or as disclosed in WO2012/135736. In certain instances, the cancer is selected from B-cell lymphoma.

[0139] Certain disclosures are directed to use of an antisense compound complementary to human STAT3 for the manufacture of a medicament for treating cancer. In certain disclosures the antisense compound complementary to human STAT3 is as described herein or as disclosed in WO2012/135736. In certain instances, the cancer is selected from B-cell lymphoma.

[0140] In particular instances of any of these aspects, the B-cell lymphoma is a non-Hodgkin's B-cell lymphoma. Examples of non-Hodgkin's B-cell lymphoma of certain aspects include, but are not limited to, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma (MCL), Burkitt lymphoma, mediastinal large B cell lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), intravascular large B-cell lymphoma, primary effusion lymphoma, and lymphomatoid granulomatosis. In certain instances, the non-Hodgkin's B-cell lymphoma is diffuse large B cell lymphoma (DLBCL).

Certain Dosing Regimens

[0141] In certain instances, pharmaceutical compositions are administered according to a dosing regimen. In certain such instances, the dosing regimen comprises a loading phase and a maintenance phase. In certain such instances, the dosing regimen is effective to treat cancer and acceptably tolerable in a subject. In certain instances, the pharmaceutical composition comprises an antisense oligonucleotide. In certain instances, the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 12. In certain instances, the antisense oligonucleotide is ISIS 481464.

[0142] In certain instances, the loading phase includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or more than 20 doses.

[0143] In certain instances, the loading phase lasts from 1 day to 6 months. In certain instances, a loading phase lasts 1 day, 2 days, 3, days, 4, days, 5 days, 6 days, or 7 days as measured from administration of the first dose of the loading phase to administration of the first dose of the maintenance phase. In certain instances a loading phase lasts 1 week, 2 weeks, 3, weeks, 4, weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, or 26 weeks as measured from administration of the first dose of the loading phase to administration of the first dose of the maintenance phase. In certain instances, the loading phase lasts 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months as measured from administration of the first dose of the loading phase to administration of the first dose of the maintenance phase.

[0144] In certain embodiments, the dose administered during the loading phase is lower than the dose administered during the maintenance phase. In certain embodiments, the dose administered during the loading phase is lower than the dose administered during the maintenance phase to avoid undesired side effects. In certain embodiments, the undesired side effect is increased liver markers. In certain embodiments, the undesired side effect is increased ALT. In certain embodiments, the undesired side effect is increased AST. In certain embodiments, the undesired side effect is thrombocytopenia or neutropenia.

[0145] In certain embodiments, the dose administered during the loading phase is higher than the dose administered during the maintenance phase. In certain embodiments, the dose administered during the loading phase is higher than the dose administered during the maintenance phase to quickly achieve steady state reduction of STAT3 mRNA expression, STAT3 protein expression, and/or STAT3 activity. In certain embodiments, the dose administered during the

loading phase is higher than the dose administered during the maintenance phase to avoid undesired side effects in the maintenance phase. In certain embodiments, the undesired side effect is increased liver markers. In certain embodiments, the undesired side effect is increased ALT. In certain embodiments, the undesired side effect is increased AST. In certain embodiments, the undesired side effect is thrombocytopenia or neutropenia.

[0146] In certain embodiments where the loading phase includes more than one dose, the doses administered during the loading phase are all the same amount as one another. In certain embodiments, the doses administered during the loading phase are not all the same amount. In certain embodiments, the doses given during the loading phase increase over time. In certain embodiments, the doses given during the loading phase decrease over time.

[0147] In certain embodiments, a loading dose is administered by parenteral administration. In certain embodiments, the parenteral administration is subcutaneous administration. In certain embodiments, the parenteral administration is intravenous infusion.

[0148] As disclosed herein, the doses administered during the loading phase are about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1.0 mg, about 1.1 mg, about 1.2 mg, about 1.3 mg, about 1.4 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2.0 mg, about 2.1 mg, about 2.2 mg, about 2.3 mg, about 2.4 mg, about 2.5 mg, about 2.6 mg, about 2.7 mg, about 2.8 mg, about 2.9 mg, about 3.0 mg, about 3.1 mg, about 3.2 mg, about 3.3 mg, about 3.4 mg, or about 3.5 mg of the antisense compound per kilogram of the subject's body weight. In certain instances, the dose is 2.0 milligrams of the antisense compound per kilogram of the subject's body weight per week (2.0 mg/kg/wk). In certain instances, the subject's body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0149] In certain instances, the doses administered during the loading phase are about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, or about 750 mg. It will be understood that the aforementioned doses of antisense oligonucleotide can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the amount by the subject's body weight per week. For example, dividing the aforementioned amounts by an average adult body weight of 70 kg, in certain disclosures the doses can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), about 250 mg/70 kg (3.6 mg/kg/wk), about 275 mg/70 kg (3.9 mg/kg/wk), about 300 mg/70 kg (4.3 mg/kg/wk), about 325 mg/70 kg (4.6 mg/kg/wk), about 350 mg/70 kg (5.0 mg/kg/wk), about 375 mg/70 kg (5.4 mg/kg/wk), about 400 mg/70 kg (5.7 mg/kg/wk), about 425 mg/70 kg (6.1 mg/kg/wk), about 450 mg/70 kg (6.4 mg/kg/wk), about 475 mg/70 kg (6.8 mg/kg/wk), about 500 mg/70 kg (7.1 mg/kg/wk), about 525 mg/70 kg (7.5 mg/kg/wk), about 550 mg/70 kg (7.9 mg/kg/wk), about 575 mg/70 kg (8.2 mg/kg/wk), about 600 mg/70 kg (8.6 mg/kg/wk), about 625 mg/70 kg (8.9 mg/kg/wk), about 650 mg/70 kg (9.3 mg/kg/wk), about 675 mg/70 kg (9.6 mg/kg/wk), about 700 mg/70 kg (10.0 mg/kg/wk), about 725 mg/70 kg (10.4 mg/kg/wk), or about 750 mg/70 kg (10.7 mg/kg/wk). In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0150] In certain embodiments, dose, dose frequency, and duration of the loading phase may be selected to achieve a desired effect. In certain embodiments, those variables are adjusted to result in a desired concentration of pharmaceutical agent in a subject. For example, in certain embodiments, dose and dose frequency are adjusted to provide plasma concentration of a pharmaceutical agent at an amount sufficient to achieve a desired effect. In certain embodiments, the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical compositions described herein are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time. In certain embodiments, the pharmaceutical composition comprises ISIS 481464.

[0151] In certain embodiments, doses, dose frequency, and duration of the loading phase may be selected to achieve a desired plasma trough concentration of a pharmaceutical composition. In certain embodiments, the pharmaceutical composition comprises ISIS 481464. In certain embodiments, the desired plasma trough concentration is from 5-100 ng/mL. In certain embodiments, the desired plasma trough concentration is from 5-50 ng/mL. In certain embodiments, the desired plasma trough concentration is from 10-40 ng/mL. In certain embodiments, the desired plasma trough concentration is from 15-35 ng/mL. In certain embodiments, the desired plasma trough concentration is from 20-30 ng/mL.

[0152] In certain embodiments, dose, dose frequency, and duration of the loading phase may be selected to achieve a desired effect within 1 to 26 weeks. In certain embodiments, the dose is the same and the dose frequency is varied to achieve the desired effect within 1 to 26 weeks. In certain embodiments, the dose increases over time and the dose

frequency remains constant. In certain embodiments, one or more doses of the loading phase are greater than one or more doses of the maintenance phase. In certain embodiments, each of the loading doses is greater than each of the maintenance doses. In certain embodiments, it is desirable to achieve a desired effect as quickly as possible. In certain embodiments, a loading phase with a high dose and/or high dose frequency may be desirable.

[0153] In certain embodiments, doses, dose frequency, and duration of the loading phase may be selected to achieve an acceptable safety profile. For example, in certain embodiments, such variables may be selected to mitigate toxicity of the pharmaceutical composition. In certain embodiments, such variables are selected to mitigate liver toxicity. In certain embodiments, such variables are selected to mitigate renal toxicity. In certain embodiments, such variables are selected to mitigate thrombocytopenia or neutropenia.

[0154] In certain embodiments, doses increase over time. In certain embodiments, one or more doses of the loading phase are lower than one or more doses of the maintenance phase. In certain embodiments, a safety profile is not acceptable when ALT is 5-10 times the upper limit of normal. In certain embodiments, a safety profile is not acceptable when ALT is 5-10 times the upper limit of normal, and bilirubin is elevated two or more times the upper limit of normal. In certain embodiments, an acceptable safety profile comprises ALT elevations that are above three times the upper limit of normal, but do not exceed five times the upper limit of normal. In certain embodiments, an acceptable safety profile comprises ALT elevations that are above three times the upper limit of normal, but do not exceed five times the upper limit of normal, and bilirubin elevations that do not exceed two times the upper limit of normal. In certain embodiments, when administration of a pharmaceutical composition of the invention results in ALT elevations that are above three times the upper limit of normal, the dose and/or dose frequency is adjusted to mitigate the ALT elevation.

[0155] In certain embodiments, the maintenance phase includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more than 20 doses.

