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(54) Title: MODULATORS OF COMPLEMENT FACTOR B

(57) Abstract: The present embodiments provide methods, compounds, and compositions for treating, preventing, or ameliorating a disease associated with dysregulation of the complement alternative pathway by administering a Complement Factor B (CFB) specific inhibitor to a subject.

MODULATORS OF COMPLEMENT FACTOR B

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0183WOSEQ_ST25.txt created September 11, 2014, which is 225 kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

The present embodiments provide methods, compounds, and compositions for treating, preventing, or ameliorating a disease associated with dysregulation of the complement alternative pathway by administering a Complement Factor B (CFB) specific inhibitor to a subject.

Background

The complement system is part of the host innate immune system involved in lysing foreign cells, enhancing phagocytosis of antigens, clumping antigen-bearing agents, and attracting macrophages and neutrophils. The complement system is divided into three initiation pathways—the classical, lectin, and alternative pathways—that converge at component C3 to generate an enzyme complex known as C3 convertase, which cleaves C3 into C3a and C3b. C3b associates with C3 convertase mediated by CFB and results in generation of C5 convertase, which cleaves C5 into C5a and C5b, which initiates the membrane attack pathway resulting in the formation of the membrane attack complex (MAC) comprising components C5b, C6, C7, C8, and C9. The membrane-attack complex (MAC) forms transmembrane channels and disrupts the phospholipid bilayer of target cells, leading to cell lysis.

In the homeostatic state, the alternative pathway is continuously activated at a low "tickover" level as a result of activation of the alternative pathway by spontaneous hydrolysis of C3 and the production of C3b, which generates C5 convertase.

Summary

The complement system mediates innate immunity and plays an important role in normal inflammatory response to injury, but its dysregulation may cause severe injury. Activation of the alternative complement pathway beyond its constitutive "tickover" level can lead to unrestrained hyperactivity and manifest as diseases of complement dysregulation.

Certain embodiments provided herein relate to methods of treating, preventing, or ameliorating a disease associated with dysregulation of the complement alternative pathway in a subject by administration of a Complement Factor B (CFB) specific inhibitor. Several embodiments provided herein are drawn to a method of inhibiting expression of CFB in a subject having, or at risk of having, a disease associated with dysregulation of the complement alternative pathway by administering a CFB specific inhibitor to the subject. In certain embodiments, a method of reducing or inhibiting accumulation of C3 deposits in the eye of a subject having, or at risk of having, a disease associated with dysregulation of the complement alternative pathway comprises administering a CFB specific inhibitor to the subject. In several embodiments, a method of reducing or inhibiting accumulation of C3 deposits in the kidney of a subject having, or at risk of having, a disease associated with dysregulation of the complement alternative pathway comprises administering a CFB specific inhibitor to the subject.

Detailed Description

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. 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.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

"2'-O-methoxyethyl" (also 2'-MOE and 2'-$O(CH_2)_2$-OCH_3) refers to an O-methoxy-ethyl modification at the 2' position of a furanose ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

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

"2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position of the furanosyl ring other than H or OH. In certain embodiments, 2' substituted nucleosides include nucleosides with bicyclic sugar modifications.

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

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

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

"About" means within ±10% of a value. For example, if it is stated, "the compounds affected at least about 70% inhibition of CFB", it is implied that CFB levels are inhibited within a range of 60% and 80%.

"Administration" or "administering" refers to routes of introducing an antisense compound provided herein to a subject to perform its intended function. An example of a route of administration that can be used includes, but is not limited to parenteral administration, such as subcutaneous, intravenous, or intramuscular injection or infusion.

"Amelioration" refers to a lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. In certain embodiments, amelioration includes a delay or slowing in the progression of one or more indicators of a condition or disease. The severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

"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.

"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.

"Antisense compound" means an oligomeric compound that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding. Examples of antisense compounds include single-stranded and double-stranded compounds, such as, antisense oligonucleotides, siRNAs, shRNAs, ssRNAs, and occupancy-based compounds.

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

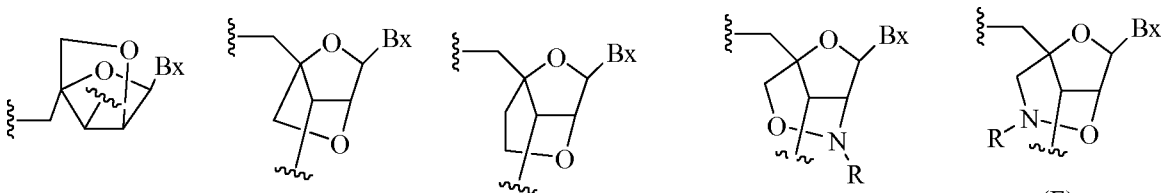
"Antisense mechanisms" are all those mechanisms involving hybridization of a compound with target nucleic acid, wherein the outcome or effect of the hybridization is either target degradation or target occupancy with concomitant stalling of the cellular machinery involving, for example, transcription or splicing.

"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.

"Base complementarity" refers to the capacity for the precise base pairing of nucleobases of an antisense oligonucleotide with corresponding nucleobases in a target nucleic acid (i.e., hybridization), and is mediated by Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen binding between corresponding nucleobases.

"Bicyclic sugar moiety" means a modified sugar moiety comprising a 4 to 7 membered ring (including but not limited to a furanosyl) comprising a bridge connecting two atoms of the 4 to 7 membered ring to form a second ring, resulting in a bicyclic structure. In certain embodiments, the 4 to 7 membered ring is a sugar ring. In certain embodiments the 4 to 7 membered ring is a furanosyl. In certain such embodiments, the bridge connects the 2'-carbon and the 4'-carbon of the furanosyl.

"Bicyclic nucleic acid" or " BNA" or "BNA nucleosides" means nucleic acid monomers having a bridge connecting two carbon atoms between the 4' and 2'position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to A) α-L-Methyleneoxy (4'-CH_2-O-2') LNA , (B) β-D-Methyleneoxy (4'-CH_2-O-2') LNA , (C) Ethyleneoxy (4'-$(CH_2)_2$-O-2') LNA , (D) Aminooxy (4'-CH_2-O-N(R)-2') LNA and (E) Oxyamino (4'-CH_2-N(R)-O-2') LNA, as depicted below.



As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-[C(R_1)(R_2)]_n-$, $-C(R_1)=C(R_2)-$, $-C(R_1)=N-$, $-C(=NR_1)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_1)_2-$, $-S(=O)_x-$ and $-N(R_1)-$; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 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, a heterocycle radical, a 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 (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-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 (C(=O)-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.

Examples of 4'- 2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: -[C(R_1)(R_2)]$_n$-, -[C(R_1)(R_2)]$_n$-O-, -C(R_1R_2)-N(R_1)-O- or –C(R_1R_2)-O-N(R_1)-. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R_1)-2' and 4'-CH_2-N(R_1)-O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a methyleneoxy (4'-CH_2-O-2') bridge to form the bicyclic sugar moiety. The bridge can also be a methylene (-CH_2-) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2-O-2') LNA is used. Furthermore; in the case of the bicylic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2-O-2') LNA is used. α -L- methyleneoxy (4'-CH_2-O-2'), an isomer of methyleneoxy (4'-CH_2-O-2') LNA is also encompassed within the definition of LNA, as used herein.

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

"cEt" or "constrained ethyl" means a bicyclic sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-CH(CH_3)-O-2'.

"Constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH_3)-O-2' bridge.

"Complement Factor B (CFB)" means any nucleic acid or protein of CFB. "CFB nucleic acid" means any nucleic acid encoding CFB. For example, in certain embodiments, a CFB nucleic acid includes a DNA sequence encoding CFB, an RNA sequence transcribed from DNA encoding CFB (including genomic DNA comprising introns and exons), including a non-protein encoding (*i.e.* non-coding) RNA sequence, and an mRNA sequence encoding CFB. "CFB mRNA" means an mRNA encoding a CFB protein.

"CFB specific inhibitor" refers to any agent capable of specifically inhibiting CFB RNA and/or CFB protein expression or activity at the molecular level. For example, CFB specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of CFB RNA and/or CFB protein.

"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.

"Chimeric antisense compounds" means antisense compounds that have at least 2 chemically distinct regions, each position having a plurality of subunits.

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

"Comprise," "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

"Contiguous nucleobases" means nucleobases immediately adjacent to each other.

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

"Designing" or "Designed to" refer to the process of designing an oligomeric compound that specifically hybridizes with a selected nucleic acid molecule.

"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.

"Efficacy" means the ability to produce a desired effect.

"Expression" includes all the functions by which a gene's coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to the products of transcription and translation.

"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.

"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."

"Hybridization" means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound

and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense oligonucleotide and a nucleic acid target.

"Identifying an animal having, or at risk for having, a disease, disorder and/or condition" means identifying an animal having been diagnosed with the disease, disorder and/or condition or identifying an animal predisposed to develop the disease, disorder and/or condition. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments.

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

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

"Inhibiting the expression or activity" refers to a reduction, blockade of the expression or activity and does not necessarily indicate a total elimination of expression or activity.

"Internucleoside linkage" refers to the chemical bond between nucleosides.

"Lengthened" antisense oligonucleotides are those that have one or more additional nucleosides relative to an antisense oligonucleotide disclosed herein.

"Linked deoxynucleoside" means a nucleic acid base (A, G, C, T, U) substituted by deoxyribose linked by a phosphate ester to form a nucleotide.

"Linked nucleosides" means adjacent nucleosides linked together by an internucleoside linkage.

"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.

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

"Modified nucleobase" means 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).

"Modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase.

"Modified nucleotide" means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, or modified nucleobase.

"Modified oligonucleotide" means an oligonucleotide comprising at least one modified internucleoside linkage, a modified sugar, and/or a modified nucleobase.

"Modified sugar" means substitution and/or any change from a natural sugar moiety.

"Modulating" refers to changing or adjusting a feature in a cell, tissue, organ or organism. For example, modulating CFB mRNA can mean to increase or decrease the level of CFB mRNA and/or CFB protein in a cell, tissue, organ or organism. A "modulator" effects the change in the cell, tissue, organ or organism. For example, a CFB antisense compound can be a modulator that decreases the amount of CFB mRNA and/or CFB protein in a cell, tissue, organ or organism.

"Monomer" refers to a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occuring or modified.

"Motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

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

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

"Non-complementary nucleobase" refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

"Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, and double-stranded nucleic acids.

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

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

"Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, and/or nucleobase modification.

"Nucleoside" means a nucleobase linked to a sugar.

"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. "Mimetic" refers to groups that are substituted for a sugar, a nucleobase, and/or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

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

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

"Oligonucleoside" means an oligonucleotide in which the internucleoside linkages do not contain a phosphorus atom.