[0156] In certain embodiments, the maintenance phase lasts from one week to the lifetime of the subject. In certain embodiments, the maintenance phase lasts 7 days as measured from administration of the last dose of the loading phase to administration of the last dose of the maintenance phase. In certain embodiments, the maintenance phase lasts 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, or 52 weeks as measured from administration of the last dose of the loading phase to administration of the last dose of the maintenance phase. In certain embodiments, the maintenance phase lasts 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months as measured from administration of the last dose of the loading phase to administration of the last dose of the maintenance phase. In certain embodiments, the maintenance phase lasts 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 21 years, 22 years, 23 years, 24 years, 25 years, 26 years, 27 years, 28 years, 29 years, 30 years, 31 years, 32 years, 33 years, 34 years, 35 years, 36 years, 37 years, 38 years, 39 years, 40 years, 41 years, 42 years, 43 years, 44 years, 45 years, 46 years, 47 years, 48 years, 49 years, or 50 years as measured from administration of the last dose of the loading phase to administration of the last dose of the maintenance phase. In certain embodiments, the maintenance phase lasts as long as the dose continues to be needed, effective, and tolerated.

[0157] In certain embodiments where the maintenance phase includes more than one dose, the doses administered during the maintenance phase are all the same as one another. In certain embodiments, the doses administered during the maintenance phase are not all the same. In certain embodiments, the doses increase over time. In certain embodiments, the doses decrease over time.

[0158] In certain embodiments, a maintenance dose is administered by parenteral administration. In certain embodiments, the parenteral administration is subcutaneous administration. In certain embodiments, the parenteral administration is intravenous infusion.

[0159] As disclosed herein, the doses during the maintenance phase are about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1.0 mg, about 1.1 mg, about 1.2 mg, about 1.3 mg, about 1.4 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2.0 mg, about 2.1 mg, about 2.2 mg, about 2.3 mg, about 2.4 mg, about 2.5 mg, about 2.6 mg, about 2.7 mg, about 2.8 mg, about 2.9 mg, about 3.0 mg, about 3.1 mg, about 3.2 mg, about 3.3 mg, about 3.4 mg, or about 3.5 mg of the antisense compound per kilogram of the subject's body weight. In certain instances, the dose is 2.0 milligrams of the antisense compound per kilogram of the subject's body weight per week (2.0 mg/kg/wk). In certain instances, the subject's body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0160] In certain instances, the doses during the maintenance phase are about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200

mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, or about 250 mg. It will be understood that the aforementioned doses of antisense oligonucleotide can be readily represented as milligrams of the antisense compound per kilogram of the subject's body weight per week (mg/kg/wk) by simply dividing the amount by the subject's body weight per week. For example, dividing the aforementioned amounts by an average adult body weight of 70 kg, in certain disclosures the doses can be represented as any of about 15 mg/70 kg (0.2 mg/kg/wk), about 20 mg/70 kg (0.3 mg/kg/wk), about 30 mg/70 kg (0.4 mg/kg/wk), about 40 mg/70 kg (0.6 mg/kg/wk), about 50 mg/70 kg (0.7 mg/kg/wk), about 75 mg/70 kg (1.1 mg/kg/wk), about 100 mg/70 kg (1.4 mg/kg/wk), about 125 mg/70 kg (1.8 mg/kg/wk), about 150 mg/70 kg (2.1 mg/kg/wk), about 175 mg/70 kg (2.5 mg/kg/wk), about 200 mg/70 kg (2.9 mg/kg/wk), about 225 mg/70 kg (3.2 mg/kg/wk), or about 250 mg/70 kg (3.6 mg/kg/wk). In certain instances, body weight is calculated as the ideal body weight using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000. 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$.

[0161] In certain embodiments, doses, dose frequency, and duration of the maintenance phase may be selected to achieve a desired effect. In certain embodiments, those variables are adjusted to result in a desired concentration of pharmaceutical agent in a subject. For example, in certain embodiments, dose and dose frequency are adjusted to provide plasma concentration of a pharmaceutical agent described herein at an amount sufficient to achieve a desired effect. In certain embodiments, the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical compositions described herein are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time.

[0162] In certain embodiments, doses, dose frequency, and duration of the maintenance phase may be selected to achieve a desired plasma trough concentration of a pharmaceutical composition. In certain embodiments, the desired plasma trough concentration is from 5-100 ng/mL. In certain embodiments, the desired plasma trough concentration is from 5-50 ng/mL. In certain embodiments, the desired plasma trough concentration is from 10-40 ng/mL. In certain embodiments, the desired plasma trough concentration is from 15-35 ng/mL. In certain embodiments, the desired plasma trough concentration is from 20-30 ng/mL.

[0163] In certain embodiments, doses, dose frequency, and duration of the maintenance phase may be selected to achieve a desired safety profile. For example, in certain embodiments, such variables may be selected to mitigate toxicity of the pharmaceutical composition. In certain embodiments, such variables are selected to mitigate liver toxicity. In certain embodiments, such variables are selected to mitigate renal toxicity. In certain embodiments, such variables are selected to mitigate thrombocytopenia or neutropenia.

[0164] In certain embodiments, doses, dose frequency, and duration of the maintenance phase may be adjusted from time to time to achieve a desired effect. In certain embodiments, subjects are monitored for effects (therapeutic and/or toxic effects) and doses, dose frequency, and/or duration of the maintenance phase may be adjusted based on the results of such monitoring.

[0165] In certain embodiments, pharmaceutical compositions are administered according to a dosing regimen comprising a first phase and a second phase, wherein the pharmaceutical composition comprises ISIS 481464.

[0166] In certain embodiments, the first phase includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or more than 20 doses.

[0167] In certain embodiments a first phase lasts 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, or 26 weeks as measured from administration of the first dose of the first phase to administration of the first dose of the second phase. In certain embodiments, the first phase lasts 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months as measured from administration of the first dose of the first phase to administration of the first dose of the second phase.

[0168] In certain embodiments, the dose administered during the first phase is lower than the dose administered during the second phase. In certain embodiments, the dose administered during the first phase is lower than the dose administered during the second phase to avoid undesired side effects. In certain embodiments, the undesired side effect is increased liver markers. In certain embodiments, the undesired side effect is increased ALT. In certain embodiments, the undesired side effect is increased AST. In certain embodiments, the undesired side effect is thrombocytopenia or neutropenia.

[0169] In certain embodiments, the dose administered during the first phase is higher than the dose administered during the second phase. In certain embodiments, the dose administered during the first phase is higher than the dose administered during the second phase to quickly achieve steady state reduction of STAT3 mRNA expression, STAT3 protein expression, and/or STAT3 activity. In certain embodiments, the dose administered during the first phase is higher than the dose administered during the second phase to avoid undesired side effects in the second phase. In certain embodiments, the undesired side effect is increased liver markers. In certain embodiments, the undesired side effect is increased ALT. In certain embodiments, the undesired side effect is increased AST. In certain embodiments, the undesired side effect is thrombocytopenia or neutropenia.

[0170] In certain embodiments where the first phase includes more than one dose, the doses administered during the first phase are all the same amount as one another. In certain embodiments, the doses administered during the first phase are not all the same amount. In certain embodiments, the doses given during the first phase increase over time. In certain embodiments, the doses given during the first phase decrease over time.

[0171] In certain embodiments, a first dose is administered by parenteral administration. In certain embodiments, the parenteral administration is subcutaneous administration. In certain embodiments, the parenteral administration is intravenous infusion.

[0172] The range of dosages capable of being administered during the "first phase" and/or "second phase" are the same as can be used for the "loading phase" and "maintenance phase" referred to above. In certain embodiments, dose, dose frequency, and duration of the first phase and/or second phase may be selected to achieve a desired effect. In certain embodiments, those variables are adjusted to result in a desired concentration of pharmaceutical agent in a subject. For example, in certain embodiments, dose and dose frequency are adjusted to provide plasma concentration of a pharmaceutical agent at an amount sufficient to achieve a desired effect. In certain embodiments, the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical compositions described herein are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time. In certain embodiments, the pharmaceutical composition comprises ISIS 481464. In certain embodiments, doses, dose frequency, and duration of the first phase and/or second phase may be selected to achieve a desired plasma trough concentration of a pharmaceutical composition. In certain embodiments, the pharmaceutical composition comprises ISIS 481464. In certain embodiments, the desired plasma trough concentration is from 5-100 ng/mL. In certain embodiments, the desired plasma trough concentration is from 5-50 ng/mL. In certain embodiments, the desired plasma trough concentration is from 10-40 ng/mL. In certain embodiments, the desired plasma trough concentration is from 15-35 ng/mL. In certain embodiments, the desired plasma trough concentration is from 20-30 ng/mL.

[0173] In certain embodiments, dose, dose frequency, and duration of the first phase and/or second phase may be selected to achieve a desired effect within 1 to 26 weeks. In certain embodiments, the dose is the same and the dose frequency is varied to achieve the desired effect within 1 to 26 weeks. In certain embodiments, the dose increases over time and the dose frequency remains constant. In certain embodiments, one or more doses of the first phase are greater than one or more doses of the second phase. In certain embodiments, each of the first doses is greater than each of the second doses. In certain embodiments, it is desirable to achieve a desired effect as quickly as possible. In certain embodiments, a first phase with a high dose and/or high dose frequency may be desirable.

In certain embodiments, doses, dose frequency, and duration of the first phase and/or second phase may be selected to achieve an acceptable safety profile. For example, in certain embodiments, such variables may be selected to mitigate toxicity of the pharmaceutical composition. In certain embodiments, such variables are selected to mitigate liver toxicity. In certain embodiments, such variables are selected to mitigate renal toxicity. In certain embodiments, such variables are selected to mitigate thrombocytopenia or neutropenia.

[0174] In certain embodiments, doses increase over time. In certain embodiments, one or more doses of the first phase are lower than one or more doses of the second phase. In certain embodiments, a safety profile is not acceptable when ALT is 5-10 times the upper limit of normal. In certain embodiments, a safety profile is not acceptable when ALT is 5-10 times the upper limit of normal, and bilirubin is elevated two or more times the upper limit of normal. In certain embodiments, an acceptable safety profile comprises ALT elevations that are above three times the upper limit of normal, but do not exceed five times the upper limit of normal. In certain embodiments, an acceptable safety profile comprises ALT elevations that are above three times the upper limit of normal, but do not exceed five times the upper limit of normal, and bilirubin elevations that do not exceed two times the upper limit of normal. In certain embodiments, when administration of a pharmaceutical composition of the invention results in ALT elevations that are above three times the upper limit of normal, the dose and/or dose frequency is adjusted to mitigate the ALT elevation. In certain embodiments, the second phase includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more than 20 doses. In certain embodiments, the second phase lasts from one day to the lifetime of the subject. In certain embodiments, the second phase lasts 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, or 52 weeks as measured from administration of the last dose of the first phase to administration of the last dose of the second phase. In certain embodiments, the second phase lasts 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months as measured from administration of the last dose of the first phase to administration of the last dose of the second phase. In certain embodiments, the second phase lasts 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 21 years, 22 years, 23 years, 24 years, 25 years, 26 years, 27 years, 28 years, 29

years, 30 years, 31 years, 32 years, 33 years, 34 years, 35 years, 36 years, 37 years, 38 years, 39 years, 40 years, 41 years, 42 years, 43 years, 44 years, 45 years, 46 years, 47 years, 48 years, 49 years, or 50 years as measured from administration of the last dose of the first phase to administration of the last dose of the second phase. In certain embodiments, the second phase lasts as long as the dose continues to be needed, effective, and tolerated.

[0175] In certain embodiments where the second phase includes more than one dose, the doses administered during the second phase are all the same as one another. In certain embodiments, the doses administered during the second phase are not all the same. In certain embodiments, the doses increase over time. In certain embodiments, the doses decrease over time.

[0176] In certain embodiments, a second dose is administered by parenteral administration. In certain embodiments, the parenteral administration is subcutaneous administration. In certain embodiments, the parenteral administration is intravenous infusion.

Antisense compounds

[0177] Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, 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.

[0178] 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.

[0179] As disclosed herein, an antisense compound targeted to a STAT3 nucleic acid is 12 to 30 subunits in length. As disclosed herein, an antisense compound targeted to a STAT3 nucleic acid is 14 to 30 subunits in length. As disclosed herein, an antisense compound targeted to a STAT3 nucleic acid is 12 to 22 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits, 14 to 30 linked subunits, or 12 to 22 linked subunits, respectively. As disclosed herein, the antisense compound is 8 to 80, 12 to 50, 13 to 30, 13 to 50, 14 to 30, 14 to 50, 15 to 30, 15 to 50, 16 to 30, 16 to 50, 17 to 30, 17 to 50, 18 to 22, 18 to 24, 18 to 30, 18 to 50, 19 to 22, 19 to 30, 19 to 50, or 20 to 30 linked subunits. As disclosed herein, 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 some instances, the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleotides.

[0180] In certain instances, antisense oligonucleotides targeted to a STAT3 nucleic acid may be shortened or truncated. For example, a single subunit may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated antisense compound targeted to a STAT3 nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the antisense compound. Alternatively, the deleted nucleosides may be dispersed throughout the antisense compound, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

[0181] When a single additional subunit is present in a lengthened antisense compound, the additional subunit may be located at the 5' or 3' end of the antisense compound. When two or more additional subunits are present, the added subunits may be adjacent to each other, for example, in an antisense compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the antisense compound. Alternatively, the added subunits may be dispersed throughout the antisense compound, for example, in an antisense compound having one subunit added to the 5' end and one subunit added to the 3' end.

[0182] 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.

[0183] 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*.

[0184] Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase antisense

oligonucleotides, and a 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

[0185] In certain instances, antisense compounds targeted to a STAT3 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.

[0186] 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 an RNA:DNA duplex.

[0187] Antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal region having a plurality of nucleotides that supports RNaseH 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. As disclosed herein, 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 constrained ethyl). As disclosed herein, wings may include several modified sugar moieties, including, for example 2'-MOE and constrained ethyl. In certain disclosures, wings may include several modified and unmodified sugar moieties. In certain disclosures, wings may include various combinations of 2'-MOE nucleosides, constrained ethyl nucleosides, and 2'-deoxynucleosides.

[0188] Each distinct region may comprise uniform sugar moieties, variants, or alternating sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5'-wing, "Y" represents the length of the gap, and "Z" represents the length of the 3'-wing. "X" and "Z" may comprise uniform, variant, or alternating sugar moieties. In certain disclosures, "X" and "Y" may include one or more 2'-deoxynucleosides. "Y" may comprise 2'-deoxynucleosides. As used herein, a gapmer described as "X-Y-Z" has a configuration such that the gap is positioned immediately adjacent to each of the 5'-wing and the 3' wing. Thus, no intervening nucleotides exist between the 5'-wing and gap, or the gap and the 3'-wing. Any of the antisense compounds described herein can have a gapmer motif. In certain disclosures, "X" and "Z" are the same, in other disclosures, they are different. In certain disclosures, "Y" is between 8 and 15 nucleosides. 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, 25, 30 or more nucleosides.

[0189] As disclosed herein, gapmers provided herein include, for example, 11-mers having a motif of 1-9-1.

[0190] As disclosed herein, gapmers provided herein include, for example, 12-mers having a motif of 1-9-2, 2-9-1, or 1-10-1.

[0191] As disclosed herein, gapmers provided herein include, for example, 13-mers having a motif of 1-9-3, 2-9-2, 3-9-1, 1-10-2, or 2-10-1.

[0192] As disclosed herein, gapmers provided herein include, for example, 14-mers having a motif of 1-9-4, 2-9-3, 3-9-2, 4-9-1, 1-10-3, 2-10-2, or 3-10-1.

[0193] As disclosed herein, gapmers provided herein include, for example, 15-mers having a motif of 1-9-5, 2-9-4, 3-9-3, 4-9-2, 5-9-1, 1-10-4, 2-10-3, 3-10-2, or 4-10-1.

[0194] As disclosed herein, gapmers provided herein include, for example, 16-mers having a motif of 2-9-5, 3-9-4, 4-9-3, 5-9-2, 1-10-5, 2-10-4, 3-10-3, 4-10-2, or 5-10-1.

[0195] As disclosed herein, gapmers provided herein include, for example, 17-mers having a motif of 3-9-5, 4-9-4, 5-9-3, 2-10-5, 3-10-4, 4-10-3, or 5-10-2.

[0196] As disclosed herein, gapmers provided herein include, for example, 18-mers having a motif of 4-9-5, 5-9-4, 3-10-5, 4-10-4, or 5-10-3.

[0197] As disclosed herein, gapmers provided herein include, for example, 19-mers having a motif of 5-9-5, 4-10-5, or 5-10-4.

[0198] As disclosed herein, gapmers provided herein include, for example, 20-mers having a motif of 5-10-5.

[0199] As disclosed herein, the antisense compound has 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 disclosed herein 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, 5-13, 5-8, or 6-8.

[0200] As disclosed herein, antisense compound targeted to a STAT3 nucleic acid has a 2-10-2 gapmer motif.

[0201] In certain embodiments, the antisense compound targeted to a STAT3 nucleic acid has a 3-10-3 gapmer motif.

[0202] As disclosed herein, the antisense compound targeted to a STAT3 nucleic acid has a 5-10-5 gapmer motif.

5 **[0203]** As disclosed herein, the antisense compound targeted to a STAT3 nucleic acid has a 1-10-5 gapmer motif.

[0204] As disclosed herein, the antisense compound targeted to a STAT3 nucleic acid has a 3-10-4 gapmer motif.

[0205] As disclosed herein, the antisense compound targeted to a STAT3 nucleic acid has a 2-10-4 gapmer motif.

[0206] As disclosed herein, the antisense compound targeted to a STAT3 nucleic acid has a 4-9-3 gapmer motif.

[0207] As disclosed herein, the antisense compound targeted to a STAT3 nucleic acid has a gap-widened motif.

10 **[0208]** As disclosed herein, the antisense compounds targeted to a STAT3 nucleic acid has any of the following sugar motifs:

k-d(10)-k

15 e-d(10)-k

k-d(10)-e

20 k-k-d(10)-k-k

k-k-d(10)-e-e

e-e-d(10)-k-k

25 k-k-k-d(10)-k-k-k

e-e-e-d(10)-k-k-k

k-k-k-d(10)-e-e-e

30 k-k-k-d(10)-k-k-k

e-k-k-d(10)-k-k-e

35 e-e-k-d(10)-k-k-e

e-d-k-d(10)-k-k-e

e-k-d(10)-k-e-k-e

40 k-d(10)-k-e-k-e-e

e-e-k-d(10)-k-e-k-e

45 e-d-d-k-d(9)-k-k-e

e-e-e-e-d(9)-k-k-e

wherein, k is a constrained ethyl nucleoside, e is a 2'-MOE substituted nucleoside, and d is a 2'-deoxynucleoside.