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

"Parenteral administration" means administration through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration.

"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.

"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.

"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 is a modified internucleoside linkage.

"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

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

"Prophylactically effective amount" refers to an amount of a pharmaceutical agent that provides a prophylactic or preventative benefit to an animal.

"Region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic.

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

"Segments" are defined as smaller or sub-portions of regions within a target nucleic acid.

"Side effects" means physiological disease and/or conditions 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.

"Sites," as used herein, are defined as unique nucleobase positions within a target nucleic acid.

"Slows progression" means decrease in the development of the said disease.

"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. "Stringent hybridization conditions" or "stringent conditions" refer to conditions under which an oligomeric compound will hybridize to its target sequence, but to a minimal number of other sequences.

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

"Target" refers to a protein, the modulation of which is desired.

"Target gene" refers to a gene encoding a target.

"Targeting" 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.

"Target nucleic acid," "target RNA," "target RNA transcript" and "nucleic acid target" all mean a nucleic acid capable of being targeted by antisense compounds.

"Target region" means a portion of a target nucleic acid to which one or more antisense compounds is targeted.

"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.

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

"Treat" refers to administering a pharmaceutical composition to an animal in order to effect an alteration or improvement of a disease, disorder, or condition in the animal. In certain embodiments, one or more pharmaceutical compositions can be administered to the animal.

"Unmodified" nucleobases mean the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U).

"Unmodified nucleotide" means a nucleotide composed of naturally occuring 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 Embodiments

Certain embodiments provide methods, compounds and compositions for inhibiting Complement Factor B (CFB) expression.

Certain embodiments provide antisense compounds targeted to a CFB nucleic acid. In certain embodiments, the CFB nucleic acid has the sequence set forth in GENBANK Accession No. NM_001710.5 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No NW_001116486.1 truncated from nucleotides 536000 to 545000 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. XM_001113553.2 (incorporated herein as SEQ ID NO: 4), or GENBANK Accession No. NM_008198.2 (incorporated herein as SEQ ID NO: 5).

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 9 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 10 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 11 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of the nucleobase sequence of any one of SEQ ID NOs: 6-808.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides complementary within nucleobases 30-49, 48-63, 150-169, 151-170, 152-171, 154-169, 154-173, 156-171, 156-175, 157-176, 158-173, 158-177, 480-499, 600-619, 638-657, 644-663, 738-757, 1089-1108, 1135-1154, 1141-1160, 1147-1166, 1150-1169, 1153-1172, 1159-1178, 1162-1181, 1165-1184, 1171-1186, 1171-1190, 1173-1188, 1173-1192, 1175-1190, 1175-1194, 1177-1196, 1183-1202, 1208-1227, 1235-1254, 1298-1317, 1304-1323, 1310-1329, 1316-1335, 1319-1338, 1322-1341, 1328-1347, 1349-1368, 1355-1374, 1393-1412, 1396-1415, 1399-1418, 1405-1424, 1421-1440, 1621-1640, 1646-1665, 1646-1665, 1647-1666, 1689-1708, 1749-1768, 1763-1782, 1912-1931, 2073-2092, 2085-2104, 2166-2185, 2172-2191, 2189-2208, 2191-2210, 2193-2212, 2195-2210, 2195-2214, 2196-2215, 2197-2212, 2197-2216, 2202-2221, 2223-2238, 2223-2242, 2225-2240, 2226-2245, 2227-2242, 2227-2246, 2238-2257, 2241-2260, 2267-2286, 2361-2380, 2388-2407, 2397-2416, 2448-2467, 2453-2472, 2455-2474, 2457-2472, 2457-2476, 2459-2474, 2459-2478, 2461-2476, 2461-2480, 2532-2551, 2550-2569, 2551-2566, 2551-2570, 2552-2568, 2552-2570, 2552-2571, 2553-2568, 2553-2570, 2553-2571, 2553-2572, 2554-2571, 2554-2572, 2554-2573, 2555-2570, 2555-2572, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2573, 2557-2574, 2557-2575, 2557-2576, 2558-2575, 2558-2576, 2558-2577, 2559-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2576, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2578, 2563-2580,

2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2566-2585, 2567-2582, 2567-2584, 2567-2586, 2568-2583, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2585, 2570-2587, 2570-2589, 2571-2586, 2571-2588, 2571-2590, 2572-2589, 2572-2590, 2572-2591, 2573-2590, 2573-2592, 2574-2590, 2574-2591, 2574-2593, 2575-2590, 2575-2591, 2575-2592, 2575-2594, 2576-2593, 2576-2595, 2577-2594, 2577-2595, 2577-2596, 2578-2594, 2578-2596, 2578-2597, 2579-2598, 2580-2596, 2580-2597, 2580-2598, 2580-2599, 2581-2597, 2581-2598, 2581-2599, 2581-2600, 2582-2598, 2582-2599, 2582-2600, 2582-2601, 2583-2599, 2583-2600, 2583-2601, 2583-2602, 2584-2600, 2584-2601, 2584-2602, 2584-2603, 2585-2601, 2585-2603, 2585-2604, 2586-2601, 2586-2602, 2586-2604, 2586-2605, 2587-2602, 2587-2603, 2587-2605, 2587-2606, 2588-2603, 2588-2604, 2588-2605, 2588-2606, 2588-2607, 2589-2604, 2589-2605, 2589-2606, 2589-2607, 2589-2608, 2590-2605, 2590-2606, 2590-2607, 2590-2608, 2590-2609, 2590-2609, 2591-2607, 2591-2608, 2591-2609, 2591-2610, 2592-2607, 2592-2608, 2592-2609, 2592-2610, 2592-2611, 2593-2608, 2593-2609, 2593-2610, 2593-2612, 2594-2609, 2594-2610, 2594-2611, 2594-2612, 2594-2613, 2595-2610, 2595-2611, 2595-2612, 2595-2613, 2595-2614, 2596-2611, 2596-2612, 2596-2613, 2596-2614, 2596-2615, 2597-2612, 2597-2612, 2597-2613, 2597-2614, 2597-2615, 2597-2616, 2598-2613, 2598-2614, 2598-2615, 2598-2616, 2598-2617, 2599-2614, 2599-2615, 2599-2616, 2599-2617, 2599-2618, 2600-2615, 2600-2616, 2600-2617, 2600-2618, 2600-2619, 2601-2616, 2601-2617, 2601-2618, 2601-2619, 2601-2620, 2602-2617, 2602-2618, 2602-2619, 2602-2620, 2602-2621, 2603-2618, 2603-2619, 2603-2620, 2603-2621, 2603-2622, 2604-2619, 2604-2620, 2604-2621, 2604-2622, 2604-2623, 2605-2620, 2605-2621, 2605-2622, 2605-2623, 2605-2624, 2606-2621, 2606-2622, 2606-2623, 2606-2624, 2606-2625, 2607-2622, 2607-2623, 2607-2624, 2607-2625, 2607-2626, 2608-2623, 2608-2624, 2608-2625, 2608-2626, 2608-2627, 2609-2624, 2609-2625, 2609-2626, 2609-2627, 2609-2628, 2610-2625, 2610-2626, 2610-2627, 2610-2628, 2610-2629, 2611-2626, 2611-2627, 2611-2628, 2611-2629, 2611-2630, 2612-2627, 2612-2628, 2612-2629, 2612-2630, 2612-2631, 2613-2628, 2613-2629, 2613-2630, 2613-2631, 2614-2629, 2614-2630, 2614-2631, 2615-2630, 2615-2631, or 2616-2631 of SEQ ID NO: 1, wherein said modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 1.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases complementary to an equal length portion of nucleobases 30-49, 48-63, 150-169, 151-170, 152-171, 154-169, 154-173, 156-171, 156-175, 157-176, 158-173, 158-177, 480-499, 600-619, 638-657, 644-663, 738-757, 1089-1108, 1135-1154, 1141-1160, 1147-1166, 1150-1169, 1153-1172, 1159-1178, 1162-1181, 1165-1184, 1171-1186, 1171-1190, 1173-1188, 1173-1192, 1175-1190, 1175-1194, 1177-1196, 1183-1202, 1208-1227, 1235-1254, 1298-1317, 1304-1323, 1310-1329, 1316-1335, 1319-1338, 1322-1341, 1328-1347, 1349-1368, 1355-1374, 1393-1412, 1396-1415, 1399-1418, 1405-1424, 1421-1440, 1621-1640, 1646-1665, 1646-1665, 1647-1666, 1689-1708, 1749-1768, 1763-1782, 1912-1931, 2073-2092, 2085-2104, 2166-2185, 2172-2191, 2189-2208, 2191-2210, 2193-2212, 2195-2210, 2195-2214, 2196-2215, 2197-2212, 2197-2216,