50 **[0209]** As disclosed herein, the antisense oligonucleotide has a sugar motif described by Formula A as follows:
 $(J)_m-(B)_n-(J)_p-(B)_r-(A)_t-(D)_g-(A)_v-(B)_w-(J)_x-(B)_y-(J)_z$ wherein:

each A is independently a 2'-substituted nucleoside;

55 each B is independently a bicyclic nucleoside;

each J is independently either a 2'-substituted nucleoside or a 2'-deoxynucleoside;

each D is a 2'-deoxynucleoside;

m is 0-4; n is 0-2; p is 0-2; r is 0-2; t is 0-2; v is 0-2; w is 0-4; x is 0-2; y is 0-2; z is 0-4; g is 6-14;

provided that:

at least one of m, n, and r is other than 0;

at least one of w and y is other than 0;

the sum of m, n, p, r, and t is from 2 to 5; and

the sum of v, w, x, y, and z is from 2 to 5.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

[0210] Nucleotide sequences that encode STAT3 include, without limitation, the following: GENBANK Accession No. NM_139276.2 (incorporated herein as SEQ ID NO: 1) and the complement of GENBANK Accession No. NT_010755.14 truncated from nucleotides 4185000 to 4264000 (incorporated herein as SEQ ID NO: 2).

[0211] It is understood that the sequence set forth in each SEQ ID NO 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.

[0212] In certain instances, a target region is a structurally defined region of the target nucleic acid. 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 STAT3 can be obtained by accession number from sequence databases such as NCBI and such information is incorporated herein by reference. 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 same target region.

[0213] 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.

[0214] A target region may contain one or more target segments. Multiple target segments within a target region may be overlapping. Alternatively, they may 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.

[0215] Suitable target segments may 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 may specifically exclude a certain structurally defined region such as the start codon or stop codon.

[0216] The determination of suitable target segments may include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm may be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that may hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

[0217] There may 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 embodiments, reductions in STAT3 mRNA levels are indicative of inhibition of STAT3 expression. Reductions in levels of a STAT3 protein are also indicative of inhibition of target mRNA expression. Further, phenotypic changes are indicative of inhibition of STAT3 expression. In certain embodiments, reduced cellular growth, reduced tumor growth, and reduced tumor volume can be indicative of inhibition of STAT3 expression. In certain embodiments, amelioration of symptoms associated with cancer can be indicative of inhibition of STAT3 expression. In certain embodiments, reduction of cachexia is indicative of inhibition of STAT3 expression. In certain embodiments, reduction of cancer markers can be indicative of inhibition of STAT3 expression.

Hybridization

[0218] In some instances, hybridization occurs between an antisense compound disclosed herein and a STAT3 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.

[0219] 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.

[0220] Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art. In certain instances, the antisense compounds provided herein are specifically hybridizable with a STAT3 nucleic acid.

Complementarity

[0221] 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 a STAT3 nucleic acid).

[0222] Non-complementary nucleobases between an antisense compound and a STAT3 nucleic acid may be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound may hybridize over one or more segments of a STAT3 nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

[0223] In certain instances, the antisense compounds provided herein, or a specified portion thereof, are, or are at least, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a STAT3 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.

[0224] For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having 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).

[0225] As disclosed herein, 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 a STAT3 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.

[0226] The location of a non-complementary nucleobase may be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they may 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.

[0227] As disclosed herein, antisense compounds that are, or are up to 11, 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 a STAT3 nucleic acid, or specified portion thereof.

[0228] As disclosed herein, antisense compounds that are, or are up to 11, 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 a STAT3 nucleic acid, or specified portion thereof.

[0229] 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. As disclosed herein, the antisense compounds, are complementary to at least an 8 nucleobase portion of a target segment. As disclosed herein, the antisense compounds are complementary to at least a 9 nucleobase portion of a target segment. As disclosed herein, the antisense compounds are complementary to at least a 10 nucleobase portion of a target segment. As disclosed herein, the antisense compounds are complementary to at least an 11 nucleobase portion of a target segment. As disclosed herein, the antisense compounds are complementary to at least a 12 nucleobase portion of a target segment. As disclosed herein, the antisense compounds are complementary to at least a 13 nucleobase portion of a target segment. As disclosed herein, the antisense compounds are complementary to at least a 14 nucleobase portion of a target segment. As disclosed herein, 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

[0230] The antisense compounds provided herein may 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 may 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.

[0231] As disclosed herein, 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.

[0232] As disclosed herein, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain disclosures, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

[0233] As disclosed herein, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain disclosures, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Modifications

[0234] 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.

[0235] 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.

[0236] Chemically modified nucleosides may 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

[0237] 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.

[0238] 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, phosphodiester, phosphotriester, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

[0239] In the invention, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

Modified Sugar Moieties

[0240] Antisense compounds provided herein 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 instances, nucleosides comprise a chemically modified ribofuranose ring moiety. 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)(R)2 (R = 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), 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).

[0241] 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, 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, O(CH₂)₂SCH₃, O(CH₂)₂-O-N(R_m)(R_n), and 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.

[0242] 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 instances, antisense compounds provided herein include one or more bicyclic nucleosides wherein the bridge comprises a 4' to 2' bicyclic nucleoside. Examples of such 4' to 2' 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 PCT International Application WO2009/006478, published January 8, 2009); 4'-CH₂-N(OCH₃)-2', and analogs thereof (see, published PCT International Application WO2008/150729, 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 PCT International Application WO 2008/154401, published on December 8, 2008). Also 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., 129(26) 8362-8379 (Jul. 4, 2007); Elayadi et al., Curr. Opinion Inven. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Patent Nos. U.S. 6,670,461, 7,053,207, 6,268,490, 6,770,748, 6,794,499, 7,034,133, 6,525,191, 7,399,845; published PCT International applications WO 2004/106356, WO 94/14226, WO 2005/021570, and WO 2007/134181; U.S. Patent Publication Nos. US2004/0171570, US2007/0287831, and US2008/0039618; and U.S. Patent Serial Nos. 12/129,154, 60/989,574, 61/026,995, 61/026,998, 61/056,564, 61/086,231, 61/097,787, and 61/099,844; and PCT International Application Nos. PCT/US2008/064591, PCT/US2008/066154, and PCT/US2008/068922. 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).

[0243] As disclosed herein, 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 $-\text{C}(\text{R}_a)(\text{R}_b)_n-$, $-\text{C}(\text{R}_a)=\text{C}(\text{R}_b)-$, $-\text{C}(\text{R}_a)=\text{N}-$, $-\text{C}(=\text{NR}_a)-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{O}-$, $-\text{Si}(\text{R}_a)_2-$, $-\text{S}(=\text{O})_x-$, and $-\text{N}(\text{R}_a)-$;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

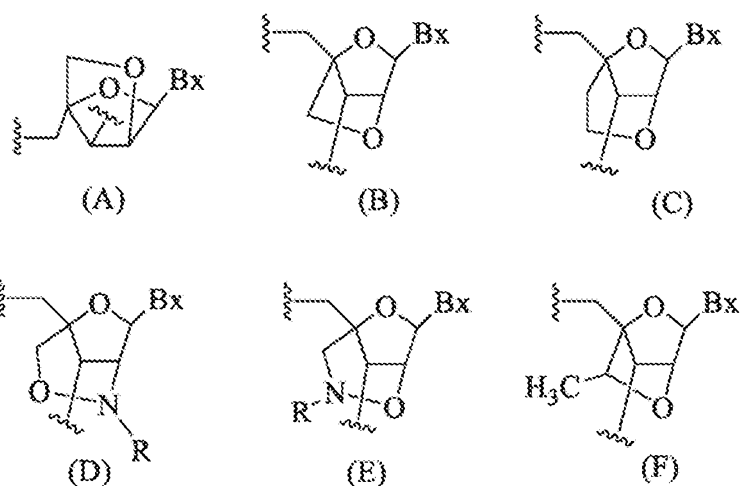
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, 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

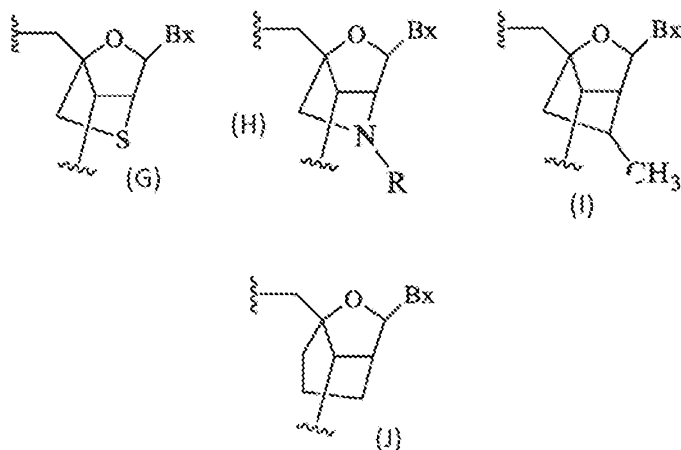
each J_1 and J_2 is, independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($\text{C}(=\text{O})-\text{H}$), substituted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

[0244] As disclosed herein, 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 $4'-\text{CH}_2-2'$, $4'-(\text{CH}_2)_2-2'$, $4'-(\text{CH}_2)_3-2'$, $4'-\text{CH}_2-\text{O}-2'$, $4'-(\text{CH}_2)_2-\text{O}-2'$, $4'-\text{CH}_2-\text{O}-\text{N}(\text{R})-2'$, and $4'-\text{CH}_2-\text{N}(\text{R})-\text{O}-2'$, wherein each R is, independently, H, a protecting group, or C_1 - C_{12} alkyl.

[0245] As disclosed herein, 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 ($4'-\text{CH}_2-\text{O}-2'$) BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

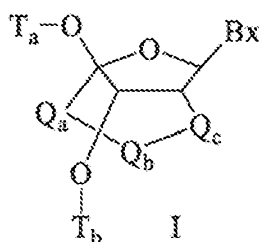
[0246] As disclosed herein, bicyclic nucleosides include, but are not limited to, (A) α -L-Methyleneoxy ($4'-\text{CH}_2-\text{O}-2'$) BNA, (B) β -D-Methyleneoxy ($4'-\text{CH}_2-\text{O}-2'$) BNA, (C) Ethyleneoxy ($4'-(\text{CH}_2)_2-\text{O}-2'$) BNA, (D) Aminooxy ($4'-\text{CH}_2-\text{O}-\text{N}(\text{R})-2'$) BNA, (E) Oxyamino ($4'-\text{CH}_2-\text{N}(\text{R})-\text{O}-2'$) BNA, (F) Methyl(methyleneoxy) ($4'-\text{CH}(\text{CH}_3)-\text{O}-2'$) BNA, (G) methylene-thio ($4'-\text{CH}_2-\text{S}-2'$) BNA, (H) methylene-amino ($4'-\text{CH}_2-\text{N}(\text{R})-2'$) BNA, (I) methyl carbocyclic ($4'-\text{CH}_2-\text{CH}(\text{CH}_3)-2'$) BNA, and (J) propylene carbocyclic ($4'-(\text{CH}_2)_3-2'$) BNA as depicted below.





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

[0247] As disclosed herein, bicyclic nucleoside having Formula I:



wherein:

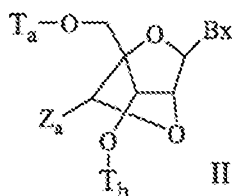
Bx is a heterocyclic base moiety;

-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.

[0248] As disclosed herein, bicyclic nucleoside having Formula II:



wherein:

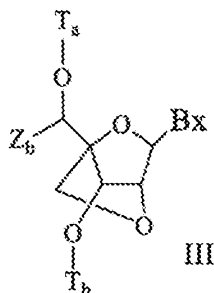
Bx is a heterocyclic base moiety;

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 C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, substituted C₁-C₆ alkyl, substituted C₂-C₆ alkenyl, substituted C₂-C₆ alkynyl, acyl, substituted acyl, substituted amide, thiol, or substituted thio.

[0249] As disclosed herein, 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 , $\text{OC}(=\text{X})\text{J}_c$, and $\text{NJ}_e\text{C}(=\text{X})\text{NJ}_c\text{J}_d$, wherein each J_c , J_d , and J_e is, independently, H, $\text{C}_1\text{-C}_6$ alkyl, or substituted $\text{C}_1\text{-C}_6$ alkyl and X is O or NJ_c .

[0250] As disclosed herein, bicyclic nucleoside having Formula III:



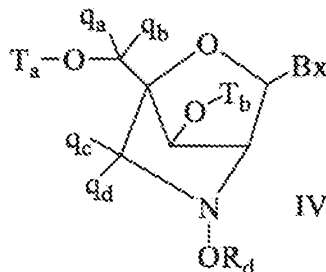
wherein:

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 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, substituted $\text{C}_1\text{-C}_6$ alkyl, substituted $\text{C}_2\text{-C}_6$ alkenyl, substituted $\text{C}_2\text{-C}_6$ alkynyl, or substituted acyl ($\text{C}(=\text{O})\text{-}$).

[0251] As disclosed herein, bicyclic nucleoside having Formula IV:



wherein:

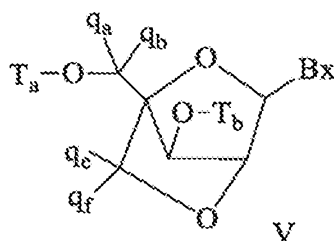
Bx is a heterocyclic base moiety;

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 $\text{C}_1\text{-C}_6$ alkyl, substituted $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, substituted $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, or substituted $\text{C}_2\text{-C}_6$ alkynyl;

each q_a , q_b , q_c and q_d is, independently, H, halogen, $\text{C}_1\text{-C}_6$ alkyl, substituted $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, substituted $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, or substituted $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, substituted $\text{C}_1\text{-C}_6$ alkoxy, acyl, substituted acyl, $\text{C}_1\text{-C}_6$ aminoalkyl, or substituted $\text{C}_1\text{-C}_6$ aminoalkyl;

[0252] As disclosed herein, bicyclic nucleoside 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_c and q_f are each, independently, hydrogen, halogen, 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_1 - C_{12} alkoxy, substituted C_1 - C_{12} alkoxy, OJ_j , SJ_j , SOJ_j , SO_2J_j , NJ_jJ_k , N_3 , 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 $N(H)C(=S)NJ_jJ_k$;

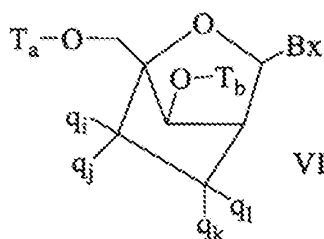
or q_c and q_f together are $=C(q_g)(q_h)$;

q_g and q_h are each, independently, H, halogen, C_1 - C_{12} alkyl, or substituted C_1 - C_{12} alkyl.

[0253] The synthesis and preparation of the methyleneoxy (4'- CH_2 -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 (see, e.g., Koshkin et al., Tetrahedron, 1998, 54, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

[0254] Analogs of methyleneoxy (4'- CH_2 -O-2') BNA, methyleneoxy (4'- CH_2 -O-2') BNA, and 2'-thio-BNAs, have also been prepared (see, e.g., 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 (see, e.g., 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 (see, e.g., Singh et al., J. Org. Chem., 1998, 63, 10035-10039). In addition, 2'-amino- and 2'-methyamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

[0255] As disclosed herein, bicyclic nucleoside 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, 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_1 - C_{12} alkoxy, substituted C_1 - C_{12} alkoxy, OJ_j , SJ_j , SOJ_j , SO_2J_j , NJ_jJ_k , N_3 , 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_i and q_k together are $=C(q_g)(q_h)$, wherein q_g and q_h are each, independently, H, halogen, C_1 - C_{12} alkyl, or substituted C_1 - C_{12} alkyl.

[0256] One carbocyclic bicyclic nucleoside having a 4'-(CH_2)₃-2' bridge and the alkenyl analog, bridge 4'-CH=CH- CH_2 -2', have been described (see, e.g., 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 (see, e.g., Srivastava et al., J. Am. Chem. Soc. 2007, 129(26), 8362-8379).

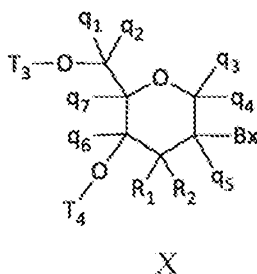
[0257] As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting the 2' carbon atom and the 4' carbon atom.

[0258] As used herein, "monocyclic nucleosides" refer to nucleosides comprising modified sugar moieties that are not bicyclic sugar moieties. In certain instances, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position.

[0259] As used herein, "2'-modified sugar" means a furanosyl sugar modified at the 2' position. In certain instances, 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 instances, 2' modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other 2'-substituent groups can also be selected from: C_1 - C_{12} alkyl; substituted alkyl; alkenyl; alkynyl; alkaryl; aralkyl; O-alkaryl or O-aralkyl; SH; SCH_3 ; OCN; Cl; Br; CN; CF_3 ; OCF_3 ; $SOCH_3$; SO_2CH_3 ; ONO_2 ; NO_2 ; N_3 ; NH_2 ; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving pharmacokinetic properties; and 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 (see, e.g., 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 (see, e.g., Martin, P., 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).

[0260] 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, C.J. Bioorg. & Med. Chem. (2002) 10:841-854), fluoro HNA (F-HNA), or those compounds having Formula X:

Formula X:



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

Bx is a heterocyclic base moiety;

T_3 and T_4 are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_3 and T_4 is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

q_1 , q_2 , q_3 , q_4 , q_5 , q_6 and q_7 are each, independently, H, 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 C_2 - C_6 alkynyl; and

one of R_1 and R_2 is hydrogen and the other is selected from halogen, substituted or unsubstituted alkoxy, NJ_1J_2 , SJ_1 , N_3 , $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, and CN, wherein X is O, S, or NJ_1 , and each J_1 , J_2 , and J_3 is,

independently, H or C₁-C₆ alkyl.

[0261] As disclosed herein, the modified THP nucleosides of Formula X are provided wherein q_m, q_n, q_p, q_r, q_s, q_t, and q_u are each H. In certain instances, at least one of q_m, q_n, q_p, q_r, q_s, q_t, and q_u is other than H. In certain instances, at least one of q_m, q_n, q_p, q_r, q_s, q_t and q_u is methyl. In certain instances, THP nucleosides of Formula X are provided wherein one of R₁ and R₂ is F. In certain instances, R₁ is fluoro and R₂ is H, R₁ is methoxy and R₂ is H, and R₁ is methoxyethoxy and R₂ is H.