2202-2221, 2223-2238, 2223-2242, 2225-2240, 2226-2245, 2227-2242, 2227-2246, 2238-2257, 2241-2260, 2267-2286, 2361-2380, 2388-2407, 2397-2416, 2448-2467, 2453-2472, 2455-2474, 2457-2472, 2457-2476, 2459-2474, 2459-2478, 2461-2476, 2461-2480, 2532-2551, 2550-2569, 2551-2566, 2551-2570, 2552-2568, 2552-2570, 2552-2571, 2553-2568, 2553-2570, 2553-2571, 2553-2572, 2554-2571, 2554-2572, 2554-2573, 2555-2570, 2555-2572, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2573, 2557-2574, 2557-2575, 2557-2576, 2558-2575, 2558-2576, 2558-2577, 2559-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2576, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2578, 2563-2580, 2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2566-2585, 2567-2582, 2567-2584, 2567-2586, 2568-2583, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2585, 2570-2587, 2570-2589, 2571-2586, 2571-2588, 2571-2590, 2572-2589, 2572-2590, 2572-2591, 2573-2590, 2573-2592, 2574-2590, 2574-2591, 2574-2593, 2575-2590, 2575-2591, 2575-2592, 2575-2594, 2576-2593, 2576-2595, 2577-2594, 2577-2595, 2577-2596, 2578-2594, 2578-2596, 2578-2597, 2579-2598, 2580-2596, 2580-2597, 2580-2598, 2580-2599, 2581-2597, 2581-2598, 2581-2599, 2581-2600, 2582-2598, 2582-2599, 2582-2600, 2582-2601, 2583-2599, 2583-2600, 2583-2601, 2583-2602, 2584-2600, 2584-2601, 2584-2602, 2584-2603, 2585-2601, 2585-2603, 2585-2604, 2586-2601, 2586-2602, 2586-2604, 2586-2605, 2587-2602, 2587-2603, 2587-2605, 2587-2606, 2588-2603, 2588-2604, 2588-2605, 2588-2606, 2588-2607, 2589-2604, 2589-2605, 2589-2606, 2589-2607, 2589-2608, 2590-2605, 2590-2606, 2590-2607, 2590-2608, 2590-2609, 2590-2609, 2591-2607, 2591-2608, 2591-2609, 2591-2610, 2592-2607, 2592-2608, 2592-2609, 2592-2610, 2592-2611, 2593-2608, 2593-2609, 2593-2610, 2593-2612, 2594-2609, 2594-2610, 2594-2611, 2594-2612, 2594-2613, 2595-2610, 2595-2611, 2595-2612, 2595-2613, 2595-2614, 2596-2611, 2596-2612, 2596-2613, 2596-2614, 2596-2615, 2597-2612, 2597-2612, 2597-2613, 2597-2614, 2597-2615, 2597-2616, 2598-2613, 2598-2614, 2598-2615, 2598-2616, 2598-2617, 2599-2614, 2599-2615, 2599-2616, 2599-2617, 2599-2618, 2600-2615, 2600-2616, 2600-2617, 2600-2618, 2600-2619, 2601-2616, 2601-2617, 2601-2618, 2601-2619, 2601-2620, 2602-2617, 2602-2618, 2602-2619, 2602-2620, 2602-2621, 2603-2618, 2603-2619, 2603-2620, 2603-2621, 2603-2622, 2604-2619, 2604-2620, 2604-2621, 2604-2622, 2604-2623, 2605-2620, 2605-2621, 2605-2622, 2605-2623, 2605-2624, 2606-2621, 2606-2622, 2606-2623, 2606-2624, 2606-2625, 2607-2622, 2607-2623, 2607-2624, 2607-2625, 2607-2626, 2608-2623, 2608-2624, 2608-2625, 2608-2626, 2608-2627, 2609-2624, 2609-2625, 2609-2626, 2609-2627, 2609-2628, 2610-2625, 2610-2626, 2610-2627, 2610-2628, 2610-2629, 2611-2626, 2611-2627, 2611-2628, 2611-2629, 2611-2630, 2612-2627, 2612-2628, 2612-2629, 2612-2630, 2612-2631, 2613-2628, 2613-2629, 2613-2630, 2613-2631, 2614-2629, 2614-2630, 2614-2631, 2615-2630, 2615-2631, or 2616-2631 of SEQ ID NO:1, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 1.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides complementary within nucleobases 1608-1627, 1685-1704, 1686-1705, 1751-1770, 1769-1784, 1871-1890, 1872-1891, 1873-1892, 1875-1890, 1875-1894, 1877-1892, 1877-1896, 1878-1897,

1879-1894, 1879-1898, 2288-2307, 2808-2827, 2846-2865, 2852-2871, 2946-2965, 3773-3792, 3819-3838, 3825-3844, 3831-3850, 3834-3853, 3837-3856, 3843-3862, 4151-4166, 4151-4170, 4153-4172, 4159-4178, 4184-4203, 4211-4230, 4609-4628, 4612-4631, 4615-4634, 4621-4640, 4642-4661, 4648-4667, 4686-4705, 4689-4708, 4692-4711, 4698-4717, 4714-4733, 5270-5289, 5295-5314, 5296-5315, 5830-5849, 5890-5909, 5904-5923, 6406-6425, 6662-6681, 6674-6693, 6954-6973, 6960-6979, 6977-6996, 6979-6998, 6981-7000, 6983-6998, 6983-7002, 6984-7003, 6985-7000, 6985-7004, 6990-7009, 7122-7141, 7125-7144, 7151-7170, 7353-7372, 7362-7381, 7683-7702, 7688-7707, 7690-7709, 7692-7707, 7692-7711, 7694-7709, 7694-7713, 7696-7711, 7696-7715, 7767-7786, 7785-7804, 7786-7801, 7787-7803, 7787-7805, 7787-7806, 7788-7803, 7788-7805, 7788-7806, 7788-7807, 7789-7806, 7789-7807, 7789-7808, 7790-7805, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7808, 7792-7809, 7792-7810, 7792-7811, 7793-7810, 7793-7811, 7793-7812, 7794-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7811, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7813, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7801-7820, 7802-7817, 7802-7819, 7802-7821, 7803-7818, 7803-7820, 7803-7822, 7804-7821, 7804-7823, 7805-7820, 7805-7822, 7805-7824, 7806-7821, 7806-7823, 7806-7825, 7807-7824, 7807-7825, 7807-7826, 7808-7825, 7808-7827, 7809-7825, 7809-7826, 7809-7828, 7810-7825, 7810-7826, 7810-7827, 7810-7829, 7811-7828, 7811-7830, 7812-7829, 7812-7830, 7812-7831, 7813-7829, 7813-7831, 7813-7832, 7814-7833, 7815-7831, 7815-7832, 7815-7833, 7815-7834, 7816-7832, 7816-7833, 7816-7834, 7816-7835, 7817-7833, 7817-7834, 7817-7835, 7817-7836, 7818-7834, 7818-7835, 7818-7836, 7818-7837, 7819-7835, 7819-7836, 7819-7837, 7819-7838, 7820-7836, 7820-7838, 7820-7839, 7821-7836, 7821-7837, 7821-7839, 7821-7840, 7822-7837, 7822-7838, 7822-7840, 7822-7841, 7823-7838, 7823-7839, 7823-7839, 7823-7840, 7823-7841, 7823-7842, 7824-7839, 7824-7840, 7824-7840, 7824-7841, 7824-7842, 7824-7843, 7825-7840, 7825-7841, 7825-7842, 7825-7843, 7825-7844, 7826-7842, 7826-7843, 7826-7844, 7826-7845, 7827-7842, 7827-7843, 7827-7844, 7827-7845, 7827-7846, 7828-7843, 7828-7844, 7828-7845, 7828-7847, 7829-7844, 7829-7845, 7829-7846, 7829-7847, 7829-7848, 7830-7845, 7830-7846, 7830-7847, 7830-7848, 7830-7849, 7831-7846, 7831-7847, 7831-7848, 7831-7849, 7831-7850, 7832-7847, 7832-7848, 7832-7849, 7832-7850, 7832-7851, 7833-7848, 7833-7849, 7833-7850, 7833-7851, 7833-7852, 7834-7849, 7834-7850, 7834-7851, 7834-7852, 7834-7853, 7835-7850, 7835-7851, 7835-7852, 7835-7853, 7835-7854, 7836-7851, 7836-7852, 7836-7853, 7836-7854, 7836-7855, 7837-7852, 7837-7853, 7837-7854, 7837-7855, 7837-7856, 7838-7853, 7838-7854, 7838-7855, 7838-7856, 7838-7857, 7839-7854, 7839-7855, 7839-7856, 7839-7857, 7839-7858, 7840-7855, 7840-7856, 7840-7857, 7840-7858, 7840-7859, 7841-7856, 7841-7857, 7841-7858, 7841-7859, 7841-7860, 7842-7857, 7842-7858, 7842-7859, 7842-7860, 7842-7861, 7843-7858, 7843-7859, 7843-7860, 7843-7861, 7843-7862, 7844-7859, 7844-7860, 7844-7861, 7844-7862, 7845-7860, 7845-7861, 7845-7862, 7846-7861, or 7846-7862 of SEQ ID NO: 2, wherein said modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 2.

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases complementary to an equal length portion of nucleobases 1608-1627, 1685-1704, 1686-1705, 1751-1770, 1769-1784, 1871-1890, 1872-1891, 1873-1892, 1875-1890, 1875-1894, 1877-1892, 1877-1896, 1878-1897, 1879-1894, 1879-1898, 2288-2307, 2808-2827, 2846-2865, 2852-2871, 2946-2965, 3773-3792, 3819-3838, 3825-3844, 3831-3850, 3834-3853, 3837-3856, 3843-3862, 4151-4166, 4151-4170, 4153-4172, 4159-4178, 4184-4203, 4211-4230, 4609-4628, 4612-4631, 4615-4634, 4621-4640, 4642-4661, 4648-4667, 4686-4705, 4689-4708, 4692-4711, 4698-4717, 4714-4733, 5270-5289, 5295-5314, 5296-5315, 5830-5849, 5890-5909, 5904-5923, 6406-6425, 6662-6681, 6674-6693, 6954-6973, 6960-6979, 6977-6996, 6979-6998, 6981-7000, 6983-6998, 6983-7002, 6984-7003, 6985-7000, 6985-7004, 6990-7009, 7122-7141, 7125-7144, 7151-7170, 7353-7372, 7362-7381, 7683-7702, 7688-7707, 7690-7709, 7692-7707, 7692-7711, 7694-7709, 7694-7713, 7696-7711, 7696-7715, 7767-7786, 7785-7804, 7786-7801, 7787-7803, 7787-7805, 7787-7806, 7788-7803, 7788-7805, 7788-7806, 7788-7807, 7789-7806, 7789-7807, 7789-7808, 7790-7805, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7808, 7792-7809, 7792-7810, 7792-7811, 7793-7810, 7793-7811, 7793-7812, 7794-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7811, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7813, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7801-7820, 7802-7817, 7802-7819, 7802-7821, 7803-7818, 7803-7820, 7803-7822, 7804-7821, 7804-7823, 7805-7820, 7805-7822, 7805-7824, 7806-7821, 7806-7823, 7806-7825, 7807-7824, 7807-7825, 7807-7826, 7808-7825, 7808-7827, 7809-7825, 7809-7826, 7809-7828, 7810-7825, 7810-7826, 7810-7827, 7810-7829, 7811-7828, 7811-7830, 7812-7829, 7812-7830, 7812-7831, 7813-7829, 7813-7831, 7813-7832, 7814-7833, 7815-7831, 7815-7832, 7815-7833, 7815-7834, 7816-7832, 7816-7833, 7816-7834, 7816-7835, 7817-7833, 7817-7834, 7817-7835, 7817-7836, 7818-7834, 7818-7835, 7818-7836, 7818-7837, 7819-7835, 7819-7836, 7819-7837, 7819-7838, 7820-7836, 7820-7838, 7820-7839, 7821-7836, 7821-7837, 7821-7839, 7821-7840, 7822-7837, 7822-7838, 7822-7840, 7822-7841, 7823-7838, 7823-7839, 7823-7839, 7823-7840, 7823-7841, 7823-7842, 7824-7839, 7824-7840, 7824-7840, 7824-7841, 7824-7842, 7824-7843, 7825-7840, 7825-7841, 7825-7842, 7825-7843, 7825-7844, 7826-7842, 7826-7843, 7826-7844, 7826-7845, 7827-7842, 7827-7843, 7827-7844, 7827-7845, 7827-7846, 7828-7843, 7828-7844, 7828-7845, 7828-7847, 7829-7844, 7829-7845, 7829-7846, 7829-7847, 7829-7848, 7830-7845, 7830-7846, 7830-7847, 7830-7848, 7830-7849, 7831-7846, 7831-7847, 7831-7848, 7831-7849, 7831-7850, 7832-7847, 7832-7848, 7832-7849, 7832-7850, 7832-7851, 7833-7848, 7833-7849, 7833-7850, 7833-7851, 7833-7852, 7834-7849, 7834-7850, 7834-7851, 7834-7852, 7834-7853, 7835-7850, 7835-7851, 7835-7852, 7835-7853, 7835-7854, 7836-7851, 7836-7852, 7836-7853, 7836-7854, 7836-7855, 7837-7852, 7837-7853, 7837-7854, 7837-7855, 7837-7856, 7838-7853, 7838-7854, 7838-7855, 7838-7856, 7838-7857, 7839-7854, 7839-7855, 7839-7856, 7839-7857, 7839-7858, 7840-7855, 7840-7856, 7840-7857, 7840-7858, 7840-7859, 7841-7856, 7841-7857, 7841-7858, 7841-7859, 7841-7860, 7842-7857, 7842-7858, 7842-7859, 7842-7860, 7842-7861,

7843-7858, 7843-7859, 7843-7860, 7843-7861, 7843-7862, 7844-7859, 7844-7860, 7844-7861, 7844-7862, 7845-7860, 7845-7861, 7845-7862, 7846-7861, and 7846-7862 of SEQ ID NO: 2, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 2.