[0262] 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.

[0263] As used herein, "2'-F" refers to a sugar comprising a fluoro group at the 2' position.

[0264] 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.

[0265] As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain instances, one or more of the plurality of nucleosides is modified. In certain instances, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA).

[0266] 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, e.g., review article: Leumann, J. C, Bioorganic & Medicinal Chemistry, 2002, 10, 841-854). Such ring systems can undergo various additional substitutions to enhance activity.

[0267] Methods for the preparations of modified sugars are well known to those skilled in the art.

[0268] 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.

[0269] As disclosed herein, antisense compounds comprise one or more nucleotides having modified sugar moieties. In certain disclosures, the modified sugar moiety is 2'-MOE. In certain disclosures, the 2'-MOE modified nucleotides are arranged in a gapmer motif. In certain disclosures, the modified sugar moiety is a cEt. In certain disclosures, the cEt modified nucleotides are arranged throughout the wings of a gapmer motif.

Compositions and Methods for Formulating Pharmaceutical Compositions

[0270] Antisense oligonucleotides may be admixed with pharmaceutically acceptable active or inert substances 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.

[0271] An antisense compound targeted to a STAT3 nucleic acid can be utilized in pharmaceutical compositions by combining the antisense compound with a suitable pharmaceutically acceptable diluent or carrier. 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 embodiment, employed in the methods described herein is a pharmaceutical composition comprising an antisense compound targeted to a STAT3 nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is PBS. In certain embodiments, the antisense compound is an antisense oligonucleotide.

[0272] Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other 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.

[0273] 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

[0274] Antisense compounds may 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.

[0275] 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.

Certain Antisense Compounds

[0276] In certain disclosures, antisense compounds useful for treating B-cell lymphoma at the doses and dosing regimens described above include any of the antisense oligonucleotides described in WO 2012/135736. Examples of antisense compounds described in WO 2012/135736 suitable for treating B-cell lymphoma include, but are not limited to, those described in Tables 1 & 2 below:

Table 1

cEt and MOE chimeric antisense oligonucleotides targeted to STAT3 (SEQ ID NO: 1)						
ISIS NO	Human Start Site	Human Stop Site	Sequence	Motif	Wing Chem	SEQ ID NO
481355	322	337	ACTGCCGCAGCTCCAT	3-10-3	cEt	3
481597	731	744	GAGATTCTCTACCA	2-10-2	cEt	4
481374	788	803	AGATCTTGCATGTCTC	3-10-3	cEt	5
481390	1305	1320	ATAATTCAACTCAGGG	3-10-3	cEt	6
481420	1948	1963	ACTTTTTCACAAGGTC	3-10-3	cEt	7
481431	2206	2221	CCATGATCTTATAGCC	3-10-3	cEt	8
481453	2681	2696	GATAGCAGAAGTAGGA	3-10-3	cEt	9
481463	3001	3016	CAAGGTTAAAAAGTGC	3-10-3	cEt	10
481688	3002	3015	AAGGTTAAAAAGTG	2-10-2	cEt	11
481464	3016	3031	CTATTTGGATGTCAGC	3-10-3	cEt	12
481689	3017	3030	TATTTGGATGTCAG	2-10-2	cEt	13
481465	3032	3047	TAGATAGTCCTATCTT	3-10-3	cEt	14
481690	3033	3046	AGATAGTCCTATCT	2-10-2	cEt	15
481466	3047	3062	AAGAAACCTAGGGCTT	3-10-3	cEt	16
481691	3048	3061	AGAAACCTAGGGCT	2-10-2	cEt	17
481467	3097	3112	GCTGATACAGTGTTTT	3-10-3	cEt	18
481692	3098	3111	CTGATACAGTGTTT	2-10-2	cEt	19
481468	3112	3127	ATACAGAAAGGCTATG	3-10-3	cEt	20
481693	3113	3126	TACAGAAAGGCTAT	2-10-2	cEt	21
481469	3127	3142	GCTTAAGTTTCTTAAA	3-10-3	cEt	22
481694	3128	3141	CTTAAGTTTCTTAA	2-10-2	cEt	23
481470	3461	3476	AGCACCAAGGAGGCTG	3-10-3	cEt	24
481695	3462	3475	GCACCAAGGAGGCT	2-10-2	cEt	25
481471	3476	3491	AAGCTGAATGCTTAAA	3-10-3	cEt	26
481696	3477	3490	AGCTGAATGCTTAA	2-10-2	cEt	27

(continued)

cEt and MOE chimeric antisense oligonucleotides targeted to STAT3 (SEQ ID NO: 1)						
	ISIS NO	Human Start Site	Human Stop Site	Sequence	Motif	Wing Chem
5	481472	3491	3506	TTACCAGCCTGAAGGA	3-10-3	cEt
	481697	3492	3505	TACCAGCCTGAAGG	2-10-2	cEt
	481473	3506	3521	CAGGGATTATATAAAT	3-10-3	cEt
10	481698	3507	3520	AGGGATTATATAAA	2-10-2	cEt
	481474	3521	3536	ACCTGAAGCCCGTTTC	3-10-3	cEt
	481699	3522	3535	CCTGAAGCCCGTTT	2-10-2	cEt
15	481475	3536	3551	TGTCTTAAGGGTTTGA	3-10-3	cEt
	481700	3537	3550	GTCTTAAGGGTTTG	2-10-2	cEt
	481476	3551	3566	GGTTGCAGCTTCAGAT	3-10-3	cEt
	481701	3552	3565	GTTGCAGCTTCAGA	2-10-2	cEt
20	481477	3567	3582	TCAACACCAAAGGCCA	3-10-3	cEt
	481702	3568	3581	CAACACCAAAGGCC	2-10-2	cEt
	481478	3585	3600	TCCTTAAACCTTCCTA	3-10-3	cEt
25	481703	3586	3599	CCTTAAACCTTCCT	2-10-2	cEt
	481479	3600	3615	AAAATGCTTAGATTCT	3-10-3	cEt
	481704	3601	3614	AAATGCTTAGATTC	2-10-2	cEt
	481480	3628	3643	AAATAAGTCTATTTAT	3-10-3	cEt
30	481705	3629	3642	AATAAGTCTATTTA	2-10-2	cEt
	481481	3648	3663	GGCCAATACATTACAA	3-10-3	cEt
	481706	3649	3662	GCCAATACATTACA	2-10-2	cEt
35	481482	3670	3685	TGCCCAGCCTTACTCA	3-10-3	cEt
	481707	3671	3684	GCCCAGCCTTACTC	2-10-2	cEt
	481483	3685	3700	GTTGTAAGCACCCCTCT	3-10-3	cEt
	481708	3686	3699	TTGTAAGCACCCCTC	2-10-2	cEt
40	481484	3700	3715	AGAAAGGGAGTCAAGG	3-10-3	cEt
	481709	3701	3714	GAAAGGGAGTCAAG	2-10-2	cEt
	481485	3717	3732	GCAGATCAAGTCCAGG	3-10-3	cEt
45	481710	3718	3731	CAGATCAAGTCCAG	2-10-2	cEt
	481486	3730	3745	AGCCTCTGAAACAGCA	3-10-3	cEt
	481711	3731	3744	GCCTCTGAAACAGC	2-10-2	cEt
	481487	3746	3761	CCCACAGAAACAACCT	3-10-3	cEt
50	481712	3747	3760	CCACAGAAACAACC	2-10-2	cEt
	481488	3761	3776	AGCCCTGATAAGGCAC	3-10-3	cEt
	481713	3762	3775	GCCCTGATAAGGCA	2-10-2	cEt
55	481489	3776	3791	AATCAGAAGTATCCCA	3-10-3	cEt
	481714	3777	3790	ATCAGAAGTATCCC	2-10-2	cEt
	481490	3833	3848	GCCTCTAGCAGGATCA	3-10-3	cEt