In certain embodiments, antisense compounds or oligonucleotides target a region of a CFB nucleic acid. In certain embodiments, such compounds or oligonucleotides targeted to a region of a CFB nucleic acid have a contiguous nucleobase portion that is complementary to an equal length nucleobase portion of the region. For example, the portion can be at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobase portion complementary to an equal length portion of a region recited herein. In certain embodiments, such compounds or oligonucleotide target the following nucleotide regions of SEQ ID NO: 1: 30-49, 48-63, 150-169, 151-170, 152-171, 154-169, 154-173, 156-171, 156-175, 157-176, 158-173, 158-177, 480-499, 600-619, 638-657, 644-663, 738-757, 1089-1108, 1135-1154, 1141-1160, 1147-1166, 1150-1169, 1153-1172, 1159-1178, 1162-1181, 1165-1184, 1171-1186, 1171-1190, 1173-1188, 1173-1192, 1175-1190, 1175-1194, 1177-1196, 1183-1202, 1208-1227, 1235-1254, 1298-1317, 1304-1323, 1310-1329, 1316-1335, 1319-1338, 1322-1341, 1328-1347, 1349-1368, 1355-1374, 1393-1412, 1396-1415, 1399-1418, 1405-1424, 1421-1440, 1621-1640, 1646-1665, 1646-1665, 1647-1666, 1689-1708, 1749-1768, 1763-1782, 1912-1931, 2073-2092, 2085-2104, 2166-2185, 2172-2191, 2189-2208, 2191-2210, 2193-2212, 2195-2210, 2195-2214, 2196-2215, 2197-2212, 2197-2216, 2202-2221, 2223-2238, 2223-2242, 2225-2240, 2226-2245, 2227-2242, 2227-2246, 2238-2257, 2241-2260, 2267-2286, 2361-2380, 2388-2407, 2397-2416, 2448-2467, 2453-2472, 2455-2474, 2457-2472, 2457-2476, 2459-2474, 2459-2478, 2461-2476, 2461-2480, 2532-2551, 2550-2569, 2551-2566, 2551-2570, 2552-2568, 2552-2570, 2552-2571, 2553-2568, 2553-2570, 2553-2571, 2553-2572, 2554-2571, 2554-2572, 2554-2573, 2555-2570, 2555-2572, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2573, 2557-2574, 2557-2575, 2557-2576, 2558-2575, 2558-2576, 2558-2577, 2559-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2576, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2578, 2563-2580, 2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2566-2585, 2567-2582, 2567-2584, 2567-2586, 2568-2583, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2585, 2570-2587, 2570-2589, 2571-2586, 2571-2588, 2571-2590, 2572-2589, 2572-2590, 2572-2591, 2573-2590, 2573-2592, 2574-2590, 2574-2591, 2574-2593, 2575-2590, 2575-2591, 2575-2592, 2575-2594, 2576-2593, 2576-2595, 2577-2594, 2577-2595, 2577-2596, 2578-2594, 2578-2596, 2578-2597, 2579-2598, 2580-2596, 2580-2597, 2580-2598, 2580-2599, 2581-2597, 2581-2598, 2581-2599, 2581-2600, 2582-2598, 2582-2599, 2582-2600, 2582-2601, 2583-2599, 2583-2600, 2583-2601, 2583-2602, 2584-2600, 2584-2601, 2584-2602, 2584-2603, 2585-2601, 2585-2603, 2585-2604, 2586-2601, 2586-2602, 2586-2604, 2586-2605, 2587-2602, 2587-2603, 2587-2605, 2587-2606, 2588-2603, 2588-2604, 2588-2605, 2588-2606, 2588-2607, 2589-2604, 2589-2605, 2589-2606, 2589-2607, 2589-2608, 2590-2605, 2590-2606, 2590-2607, 2590-2608, 2590-2609, 2590-2609, 2591-2607, 2591-2608, 2591-2609, 2591-2610, 2592-2607, 2592-2608, 2592-2609, 2592-2610, 2592-

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In certain embodiments, antisense compounds or oligonucleotides target a region of a CFB nucleic acid. In certain embodiments, such compounds or oligonucleotides targeted to a region of a CFB nucleic acid have a contiguous nucleobase portion that is complementary to an equal length nucleobase portion of the region. For example, the portion can be at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobase portion complementary to an equal length portion of a region recited herein. In certain embodiments, such compounds or oligonucleotide target the following nucleotide regions of SEQ ID NO: 2: 1608-1627, 1685-1704, 1686-1705, 1751-1770, 1769-1784, 1871-1890, 1872-1891, 1873-1892, 1875-1890, 1875-1894, 1877-1892, 1877-1896, 1878-1897, 1879-1894, 1879-1898, 2288-2307, 2808-2827, 2846-2865, 2852-2871, 2946-2965, 3773-3792, 3819-3838, 3825-3844, 3831-3850, 3834-3853, 3837-3856, 3843-3862, 4151-4166, 4151-4170, 4153-4172, 4159-4178, 4184-4203, 4211-4230, 4609-4628, 4612-4631, 4615-4634, 4621-4640, 4642-4661, 4648-4667, 4686-4705, 4689-4708, 4692-4711, 4698-4717, 4714-4733, 5270-5289, 5295-5314, 5296-5315, 5830-5849, 5890-5909, 5904-5923, 6406-6425, 6662-6681, 6674-6693, 6954-6973, 6960-6979, 6977-6996, 6979-6998, 6981-7000, 6983-6998, 6983-7002, 6984-7003, 6985-7000, 6985-7004, 6990-7009, 7122-7141, 7125-7144, 7151-7170, 7353-7372, 7362-7381, 7683-7702, 7688-7707, 7690-7709, 7692-7707, 7692-7711, 7694-7709, 7694-7713, 7696-7711, 7696-7715, 7767-7786, 7785-7804, 7786-7801, 7787-7803, 7787-7805, 7787-7806, 7788-7803, 7788-7805, 7788-7806, 7788-7807, 7789-7806, 7789-7807, 7789-7808, 7790-7805, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7808, 7792-7809, 7792-7810, 7792-7811, 7793-7810, 7793-7811, 7793-7812, 7794-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7811, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7813, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7801-7820, 7802-7817, 7802-7819, 7802-7821, 7803-7818, 7803-7820, 7803-7822, 7804-7821, 7804-7823, 7805-7820, 7805-7822, 7805-7824, 7806-7821, 7806-7823, 7806-7825, 7807-7824, 7807-7825, 7807-7826, 7808-7825, 7808-7827, 7809-7825, 7809-

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In certain embodiments, antisense compounds or oligonucleotides target the 3'UTR of a CFB nucleic acid. In certain embodiments, antisense compounds or oligonucleotides target within nucleotides 2574-2626 of a CFB nucleic acid having the nucleobase sequence of SEQ ID NO: 1. In certain embodiments, antisense compounds or oligonucleotides have at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobase portion complementary to an equal length portion within nucleotides 2574-2626 of a CFB nucleic acid having the nucleobase sequence of SEQ ID NO: 1.

In certain embodiments, antisense compounds or oligonucleotides target a region of a CFB nucleic acid having the nucleobase sequence of SEQ ID NO: 1 within nucleobases 2457-2631, 2457-2472, 2457-2474, 2457-2476, 2457-2566, 2457-2570, 2457-2571, 2457-2572, 2457-2573, 2457-2574, 2457-2575, 2457-2576, 2457-2577, 2457-2578, 2457-2579, 2457-2580, 2457-2581, 2457-2582, 2457-2583, 2457-2584, 2457-2585, 2457-2586, 2457-2587, 2457-2588, 2457-2589, 2457-2590, 2457-2591, 2457-2592, 2457-2593, 2457-2594, 2457-2595, 2457-2596, 2457-2597, 2457-2598, 2457-2599, 2457-2600, 2457-2601, 2457-2602, 2457-2603, 2457-2604, 2457-2605, 2457-2606, 2457-2607, 2457-2608, 2457-2609, 2457-2610, 2457-2611, 2457-2612, 2457-2613, 2457-2614, 2457-2615, 2457-2616, 2457-2617, 2457-2618, 2457-2619, 2457-2620, 2457-2621, 2457-2622, 2457-2623, 2457-2624, 2457-2625, 2457-2626, 2457-2627, 2457-2628, 2457-2629, 2457-2630, 2457-2631, 2459-2474, 2459-2476, 2459-2566, 2459-2570, 2459-2571, 2459-2572, 2459-2573, 2459-2574, 2459-2575, 2459-2576, 2459-2577, 2459-2578, 2459-2579, 2459-2580, 2459-2581, 2459-2582, 2459-

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In certain embodiments, the following nucleotide regions of SEQ ID NO: 1, when targeted by antisense compounds or oligonucleotides, display at least 50% inhibition: 30-49, 48-63, 150-169, 151-170, 152-171, 154-169, 154-173, 156-171, 156-175, 157-176, 158-173, 158-177, 480-499, 600-619, 638-657, 644-663, 738-757, 1089-1108, 1135-1154, 1141-1160, 1147-1166, 1150-1169, 1153-1172, 1159-1178, 1162-1181, 1165-1184, 1171-1186, 1171-1190, 1173-1188, 1173-1192, 1175-1190, 1175-1194, 1177-1196, 1183-1202, 1208-1227, 1235-1254, 1298-1317, 1304-1323, 1310-1329, 1316-1335, 1319-1338, 1322-1341, 1328-1347, 1349-1368, 1355-1374, 1393-1412, 1396-1415, 1399-1418, 1405-1424, 1421-1440, 1621-1640, 1646-1665, 1646-1665, 1647-1666, 1689-1708, 1749-1768, 1763-1782, 1912-1931, 2073-2092, 2085-2104, 2166-