(continued)

	cEt and MOE chimeric antisense oligonucleotides targeted to STAT3 (SEQ ID NO: 1)						
	ISIS NO	Human Start Site	Human Stop Site	Sequence	Motif	Wing Chem	SEQ ID NO
5	481715	3834	3847	CCTCTAGCAGGATC	2-10-2	cEt	65
	481491	3848	3863	CACGCAAGGAGACATG	3-10-3	cEt	66
	481716	3849	3862	ACGCAAGGAGACAT	2-10-2	cEt	67
10	481492	3863	3878	TGAGGGACCTTTAGAC	3-10-3	cEt	68
	481717	3864	3877	GAGGGACCTTTAGA	2-10-2	cEt	69
	481493	3886	3901	CAGGATTCCTAAAACA	3-10-3	cEt	70
15	481718	3887	3900	AGGATTCCTAAAAC	2-10-2	cEt	71
	481494	3901	3916	ATGAGGTCCTGAGACC	3-10-3	cEt	72
	481719	3902	3915	TGAGGTCCTGAGAC	2-10-2	cEt	73
	481495	3940	3955	CATCATGTCCAACCTG	3-10-3	cEt	74
20	481720	3941	3954	ATCATGTCCAACCT	2-10-2	cEt	75
	481496	3955	3970	GGGCCCCATAGTGTGC	3-10-3	cEt	76
	481721	3956	3969	GGCCCCATAGTGTG	2-10-2	cEt	77
25	481497	3977	3992	AGCTCAACCAGACACG	3-10-3	cEt	78
	481722	3978	3991	GCTCAACCAGACAC	2-10-2	cEt	79
	481498	3992	4007	GAACCATATTCCCTGA	3-10-3	cEt	80
	481723	3993	4006	AACCATATTCCCTG	2-10-2	cEt	81
30	481499	4007	4022	CAAGAACTGGCTAAG	3-10-3	cEt	82
	481724	4008	4021	AAGAACTGGCTAA	2-10-2	cEt	83
	481500	4022	4037	GCCACTGGATATCACC	3-10-3	cEt	84
35	481501	4048	4063	AACTGAATGAAGACGC	3-10-3	cEt	85
	481523	4489	4504	GCTTATTATGTACTGA	3-10-3	cEt	86
	481748	4490	4503	CTTATTATGTACTG	2-10-2	cEt	87
	481524	4530	4545	GCCCAAGTCTCACCTT	3-10-3	cEt	88
40	481749	4531	4544	CCCAAGTCTCACCT	2-10-2	cEt	89
	481525	4541	4556	CCCAATGGTAAGCCCA	3-10-3	cEt	90
	481750	4542	4555	CCAATGGTAAGCCC	2-10-2	cEt	91
45	481526	4543	4558	AACCCAATGGTAAGCC	3-10-3	cEt	92
	481751	4544	4557	ACCCAATGGTAAGC	2-10-2	cEt	93
	481527	4560	4575	TAGGTCCCTATGATTT	3-10-3	cEt	94
	481752	4561	4574	AGGTCCCTATGATT	2-10-2	cEt	95
50	481528	4579	4594	AAGCCCTGAACCCTCG	3-10-3	cEt	96
	481753	4580	4593	AGCCCTGAACCCTC	2-10-2	cEt	97
	481529	4615	4630	CCTAAGGCCATGAACT	3-10-3	cEt	98
55	481754	4616	4629	CTAAGGCCATGAAC	2-10-2	cEt	99
	481530	4630	4645	ACCAGATACATGCTAC	3-10-3	cEt	100
	481755	4631	4644	CCAGATACATGCTA	2-10-2	cEt	101

(continued)

cEt and MOE chimeric antisense oligonucleotides targeted to STAT3 (SEQ ID NO: 1)						
ISIS NO	Human Start Site	Human Stop Site	Sequence	Motif	Wing Chem	SEQ ID NO
481531	4646	4661	TACAATCAGAGTTAAG	3-10-3	cEt	102
481756	4647	4660	ACAATCAGAGTTAA	2-10-2	cEt	103
481532	4664	4679	TCCTCTCAGAACTTTT	3-10-3	cEt	104
481757	4665	4678	CCTCTCAGAACTTT	2-10-2	cEt	105
481533	4666	4681	GCTCCTCTCAGAACTT	3-10-3	cEt	106
481758	4667	4680	CTCCTCTCAGAACT	2-10-2	cEt	107
481534	4693	4708	TTCTTTAATGGGCCAC	3-10-3	cEt	108
481759	4694	4707	TCTTTAATGGGCCA	2-10-2	cEt	109
481535	4767	4782	ACGGGATTCCCTCGGC	3-10-3	cEt	110
481760	4768	4781	CGGGATTCCCTCGG	2-10-2	cEt	111
481536	4782	4797	GTAGGTAAGCAACCCA	3-10-3	cEt	112
481761	4783	4796	TAGGTAAGCAACCC	2-10-2	cEt	113
481537	4830	4845	GAATTTGAATGCAGTG	3-10-3	cEt	114
481762	4831	4844	AATTTGAATGCAGT	2-10-2	cEt	115
481538	4844	4859	TGAAGTACACATTGGA	3-10-3	cEt	116
481763	4845	4858	GAAGTACACATTGG	2-10-2	cEt	117
481539	4860	4875	ATAAATTTTACACTA	3-10-3	cEt	118
481764	4861	4874	TAAATTTTACACT	2-10-2	cEt	119
481765	4869	4882	CAATAATATAAATT	2-10-2	cEt	120
481541	4934	4949	CTGGAAGTTAAAGTAG	3-10-3	cEt	121
481766	4935	4948	TGGAAGTTAAAGTA	2-10-2	cEt	122

Table 2

Chimeric antisense oligonucleotides targeted to STAT3 (SEQ ID NO: 2)					
Human Start Site	Human Stop Site	ISIS No	Sequence	Chemistry	SEQ ID NO
5701	5716	GTACTCTTTCAGTGGT	529962	e-e-e-d(10)-k-k-k	123
74784	74799	ATGCTTAGATTCTCCT	529979	k-k-k-d(10)-e-e-e	124
74905	74920	AGCAGATCAAGTCCA G	529982	k-k-k-d(10)-e-e-e	125
75423	75438	AGGTGTTCCCATACGC	529983	k-k-k-d(10)-e-e-e	126
75424	75439	TAGGTGTTCCCATACG	529984	k-k-k-d(10)-e-e-e	127
5701	5716	GTACTCTTTCAGTGGT	529999	k-k-k-d(10)-e-e-e	123

(continued)

Chimeric antisense oligonucleotides targeted to STAT3 (SEQ ID NO: 2)					
Human Start Site	Human Stop Site	ISIS No	Sequence	Chemistry	SEQ ID NO
9878	9893	GGTTCCTCCTGTTGGC	530006	k-k-k-d(10)-e-e-e	128
12361	12376	GGTTCCTCCTGTTGGC	530006	k-k-k-d(10)-e-e-e	128
74783	74799	ATGCTTAGATTCTCCT T	530020	e-e-k-d(10)-k-e-k-e	129

Certain Combination Therapies

[0277] In certain embodiments, one or more pharmaceutical compositions provided herein are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease, disorder, or condition as the one or more pharmaceutical compositions provided herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease, disorder, or condition as the one or more pharmaceutical compositions provided herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired side effect of one or more pharmaceutical compositions provided herein. In certain embodiments, one or more pharmaceutical compositions provided herein are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions provided herein are co-administered with another pharmaceutical agent to produce a combinational effect. In certain embodiments, one or more pharmaceutical compositions provided herein are co-administered with another pharmaceutical agent to produce a synergistic effect.

[0278] In certain embodiments, one or more pharmaceutical compositions provided herein and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions provided herein and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions provided herein and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions provided herein and one or more other pharmaceutical agents are prepared separately. In certain embodiments, one or more other pharmaceutical agents include all-trans retinoic acid, azacitidine, azathioprine, bleomycin, carboplatin, capecitabine, cisplatin, chlorambucil, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxorubicin, epirubicin, epothilone, etoposide, fluorouracil, gemcitabine, hydroxyurea, idarubicin, imatinib, mechlorethamine, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, pemetrexed, teniposide, tioguanine, valrubicin, vinblastine, vincristine, vindesine, or vinorelbine. In certain embodiments, one or more other pharmaceutical agents include a combination of cyclophosphamide, hydroxydanorubicin, oncovin (vincristine), prednisone or prednisolone (CHOP). In certain embodiments, one or more other pharmaceutical agents include a combination of rituximab and CHOP (R-CHOP). In certain embodiments, one or more other pharmaceutical agents include another antisense oligonucleotide. In certain embodiments, another antisense oligonucleotide is a second STAT3 antisense oligonucleotide.

[0279] In certain embodiments, one or more other pharmaceutical agents include molecular targeted therapies. In certain embodiments, the molecular targeted therapy is an EGFR inhibitor, a mTOR inhibitor, a HER2 inhibitor, or a VEGF/VEGFR inhibitor. In certain embodiments, EGFR inhibitors include gefitinib, erlotinib, lapatinib, cetuximab, panitumumab. In certain embodiments, mTOR inhibitors include everolimus and temsirolimus. In certain embodiments, HER2 inhibitors include trastuzumab and lapatinib. In certain embodiments, VEGF/VEGFR inhibitors include pazopanib, bevacizumab, sunitinib, and sorafenib.

[0280] In certain embodiments, one or more pharmaceutical compositions provided herein are administered with radiation therapy. In certain embodiments, one or more pharmaceutical compositions are administered at the same time as radiation therapy. In certain embodiments, one or more pharmaceutical compositions are administered before radiation therapy. In certain embodiments, one or more pharmaceutical compositions are administered after radiation therapy. In certain embodiments, one or more pharmaceutical compositions are administered at various time points throughout a radiation therapy regimen.

[0281] In certain embodiments, radiation therapy is useful for inhibiting tumor growth. In certain embodiments, radiation therapy is useful for increasing overall survival. In certain embodiments, radiation therapy used in conjunction with administration of one or more pharmaceuticals provided herein is advantageous over using either therapy alone because

both radiation therapy and administration with one or more pharmaceuticals can be limited to achieve effective antiproliferative response with limited toxicity.

[0282] In certain instances, a physician designs a therapy regimen including both radiation therapy and administration of one or more pharmaceutical compositions provided herein. In certain instances, a physician designs a therapy regimen including radiation therapy, administration of one or more pharmaceutical compositions provided herein, and administration of one or more other chemotherapeutic agents.

EXAMPLES

Non-limiting disclosure

[0283] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following example 1 serves only to illustrate certain embodiments described herein and is not intended to limit the same.