2185, 2172-2191, 2189-2208, 2191-2210, 2193-2212, 2195-2210, 2195-2214, 2196-2215, 2197-2212, 2197-2216, 2202-2221, 2223-2238, 2223-2242, 2225-2240, 2226-2245, 2227-2242, 2227-2246, 2238-2257, 2241-2260, 2267-2286, 2361-2380, 2388-2407, 2397-2416, 2448-2467, 2453-2472, 2455-2474, 2457-2472, 2457-2476, 2459-2474, 2459-2478, 2461-2476, 2461-2480, 2532-2551, 2550-2569, 2551-2566, 2551-2570, 2552-2568, 2552-2570, 2552-2571, 2553-2568, 2553-2570, 2553-2571, 2553-2572, 2554-2571, 2554-2572, 2554-2573, 2555-2570, 2555-2572, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2573, 2557-2574, 2557-2575, 2557-2576, 2558-2575, 2558-2576, 2558-2577, 2559-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2576, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2578, 2563-2580, 2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2566-2585, 2567-2582, 2567-2584, 2567-2586, 2568-2583, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2585, 2570-2587, 2570-2589, 2571-2586, 2571-2588, 2571-2590, 2572-2589, 2572-2590, 2572-2591, 2573-2590, 2573-2592, 2574-2590, 2574-2591, 2574-2593, 2575-2590, 2575-2591, 2575-2592, 2575-2594, 2576-2593, 2576-2595, 2577-2594, 2577-2595, 2577-2596, 2578-2594, 2578-2596, 2578-2597, 2579-2598, 2580-2596, 2580-2597, 2580-2598, 2580-2599, 2581-2597, 2581-2598, 2581-2599, 2581-2600, 2582-2598, 2582-2599, 2582-2600, 2582-2601, 2583-2599, 2583-2600, 2583-2601, 2583-2602, 2584-2600, 2584-2601, 2584-2602, 2584-2603, 2585-2601, 2585-2603, 2585-2604, 2586-2601, 2586-2602, 2586-2604, 2586-2605, 2587-2602, 2587-2603, 2587-2605, 2587-2606, 2588-2603, 2588-2604, 2588-2605, 2588-2606, 2588-2607, 2589-2604, 2589-2605, 2589-2606, 2589-2607, 2589-2608, 2590-2605, 2590-2606, 2590-2607, 2590-2608, 2590-2609, 2590-2609, 2591-2607, 2591-2608, 2591-2609, 2591-2610, 2592-2607, 2592-2608, 2592-2609, 2592-2610, 2592-2611, 2593-2608, 2593-2609, 2593-2610, 2593-2612, 2594-2609, 2594-2610, 2594-2611, 2594-2612, 2594-2613, 2595-2610, 2595-2611, 2595-2612, 2595-2613, 2595-2614, 2596-2611, 2596-2612, 2596-2613, 2596-2614, 2596-2615, 2597-2612, 2597-2612, 2597-2613, 2597-2614, 2597-2615, 2597-2616, 2598-2613, 2598-2614, 2598-2615, 2598-2616, 2598-2617, 2599-2614, 2599-2615, 2599-2616, 2599-2617, 2599-2618, 2600-2615, 2600-2616, 2600-2617, 2600-2618, 2600-2619, 2601-2616, 2601-2617, 2601-2618, 2601-2619, 2601-2620, 2602-2617, 2602-2618, 2602-2619, 2602-2620, 2602-2621, 2603-2618, 2603-2619, 2603-2620, 2603-2621, 2603-2622, 2604-2619, 2604-2620, 2604-2621, 2604-2622, 2604-2623, 2605-2620, 2605-2621, 2605-2622, 2605-2623, 2605-2624, 2606-2621, 2606-2622, 2606-2623, 2606-2624, 2606-2625, 2607-2622, 2607-2623, 2607-2624, 2607-2625, 2607-2626, 2608-2623, 2608-2624, 2608-2625, 2608-2626, 2608-2627, 2609-2624, 2609-2625, 2609-2626, 2609-2627, 2609-2628, 2610-2625, 2610-2626, 2610-2627, 2610-2628, 2610-2629, 2611-2626, 2611-2627, 2611-2628, 2611-2629, 2611-2630, 2612-2627, 2612-2628, 2612-2629, 2612-2630, 2612-2631, 2613-2628, 2613-2629, 2613-2630, 2613-2631, 2614-2629, 2614-2630, 2614-2631, 2615-2630, 2615-2631, and 2616-2631.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 2, when targeted by antisense compounds or oligonucleotides, display at least 50% inhibition: 1608-1627, 1685-1704, 1686-1705, 1751-1770, 1769-1784, 1871-1890, 1872-1891, 1873-1892, 1875-1890, 1875-1894, 1877-1892, 1877-1896,

1878-1897, 1879-1894, 1879-1898, 2288-2307, 2808-2827, 2846-2865, 2852-2871, 2946-2965, 3773-3792, 3819-3838, 3825-3844, 3831-3850, 3834-3853, 3837-3856, 3843-3862, 4151-4166, 4151-4170, 4153-4172, 4159-4178, 4184-4203, 4211-4230, 4609-4628, 4612-4631, 4615-4634, 4621-4640, 4642-4661, 4648-4667, 4686-4705, 4689-4708, 4692-4711, 4698-4717, 4714-4733, 5270-5289, 5295-5314, 5296-5315, 5830-5849, 5890-5909, 5904-5923, 6406-6425, 6662-6681, 6674-6693, 6954-6973, 6960-6979, 6977-6996, 6979-6998, 6981-7000, 6983-6998, 6983-7002, 6984-7003, 6985-7000, 6985-7004, 6990-7009, 7122-7141, 7125-7144, 7151-7170, 7353-7372, 7362-7381, 7683-7702, 7688-7707, 7690-7709, 7692-7707, 7692-7711, 7694-7709, 7694-7713, 7696-7711, 7696-7715, 7767-7786, 7785-7804, 7786-7801, 7787-7803, 7787-7805, 7787-7806, 7788-7803, 7788-7805, 7788-7806, 7788-7807, 7789-7806, 7789-7807, 7789-7808, 7790-7805, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7808, 7792-7809, 7792-7810, 7792-7811, 7793-7810, 7793-7811, 7793-7812, 7794-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7811, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7813, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7801-7820, 7802-7817, 7802-7819, 7802-7821, 7803-7818, 7803-7820, 7803-7822, 7804-7821, 7804-7823, 7805-7820, 7805-7822, 7805-7824, 7806-7821, 7806-7823, 7806-7825, 7807-7824, 7807-7825, 7807-7826, 7808-7825, 7808-7827, 7809-7825, 7809-7826, 7809-7828, 7810-7825, 7810-7826, 7810-7827, 7810-7829, 7811-7828, 7811-7830, 7812-7829, 7812-7830, 7812-7831, 7813-7829, 7813-7831, 7813-7832, 7814-7833, 7815-7831, 7815-7832, 7815-7833, 7815-7834, 7816-7832, 7816-7833, 7816-7834, 7816-7835, 7817-7833, 7817-7834, 7817-7835, 7817-7836, 7818-7834, 7818-7835, 7818-7836, 7818-7837, 7819-7835, 7819-7836, 7819-7837, 7819-7838, 7820-7836, 7820-7838, 7820-7839, 7821-7836, 7821-7837, 7821-7839, 7821-7840, 7822-7837, 7822-7838, 7822-7840, 7822-7841, 7823-7838, 7823-7839, 7823-7839, 7823-7840, 7823-7841, 7823-7842, 7824-7839, 7824-7840, 7824-7840, 7824-7841, 7824-7842, 7824-7843, 7825-7840, 7825-7841, 7825-7842, 7825-7843, 7825-7844, 7826-7842, 7826-7843, 7826-7844, 7826-7845, 7827-7842, 7827-7843, 7827-7844, 7827-7845, 7827-7846, 7828-7843, 7828-7844, 7828-7845, 7828-7847, 7829-7844, 7829-7845, 7829-7846, 7829-7847, 7829-7848, 7830-7845, 7830-7846, 7830-7847, 7830-7848, 7830-7849, 7831-7846, 7831-7847, 7831-7848, 7831-7849, 7831-7850, 7832-7847, 7832-7848, 7832-7849, 7832-7850, 7832-7851, 7833-7848, 7833-7849, 7833-7850, 7833-7851, 7833-7852, 7834-7849, 7834-7850, 7834-7851, 7834-7852, 7834-7853, 7835-7850, 7835-7851, 7835-7852, 7835-7853, 7835-7854, 7836-7851, 7836-7852, 7836-7853, 7836-7854, 7836-7855, 7837-7852, 7837-7853, 7837-7854, 7837-7855, 7837-7856, 7838-7853, 7838-7854, 7838-7855, 7838-7856, 7838-7857, 7839-7854, 7839-7855, 7839-7856, 7839-7857, 7839-7858, 7840-7855, 7840-7856, 7840-7857, 7840-7858, 7840-7859, 7841-7856, 7841-7857, 7841-7858, 7841-7859, 7841-7860, 7842-7857, 7842-7858, 7842-7859, 7842-7860, 7842-7861, 7843-7858, 7843-7859, 7843-7860, 7843-7861, 7843-7862, 7844-7859, 7844-7860, 7844-7861, 7844-7862, 7845-7860, 7845-7861, 7845-7862, 7846-7861, and 7846-7862.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 1, when targeted by antisense compounds or oligonucleotides, display at least 60% inhibition: 48-63, 150-169, 152-171, 154-169,

154-173, 156-171, 156-175, 158-173, 158-177, 600-619, 1135-1154, 1141-1160, 1147-1166, 1153-1172, 1171-1186, 1173-1188, 1175-1190, 1749-1768, 1763-1782, 1763-1782, 1912-1931, 2189-2208, 2191-2210, 2193-2212, 2195-2210, 2195-2214, 2197-2212, 2197-2216, 2223-2238, 2225-2240, 2227-2242, 2238-2257, 2448-2467, 2453-2472, 2455-2474, 2457-2472, 2457-2476, 2459-2474, 2459-2478, 2461-2476, 2461-2480, 2550-2569, 2551-2566, 2552-2571, 2553-2568, 2553-2570, 2553-2571, 2553-2572, 2554-2571, 2554-2572, 2554-2573, 2555-2572, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2574, 2557-2575, 2557-2576, 2558-2575, 2558-2576, 2558-2577, 2559-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2578, 2563-2580, 2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2566-2585, 2567-2582, 2567-2584, 2567-2586, 2568-2583, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2587, 2570-2589, 2571-2588, 2572-2590, 2572-2591, 2573-2590, 2573-2592, 2574-2591, 2574-2593, 2575-2590, 2575-2592, 2575-2594, 2576-2593, 2576-2595, 2577-2594, 2577-2595, 2577-2596, 2578-2594, 2578-2597, 2579-2598, 2580-2596, 2580-2597, 2580-2598, 2580-2599, 2581-2597, 2581-2598, 2581-2599, 2581-2600, 2582-2598, 2582-2599, 2582-2600, 2582-2601, 2583-2599, 2583-2600, 2583-2601, 2583-2602, 2584-2600, 2584-2602, 2584-2603, 2585-2601, 2585-2603, 2585-2604, 2586-2602, 2586-2604, 2586-2605, 2587-2603, 2587-2605, 2587-2606, 2588-2603, 2588-2604, 2588-2606, 2588-2607, 2589-2605, 2589-2606, 2589-2607, 2589-2608, 2590-2605, 2590-2606, 2590-2607, 2590-2608, 2590-2609, 2591-2607, 2591-2609, 2591-2610, 2592-2608, 2592-2609, 2592-2611, 2593-2608, 2593-2609, 2593-2612, 2594-2609, 2594-2610, 2594-2611, 2594-2612, 2594-2613, 2595-2610, 2595-2611, 2595-2612, 2595-2613, 2595-2614, 2596-2611, 2596-2612, 2596-2613, 2596-2614, 2596-2615, 2597-2612, 2597-2613, 2597-2614, 2597-2615, 2597-2616, 2598-2613, 2598-2614, 2598-2615, 2598-2616, 2598-2617, 2599-2614, 2599-2615, 2599-2616, 2599-2617, 2599-2618, 2600-2615, 2600-2616, 2600-2617, 2600-2618, 2600-2619, 2601-2616, 2601-2617, 2601-2618, 2601-2619, 2601-2620, 2602-2617, 2602-2618, 2602-2619, 2602-2620, 2602-2621, 2603-2618, 2603-2619, 2603-2620, 2603-2621, 2603-2622, 2604-2619, 2604-2620, 2604-2621, 2604-2622, 2604-2623, 2605-2620, 2605-2621, 2605-2622, 2605-2623, 2605-2624, 2606-2621, 2606-2622, 2606-2623, 2606-2624, 2606-2625, 2607-2622, 2607-2623, 2607-2624, 2607-2625, 2607-2626, 2608-2623, 2608-2624, 2608-2625, 2608-2625, 2608-2626, 2608-2627, 2609-2624, 2609-2625, 2609-2626, 2609-2627, 2609-2628, 2610-2625, 2610-2626, 2610-2627, 2610-2628, 2610-2629, 2611-2626, 2611-2626, 2611-2627, 2611-2628, 2611-2629, 2611-2630, 2612-2627, 2612-2628, 2612-2629, 2612-2630, 2612-2631, 2613-2628, 2613-2629, 2613-2630, 2613-2631, 2614-2629, 2614-2630, 2614-2631, 2615-2630, 2615-2630, 2615-2631, 2615-2631, and 2616-2631.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 2, when targeted by antisense compounds or oligonucleotides, display at least 60% inhibition: 1685-1704, 1686-1705, 1769-1784, 1871-1890, 1873-1892, 1875-1890, 1875-1894, 1877-1892, 1877-1896, 1879-1894, 1879-1898, 2808-2827, 3819-3838, 3825-3844, 3831-3850, 3837-3856, 4151-4166, 5890-5909, 5904-5923, 5904-5923, 6406-6425, 6977-6996, 6979-6998, 6981-7000, 6983-6998, 6983-7002, 6985-7000, 6985-7004, 7122-7141, 7683-7702,

7688-7707, 7690-7709, 7692-7707, 7692-7711, 7694-7709, 7696-7711, 7696-7715, 7786-7801, 7787-7806, 7788-7803, 7788-7805, 7788-7806, 7788-7807, 7789-7806, 7789-7807, 7789-7808, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7809, 7792-7810, 7792-7811, 7793-7810, 7793-7811, 7793-7812, 7794-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7813, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7801-7820, 7802-7817, 7802-7819, 7802-7821, 7803-7818, 7803-7820, 7803-7822, 7804-7821, 7804-7823, 7805-7822, 7805-7824, 7806-7823, 7806-7825, 7807-7824, 7807-7825, 7807-7826, 7808-7825, 7808-7827, 7809-7826, 7809-7828, 7810-7825, 7810-7827, 7810-7829, 7811-7828, 7811-7830, 7812-7829, 7812-7830, 7812-7831, 7813-7829, 7813-7832, 7814-7833, 7815-7831, 7815-7832, 7815-7833, 7815-7834, 7816-7832, 7816-7833, 7816-7834, 7816-7835, 7817-7833, 7817-7834, 7817-7835, 7817-7836, 7818-7834, 7818-7835, 7818-7836, 7818-7837, 7819-7835, 7819-7837, 7819-7838, 7820-7836, 7820-7838, 7820-7839, 7821-7837, 7821-7839, 7821-7840, 7822-7838, 7822-7840, 7822-7841, 7823-7838, 7823-7839, 7823-7841, 7823-7842, 7824-7840, 7824-7841, 7824-7842, 7824-7843, 7825-7840, 7825-7841, 7825-7842, 7825-7843, 7825-7844, 7826-7842, 7826-7844, 7826-7845, 7827-7843, 7827-7844, 7827-7846, 7828-7843, 7828-7844, 7828-7847, 7829-7844, 7829-7845, 7829-7846, 7829-7847, 7829-7848, 7830-7845, 7830-7846, 7830-7847, 7830-7848, 7830-7849, 7831-7846, 7831-7847, 7831-7848, 7831-7849, 7831-7850, 7832-7847, 7832-7848, 7832-7849, 7832-7850, 7832-7851, 7833-7848, 7833-7849, 7833-7850, 7833-7851, 7833-7852, 7834-7849, 7834-7850, 7834-7851, 7834-7852, 7834-7853, 7835-7850, 7835-7851, 7835-7852, 7835-7853, 7835-7854, 7836-7851, 7836-7852, 7836-7853, 7836-7854, 7836-7855, 7837-7852, 7837-7853, 7837-7854, 7837-7855, 7837-7856, 7838-7853, 7838-7854, 7838-7855, 7838-7856, 7838-7857, 7839-7854, 7839-7855, 7839-7856, 7839-7857, 7839-7858, 7840-7855, 7840-7856, 7840-7857, 7840-7858, 7840-7859, 7841-7856, 7841-7857, 7841-7858, 7841-7859, 7841-7860, 7842-7857, 7842-7858, 7842-7859, 7842-7860, 7842-7861, 7843-7858, 7843-7859, 7843-7860, 7843-7861, 7843-7862, 7844-7859, 7844-7860, 7844-7861, 7844-7862, 7845-7860, 7845-7861, 7845-7862, 7846-7861, 7846-7862, and 7847-7862.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 1, when targeted by antisense compounds or oligonucleotides, display at least 70% inhibition: 48-63, 150-169, 152-171, 154-169, 154-173, 156-171, 156-175, 158-173, 158-177, 1135-1154, 1141-1160, 1147-1166, 1171-1186, 1173-1188, 1175-1190, 1749-1768, 1763-1782, 1912-1931, 2193-2212, 2195-2210, 2195-2214, 2197-2212, 2197-2216, 2223-2238, 2225-2240, 2227-2242, 2453-2472, 2455-2474, 2457-2472, 2457-2476, 2459-2474, 2461-2476, 2461-2480, 2550-2569, 2551-2566, 2552-2571, 2553-2570, 2553-2571, 2553-2572, 2554-2571, 2554-2572, 2554-2573, 2554-2573, 2555-2572, 2555-2574, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2574, 2557-2576, 2558-2575, 2558-2576, 2558-2577, 2559-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2578, 2563-2580, 2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2566-2585, 2567-2582, 2567-2584, 2567-2586, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2587, 2570-2589, 2571-2588, 2571-2590, 2572-2589,

2572-2591, 2573-2590, 2573-2592, 2574-2591, 2574-2593, 2575-2592, 2575-2594, 2576-2593, 2576-2595, 2577-2594, 2577-2596, 2578-2597, 2579-2598, 2580-2596, 2580-2598, 2580-2599, 2581-2597, 2581-2600, 2582-2598, 2582-2600, 2582-2601, 2583-2599, 2583-2601, 2583-2602, 2584-2600, 2584-2602, 2584-2603, 2585-2601, 2585-2603, 2585-2604, 2586-2605, 2587-2606, 2588-2604, 2588-2606, 2588-2607, 2589-2605, 2589-2606, 2589-2607, 2589-2608, 2590-2605, 2590-2606, 2590-2607, 2590-2609, 2591-2607, 2591-2610, 2592-2611, 2593-2608, 2593-2612, 2594-2609, 2594-2610, 2594-2612, 2594-2613, 2595-2610, 2595-2611, 2595-2612, 2595-2613, 2595-2614, 2596-2611, 2596-2614, 2596-2615, 2597-2612, 2597-2613, 2597-2614, 2597-2615, 2597-2616, 2598-2613, 2598-2614, 2598-2615, 2598-2616, 2598-2617, 2599-2614, 2599-2615, 2599-2616, 2599-2617, 2599-2618, 2600-2615, 2600-2616, 2600-2617, 2600-2618, 2600-2619, 2601-2616, 2601-2617, 2601-2618, 2601-2619, 2601-2620, 2602-2617, 2602-2618, 2602-2619, 2602-2620, 2602-2621, 2603-2619, 2603-2620, 2603-2621, 2603-2622, 2604-2619, 2604-2620, 2604-2621, 2604-2622, 2604-2623, 2605-2620, 2605-2621, 2605-2622, 2605-2623, 2605-2624, 2606-2621, 2606-2622, 2606-2623, 2606-2624, 2606-2625, 2607-2622, 2607-2623, 2607-2624, 2607-2625, 2607-2626, 2608-2623, 2608-2624, 2608-2625, 2608-2626, 2608-2627, 2609-2624, 2609-2625, 2609-2626, 2609-2627, 2609-2628, 2610-2625, 2610-2626, 2610-2627, 2610-2628, 2610-2629, 2611-2626, 2611-2627, 2611-2629, 2611-2630, 2612-2627, 2612-2628, 2612-2629, 2612-2630, 2612-2631, 2613-2628, 2613-2629, 2613-2630, 2613-2631, 2614-2629, 2614-2630, 2614-2631, 2615-2630, 2615-2630, 2615-2631, and 2616-2631.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 2, when targeted by antisense compounds or oligonucleotides, display at least 70% inhibition: 1685-1704, 1686-1705, 1769-1784, 1871-1890, 1873-1892, 1875-1890, 1875-1894, 1877-1892, 1877-1896, 1879-1894, 1879-1898, 3819-3838, 3825-3844, 3831-3850, 4151-4166, 5890-5909, 5904-5923, 5904-5923, 6406-6425, 6983-6998, 6983-7002, 6985-7000, 6985-7004, 7688-7707, 7690-7709, 7692-7707, 7692-7711, 7694-7709, 7696-7711, 7696-7715, 7786-7801, 7787-7806, 7788-7805, 7788-7806, 7788-7807, 7789-7806, 7789-7807, 7789-7808, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7809, 7792-7811, 7793-7810, 7793-7811, 7793-7812, 7794-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7813, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7801-7820, 7802-7817, 7802-7819, 7802-7821, 7803-7820, 7803-7822, 7804-7821, 7804-7823, 7805-7822, 7805-7824, 7806-7823, 7806-7825, 7807-7824, 7807-7826, 7808-7825, 7808-7827, 7809-7826, 7809-7828, 7810-7827, 7811-7828, 7811-7830, 7812-7829, 7812-7831, 7813-7832, 7814-7833, 7815-7831, 7815-7833, 7815-7834, 7816-7832, 7816-7835, 7817-7833, 7817-7835, 7817-7836, 7818-7834, 7818-7836, 7818-7837, 7819-7835, 7819-7837, 7819-7838, 7820-7836, 7820-7838, 7820-7839, 7821-7840, 7822-7841, 7823-7839, 7823-7841, 7823-7842, 7824-7840, 7824-7841, 7824-7842, 7824-7843, 7825-7840, 7825-7841, 7825-7842, 7825-7844, 7826-7842, 7826-7845, 7827-7846, 7828-7843, 7828-7847, 7829-7844, 7829-7845, 7829-7847, 7829-7848, 7830-7845, 7830-7846, 7830-7847, 7830-7848, 7830-7849, 7831-7846, 7831-7849, 7831-7850, 7832-7847, 7832-7848, 7832-7849, 7832-7850, 7832-7851, 7833-7848, 7833-7849, 7833-7850,