Example 1: Phase 1, open-label, study for treating a patient having advanced B cell lymphoma with a STAT3 antisense oligonucleotide

[0284] The effect of intravenous infusion of the STAT3 antisense oligonucleotide, ISIS 481464, in patients with advanced B cell lymphomas was studied. Patients with diffuse large B-cell lymphomas (DLBCL) were recruited for this study.

[0285] The criteria for patient inclusion with respect to their tumor status was that the tumors should be relapsed or refractory to at least one prior anti-cancer systemic therapy, and/or for which no standard therapy exists; that their disease should be measurable or evaluable, according to RECIST version 1.1 for solid tumors, or according to the International Workshop Response Criteria for Non-Hodgkin's Lymphoma for NHL tumors (Cheson, B.D. et al., J. Clin. Oncol. 1999, 17: 1244; Cheson, B.D. et al., J. Clin. Oncol. 2007, 25(5):579-86), or according to appropriate criteria for other advanced cancers. RECIST (Response Evaluation Criteria in Solid Tumors) is an internationally accepted set of guidelines used in clinical trials for solid tumor disease.

[0286] One patient fitting the criteria above is a 63 year old female with DLBCL designated herein as Patient #1001. Prior to commencing therapy, Patient #1001 showed multiple areas of hypermetabolic adenopathy, both above and below the diaphragm, including the supraclavicular, left paratracheal, right internal mammary, pericardial, left intramammary, pre-hepatic, retroperitoneal, and mesenteric regions. In addition, the patient suffered from fatigue, nausea, night sweats, shortness of breath on exertion, and peripheral neuropathy. The patient also noted 5-6 days of right-sided abdominal fullness and associated pain. Patient therapy was commenced with a treatment period comprising administration during a first phase of 3 loading doses of ISIS 481464: a 3-hr intravenous infusion of 2 mg/kg ideal body weight of ISIS 481464 administered on days 1, 3, and 5 of cycle 0. The ideal body weight was determined using the Devine formula (Pai, M.P. and Paloucek, F.P. Ann. Pharmacol. 2000, 34: 1066-1069): for men (in kg) = $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$; for women (in kg) = $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$. Treatment was then continued in a second phase by once-weekly administrations (Cycle 1 and beyond) of 2 mg/kg ideal body weight of ISIS 481464 until disease progression, unacceptable toxicity, or patient discontinuation for any other reason occurred. Disease assessments were performed at the end of even cycles.

[0287] Tumor lesions were evaluated on each even-numbered cycle, starting with Cycle 2, day 15, by positron emission tomography (PET) scan. According to RECIST guidelines, a complete tumor response is achieved when all target lesions have disappeared. Partial response is achieved when the sum of the diameters of all tumor lesions is reduced at least 30% compared to the sum of the tumor lesion diameters at pre-dose. The sum of the lesion diameters, if any, was calculated, per RECIST guidelines (Eisenhauer, E.A. et al., Eur. J. Cancer 45: 228-247, 2009).

[0288] After 28 days of treatment with ISIS 481464, the patient reported reduced fatigue and night sweats, and was tolerating the treatment well.

[0289] After 49 days of treatment with ISIS 481464, a PET scan was performed and revealed a 55% reduction in tumor size. Tumors were reduced in all compartments, but most notably, in the supraclavicular, paratracheal, pericardial, and mesenteric regions.

[0290] After 91 days of treatment with ISIS 481464, Patient #1001 had a second PET scan and the partial response observed in the first scan was found to be maintained at a 55% reduction in tumor size.

[0291] After 133 days of treatment with ISIS 481464, Patient #1001 had a third PET scan and the partial response was found to be maintained at a 55% reduction in tumor size.

[0292] After 162 days of treatment with ISIS 481464, further treatment was paused for a month during which Patient #1001 had a fourth PET scan, and the partial response was maintained at a 55% reduction in tumor size. Patient #1001 is scheduled for further scans.

Example 2 (not illustrating the invention): Phase 1, open-label, study for treating a patient having advanced/metastatic hepatocellular carcinoma with a STAT3 antisense oligonucleotide

[0293] The effect of intravenous infusion of the STAT3 antisense oligonucleotide, ISIS 481464, in patients with advanced/metastatic hepatocellular carcinoma is being studied in an on-going clinical trial.

[0294] In the study described in this protocol, AZD9150 will be administered to patients with advanced/metastatic hepatocellular carcinoma at a starting dose of 1 mg/kg intravenously 3x during week 1 followed by 1x weekly and dose intensity will be escalated or de-escalated in subsequent cohorts through modification of unit dose administered and/or interval of administration to determine a maximum tolerated dose and recommended phase II dose in patients with advanced/metastatic hepatocellular carcinoma (HCC).

[0295] Following the dose escalation phase of the study additional patients will be enrolled to a dose expansion phase to explore further the safety, tolerability, pharmacokinetics and biological activity at selected dose(s)/schedules. Patients included in the study are relapsed, refractory, intolerant or unlikely to benefit from first-line systemic therapy (sorafenib).

[0296] To date, the 1 mg/kg and 1.5 mg/kg cohorts have completed. From the 1 mg/kg cohort 4 patients remain on study with stable disease in excess of 3 months. Stable disease has also been seen in 1.5 mg/kg cohort. These patients and future patients will be monitored further for clinical activity as the trial progresses.

SEQUENCE LISTING

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REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Antisense-forbindelse, der er komplementær til human STAT3, til anvendelse i en fremgangsmåde til behandling af B-cellelymfom hos en person, der har brug for det, hvor fremgangsmåden omfatter administrering til personen af antisense-forbindelsen i en første fase og herefter en anden fase, hvor den første fase medfører administrering af en samlet ugentlig dosis af forbindelsen i intervallet 100-750 mg ($\pm 12\%$) i de første 1-10 uger, og den anden fase medfører administrering af en samlet ugentlig dosis i intervallet 100-250 mg ($\pm 12\%$) i mindst 1 uge efter den første fase; og hvor antisense-forbindelsen er et enkeltstrenget modificeret oligonukleotid, der består af 16 koblede nukleosider med en nukleobasesekvens, der består af SEQ ID NO: 12, som omfatter: et gapsegment, der består af 10 koblede deoxynukleosider; et 5'-vingesegment, der består af 3 koblede nukleosider; og et 3'-vingesegment, der består af 3 koblede nukleosider; hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet; hvor hvert nukleosid i hvert vingesegment omfatter et indskrænket ethylnukleosid; hvor hver internukleosidkobling i det modificerede oligonukleotid er en phosphorothioat-kobling; og hvor hver cytosin i det modificerede oligonukleotid er en 5-methylcytosin.
2. Forbindelse til anvendelse ifølge krav 1, hvor B-cellelymfomet er et ikke-Hodgkins B-cellelymfom.
3. Forbindelse til anvendelse ifølge krav 2, hvor ikke-Hodgkins B-cellelymfomet er et diffust storcellet B-cellelymfom (DLBCL).
4. Forbindelse til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den første fase er 1 uge.
5. Forbindelse til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den første fase omfatter administrering af forbindelsen i 3 lige store doser inden for en uge.

6. Forbindelse til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den samlede ugentlige dosis af antisense-forbindelsen i den første fase er en hvilken som helst mængde af 100 mg ($\pm 12\%$), 125 mg ($\pm 12\%$), 150 mg ($\pm 12\%$), 175 mg ($\pm 12\%$), 200 mg ($\pm 12\%$), 225 mg ($\pm 12\%$), 250 mg ($\pm 12\%$), 275 mg ($\pm 12\%$), 300 mg ($\pm 12\%$), 325 mg ($\pm 12\%$), 350 mg ($\pm 12\%$), 375 mg ($\pm 12\%$), 400 mg ($\pm 12\%$), 425 mg ($\pm 12\%$), 450 mg ($\pm 12\%$), 475 mg ($\pm 12\%$), 500 mg ($\pm 12\%$), 525 mg ($\pm 12\%$), 550 mg ($\pm 12\%$), 575 mg ($\pm 12\%$), 600 mg ($\pm 12\%$), 625 mg ($\pm 12\%$), 650 mg ($\pm 12\%$), 675 mg ($\pm 12\%$), 700 mg ($\pm 12\%$), 725 mg ($\pm 12\%$) eller 750 mg ($\pm 12\%$).
7. Forbindelse til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den samlede ugentlige dosis af antisense-forbindelsen i den anden fase er en hvilken som helst mængde af 100 mg ($\pm 12\%$), 110 mg ($\pm 12\%$), 120 mg ($\pm 12\%$), 130 mg ($\pm 12\%$), 140 mg ($\pm 12\%$), 150 mg ($\pm 12\%$), 160 mg ($\pm 12\%$), 170 mg ($\pm 12\%$), 180 mg ($\pm 12\%$), 190 mg ($\pm 12\%$), 200 mg ($\pm 12\%$), 210 mg ($\pm 12\%$), 220 mg ($\pm 12\%$), 230 mg ($\pm 12\%$), 240 mg ($\pm 12\%$) eller 250 mg ($\pm 12\%$).
8. Forbindelse til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den samlede ugentlige dosis af antisense-forbindelsen i den første fase er en mængde på 600 mg ($\pm 12\%$).
9. Forbindelse til anvendelse ifølge et hvilket som helst af ovennævnte krav, hvor den samlede ugentlige dosis af antisense-forbindelsen i den anden fase er en mængde på 200 mg ($\pm 12\%$).