7833-7851, 7833-7852, 7834-7849, 7834-7850, 7834-7851, 7834-7852, 7834-7853, 7835-7850, 7835-7851, 7835-7852, 7835-7853, 7835-7854, 7836-7851, 7836-7852, 7836-7853, 7836-7854, 7836-7855, 7837-7852, 7837-7853, 7837-7854, 7837-7855, 7837-7856, 7838-7854, 7838-7855, 7838-7856, 7838-7857, 7839-7854, 7839-7855, 7839-7856, 7839-7857, 7839-7858, 7840-7855, 7840-7856, 7840-7857, 7840-7858, 7840-7859, 7841-7856, 7841-7857, 7841-7858, 7841-7859, 7841-7860, 7842-7857, 7842-7858, 7842-7859, 7842-7860, 7842-7861, 7843-7858, 7843-7859, 7843-7860, 7843-7861, 7843-7862, 7844-7859, 7844-7860, 7844-7861, 7844-7862, 7845-7860, 7845-7861, 7845-7862, 7846-7861, 7846-7862, and 7847-7862.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 1, when targeted by antisense compounds or oligonucleotides, display at least 80% inhibition: 152-171, 154-169, 156-171, 158-173, 1135-1154, 1171-1186, 1173-1188, 1175-1190, 1763-1782, 1912-1931, 2197-2212, 2223-2238, 2225-2240, 2227-2242, 2457-2472, 2459-2474, 2461-2476, 2551-2566, 2553-2570, 2553-2571, 2553-2572, 2554-2573, 2555-2572, 2555-2574, 2556-2573, 2556-2574, 2556-2575, 2557-2574, 2557-2576, 2558-2575, 2558-2576, 2559-2577, 2559-2578, 2560-2577, 2560-2578, 2560-2579, 2561-2578, 2561-2579, 2561-2580, 2562-2577, 2562-2579, 2562-2581, 2563-2580, 2563-2582, 2564-2581, 2564-2583, 2565-2584, 2566-2583, 2567-2584, 2567-2586, 2568-2585, 2568-2587, 2569-2586, 2569-2588, 2570-2587, 2571-2588, 2571-2590, 2572-2589, 2572-2591, 2573-2590, 2573-2592, 2574-2591, 2574-2593, 2575-2592, 2576-2593, 2576-2595, 2577-2594, 2577-2596, 2578-2597, 2580-2598, 2580-2599, 2581-2597, 2581-2600, 2582-2601, 2583-2602, 2584-2603, 2585-2604, 2586-2605, 2587-2606, 2588-2607, 2589-2608, 2590-2606, 2590-2607, 2590-2609, 2591-2610, 2592-2611, 2593-2608, 2593-2612, 2594-2613, 2595-2611, 2595-2614, 2596-2615, 2597-2612, 2597-2613, 2597-2614, 2597-2615, 2597-2616, 2598-2613, 2598-2613, 2598-2614, 2598-2615, 2598-2616, 2598-2617, 2599-2614, 2599-2617, 2599-2618, 2600-2615, 2600-2617, 2600-2618, 2600-2619, 2601-2616, 2601-2617, 2601-2619, 2601-2620, 2602-2618, 2602-2621, 2603-2620, 2603-2621, 2603-2622, 2604-2619, 2604-2620, 2604-2621, 2604-2622, 2604-2623, 2605-2620, 2605-2621, 2605-2622, 2605-2623, 2605-2624, 2606-2621, 2606-2622, 2606-2623, 2606-2624, 2606-2625, 2607-2622, 2607-2623, 2607-2624, 2607-2625, 2607-2626, 2608-2623, 2608-2624, 2608-2625, 2608-2627, 2609-2624, 2609-2626, 2609-2627, 2609-2628, 2610-2625, 2610-2626, 2610-2628, 2610-2629, 2611-2626, 2611-2627, 2611-2629, 2611-2630, 2612-2627, 2612-2628, 2612-2630, 2612-2631, 2613-2628, 2613-2629, 2613-2631, 2614-2629, 2614-2630, 2614-2631, 2615-2630, and 2616-2631.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 2, when targeted by antisense compounds or oligonucleotides, display at least 80% inhibition: 1685-1704, 1686-1705, 1873-1892, 1875-1890, 1877-1892, 1879-1894, 3819-3838, 4151-4166, 5904-5923, 6406-6425, 6985-7000, 7692-7707, 7694-7709, 7696-7711, 7786-7801, 7788-7805, 7788-7806, 7788-7807, 7789-7808, 7790-7807, 7790-7809, 7791-7808, 7791-7809, 7791-7810, 7792-7809, 7792-7811, 7793-7810, 7793-7811, 7794-7812, 7794-7813, 7795-7812, 7795-7813, 7795-7814, 7796-7813, 7796-7814, 7796-7815, 7797-7812, 7797-7814, 7797-7816, 7798-7815, 7798-7817, 7799-7816, 7799-7818, 7800-7819, 7801-7818, 7802-7819, 7802-7821, 7803-7820,

7803-7822, 7804-7821, 7804-7823, 7805-7822, 7806-7823, 7806-7825, 7807-7824, 7807-7826, 7808-7825, 7808-7827, 7809-7826, 7809-7828, 7810-7827, 7811-7828, 7812-7829, 7812-7831, 7813-7832, 7814-7833, 7815-7834, 7816-7832, 7816-7835, 7817-7836, 7818-7837, 7819-7838, 7820-7839, 7821-7840, 7822-7841, 7823-7842, 7824-7843, 7825-7841, 7825-7842, 7825-7844, 7826-7845, 7827-7846, 7828-7843, 7828-7847, 7829-7848, 7830-7846, 7830-7849, 7831-7850, 7832-7847, 7832-7848, 7832-7849, 7832-7850, 7832-7851, 7833-7848, 7833-7849, 7833-7850, 7833-7851, 7833-7852, 7834-7849, 7834-7852, 7834-7853, 7835-7850, 7835-7852, 7835-7853, 7835-7854, 7836-7851, 7836-7852, 7836-7854, 7836-7855, 7837-7853, 7837-7856, 7838-7855, 7838-7856, 7838-7857, 7839-7854, 7839-7855, 7839-7856, 7839-7857, 7839-7858, 7840-7855, 7840-7856, 7840-7857, 7840-7858, 7840-7859, 7841-7856, 7841-7857, 7841-7858, 7841-7859, 7841-7860, 7842-7857, 7842-7858, 7842-7859, 7842-7860, 7842-7861, 7843-7858, 7843-7859, 7843-7860, 7843-7862, 7844-7859, 7844-7861, 7844-7862, 7845-7860, 7845-7861, 7846-7862, and 7847-7862.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 1, when targeted by antisense compounds or oligonucleotides, display at least 90% inhibition: 154-169, 156-171, 158-173, 1135-1154, 1171-1186, 1173-1188, 1763-1782, 1912-1931, 2223-2238, 2227-2242, 2459-2474, 2461-2476, 2554-2573, 2555-2574, 2560-2577, 2561-2578, 2561-2579, 2562-2581, 2563-2580, 2563-2582, 2564-2581, 2566-2583, 2567-2584, 2568-2585, 2568-2587, 2569-2586, 2570-2587, 2576-2593, 2577-2594, 2577-2596, 2578-2597, 2580-2599, 2581-2600, 2582-2601, 2583-2602, 2584-2603, 2586-2605, 2587-2605, 2587-2606, 2588-2607, 2589-2608, 2590-2607, 2590-2609, 2592-2611, 2595-2614, 2596-2615, 2597-2612, 2597-2613, 2597-2615, 2597-2616, 2598-2613, 2598-2613, 2598-2617, 2599-2614, 2599-2618, 2600-2615, 2600-2619, 2601-2617, 2601-2620, 2602-2621, 2603-2622, 2604-2623, 2605-2621, 2605-2622, 2605-2624, 2606-2625, 2607-2626, 2608-2623, 2608-2625, 2609-2628, 2611-2627, 2611-2630, 2612-2628, 2612-2631, 2613-2629, 2614-2629, 2615-2630, and 2616-2631.

In certain embodiments, the following nucleotide regions of SEQ ID NO: 2, when targeted by antisense compounds or oligonucleotides, display at least 90% inhibition: 1685-1704, 1686-1705, 1875-1890, 1877-1892, 1879-1894, 3819-3838, 5904-5923, 6406-6425, 7694-7709, 7696-7711, 7789-7808, 7790-7809, 7795-7812, 7795-7813, 7796-7813, 7796-7814, 7797-7814, 7797-7816, 7798-7815, 7798-7817, 7799-7816, 7801-7818, 7802-7819, 7803-7820, 7803-7822, 7804-7821, 7805-7822, 7811-7828, 7812-7829, 7812-7831, 7813-7832, 7815-7834, 7818-7837, 7819-7838, 7821-7840, 7822-7840, 7822-7841, 7825-7842, 7832-7847, 7832-7848, 7832-7850, 7833-7848, 7833-7852, 7834-7849, 7834-7853, 7835-7850, 7836-7852, 7836-7855, 7837-7856, 7838-7856, 7839-7857, 7839-7858, 7840-7856, 7840-7857, 7840-7859, 7843-7858, 7843-7860, and 7846-7862.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 50% inhibition of a CFB mRNA, ISIS NOs: 516350, 532614, 532632, 532635, 532638, 532639, 532686, 532687, 532688, 532689, 532690, 532691, 532692, 532692, 532693, 532694, 532695, 532696, 532697, 532698, 532699, 532700, 532701, 532702, 532703, 532704, 532705,

532706, 532707, 532770, 532775, 532778, 532780, 532791, 532800, 532809, 532810, 532811, 532917, 532952, 588509, 588510, 588511, 588512, 588513, 588514, 588515, 588516, 588517, 588518, 588519, 588520, 588522, 588523, 588524, 588525, 588527, 588528, 588529, 588530, 588531, 588532, 588533, 588534, 588535, 588536, 588537, 588538, 588539, 588540, 588541, 588542, 588543, 588544, 588545, 588546, 588547, 588548, 588549, 588550, 588551, 588552, 588553, 588554, 588555, 588556, 588557, 588558, 588559, 588560, 588561, 588562, 588563, 588564, 588565, 588566, 588567, 588568, 588569, 588570, 588571, 588572, 588573, 588574, 588575, 588576, 588577, 588580, 588581, 588585, 588586, 588589, 588590, 588599, 588603, 588606, 588608, 588610, 588614, 588616, 588628, 588631, 588632, 588634, 588636, 588638, 588640, 588645, 588646, 588654, 588656, 588658, 588660, 588662, 588664, 588670, 588672, 588676, 588682, 588688, 588696, 588698, 588807, 588808, 588809, 588813, 588814, 588815, 588819, 588820, 588822, 588823, 588838, 588839, 588840, 588841, 588842, 588846, 588847, 588848, 588849, 588850, 588851, 588852, 588853, 588854, 588855, 588856, 588857, 588858, 588859, 588860, 588861, 588862, 588863, 588864, 588865, 588866, 588867, 588868, 588870, 588871, 588872, 588873, 588874, 588875, 588876, 588877, 588878, 588879, 588880, 588881, 588882, 588883, 588884, 598999, 599000, 599001, 599002, 599003, 599004, 599005, 599006, 599007, 599008, 599009, 599010, 599011, 599012, 599013, 599014, 599015, 599018, 599019, 599023, 599024, 599025, 599026, 599027, 599028, 599029, 599030, 599031, 599032, 599033, 599034, 599035, 599058, 599062, 599063, 599064, 599065, 599070, 599071, 599072, 599073, 599074, 599076, 599077, 599078, 599079, 599080, 599081, 599082, 599083, 599084, 599085, 599086, 599087, 599088, 599089, 599090, 599091, 599092, 599093, 599094, 599095, 599096, 599097, 599098, 599102, 599119, 599123, 599124, 599125, 599126, 599127, 599128, 599132, 599133, 599134, 599135, 599136, 599137, 599138, 599139, 599140, 599141, 599142, 599143, 599144, 599145, 599147, 599148, 599149, 599150, 599151, 599152, 599153, 599154, 599155, 599156, 599157, 599158, 599159, 599178, 599179, 599180, 599181, 599182, 599186, 599187, 599188, 599189, 599190, 599191, 599192, 599193, 599194, 599195, 599196, 599197, 599198, 599199, 599200, 599201, 599202, 599203, 599204, 599205, 599206, 599207, 599208, 599209, 599210, 599211, 599212, 599213, 599214, 599215, 599216, 599217, 599218, 599219, 599220, 599221, 599221, 599222, 599223, 599224, 599225, 599226, 599227, 599228, 599229, 599230, 599231, 599232, 599233, 599234, 599235, 599236, 599241, 599247, 599248, 599249, 599255, 599256, 599257, 599258, 599260, 599261, 599262, 599263, 599264, 599265, 599266, 599267, 599268, 599269, 599270, 599271, 599272, 599273, 599274, 599275, 599276, 599277, 599278, 599279, 599280, 599297, 599299, 599306, 599307, 599308, 599309, 599311, 599312, 599313, 599314, 599315, 599316, 599317, 599318, 599319, 599320, 599321, 599322, 599323, 599324, 599325, 599326, 599327, 599328, 599329, 599330, 599338, 599349, 599353, 599354, 599355, 599356, 599357, 599358, 599359, 599360, 599361, 599362, 599363, 599364, 599369, 599371, 599372, 599373, 599376, 599378, 599379, 599382, 599383, 599384, 599385, 599386, 599387, 599388, 599389, 599390, 599391, 599392, 599393, 599394, 599395, 599396, 599397, 599398, 599399, 599400,

599401, 599402, 599403, 599404, 599405, 599406, 599407, 599408, 599409, 599410, 599412, 599413, 599414, 599415, 599416, 599417, 599418, 599419, 599420, 599421, 599422, 599423, 599424, 599425, 599426, 599433, 599434, 599435, 599436, 599437, 599438, 599439, 599440, 599441, 599442, 599443, 599444, 599445, 599446, 599447, 599448, 599450, 599454, 599455, 599456, 599467, 599468, 599469, 599471, 599472, 599473, 599474, 599475, 599476, 599477, 599478, 599479, 599480, 599481, 599482, 599483, 599484, 599485, 599486, 599487, 599488, 599489, 599490, 599491, 599492, 599493, 599494, 599495, 599496, 599497, 599498, 599499, 599500, 599501, 599502, 599503, 599504, 599505, 599506, 599507, 599508, 599509, 599512, 599515, 599518, 599531, 599541, 599541, 599546, 599547, 599548, 599549, 599550, 599552, 599553, 599554, 599555, 599557, 599558, 599561, 599562, 599563, 599564, 599565, 599566, 599567, 599568, 599569, 599570, 599577, 599578, 599579, 599580, 599581, 599581, 599582, 599584, 599585, 599586, 599587, 599588, 599589, 599590, 599591, 599592, 599593, 599594, 599595, 601321, 601322, 601323, 601325, 601327, 601328, 601329, 601330, 601332, 601333, 601334, 601335, 601336, 601337, 601338, 601339, 601341, 601342, 601343, 601344, 601345, 601346, 601347, 601348, 601349, 601362, 601367, 601368, 601369, 601371, 601372, 601373, 601374, 601375, 601377, 601378, 601380, 601381, 601382, 601383, 601384, 601385, 601386, 601387, and 601388.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 50% inhibition of a CFB mRNA, SEQ ID NOs: 12, 30, 33, 36, 37, 84, 85, 86, 87, 88, 89, 90, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 198, 203, 206, 208, 219, 228, 237, 238, 239, 317, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 468, 472, 473, 475, 478, 479, 488, 492, 494, 495, 498, 499, 500, 502, 503, 509, 510, 511, 512, 513, 514, 515, 517, 518, 522, 523, 524, 525, 529, 530, 531, 534, 535, 537, 540, 541, 542, 543, 544, 545, 546, 547, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 563, 564, 565, 569, 570, 572, 573, 577, 588, 589, 590, 591, 592, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 623, 640, 641, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 700, 704, 705, 706, 707, 708, 709, 711, 712, 713, 714, 715, 716, 717, 718, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 758, 759, 760, 761, 762, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 813, 833, 834, 841, 846, 849, 850, 867, and 873.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 60% inhibition of a CFB mRNA, ISIS NOs: 516350, 532614, 532635,

532686, 532687, 532688, 532689, 532770, 532800, 532809, 532810, 532811, 532917, 532952, 588512, 588513, 588514, 588515, 588516, 588517, 588518, 588519, 588522, 588523, 588524, 588525, 588527, 588528, 588529, 588530, 588531, 588532, 588533, 588534, 588535, 588536, 588537, 588538, 588539, 588540, 588541, 588542, 588543, 588544, 588545, 588546, 588547, 588548, 588549, 588550, 588551, 588552, 588553, 588554, 588555, 588556, 588557, 588558, 588559, 588560, 588561, 588562, 588563, 588564, 588565, 588566, 588567, 588568, 588569, 588570, 588571, 588572, 588573, 588574, 588575, 588576, 588577, 588636, 588638, 588640, 588664, 588676, 588696, 588698, 588807, 588808, 588814, 588815, 588819, 588820, 588840, 588842, 588846, 588847, 588848, 588849, 588850, 588851, 588852, 588853, 588854, 588855, 588856, 588857, 588858, 588859, 588860, 588861, 588862, 588863, 588864, 588866, 588867, 588868, 588870, 588871, 588872, 588873, 588874, 588875, 588876, 588877, 588878, 588879, 588880, 588881, 588882, 588883, 588884, 598999, 599000, 599001, 599002, 599003, 599004, 599005, 599006, 599007, 599008, 599009, 599010, 599011, 599012, 599013, 599014, 599015, 599019, 599024, 599025, 599026, 599027, 599028, 599029, 599030, 599031, 599032, 599033, 599034, 599035, 599064, 599065, 599071, 599072, 599077, 599078, 599079, 599080, 599083, 599084, 599085, 599086, 599087, 599088, 599089, 599090, 599091, 599092, 599093, 599094, 599095, 599096, 599097, 599125, 599126, 599127, 599133, 599134, 599135, 599136, 599138, 599139, 599140, 599141, 599142, 599148, 599149, 599150, 599151, 599152, 599154, 599155, 599156, 599157, 599158, 599159, 599178, 599179, 599180, 599181, 599187, 599188, 599190, 599192, 599193, 599194, 599195, 599196, 599197, 599198, 599199, 599200, 599201, 599202, 599203, 599204, 599205, 599206, 599207, 599208, 599209, 599210, 599211, 599212, 599213, 599214, 599215, 599216, 599217, 599218, 599219, 599220, 599221, 599222, 599223, 599224, 599225, 599226, 599227, 599228, 599229, 599230, 599231, 599232, 599233, 599234, 599235, 599236, 599247, 599255, 599256, 599257, 599263, 599264, 599265, 599266, 599270, 599271, 599272, 599273, 599274, 599275, 599276, 599277, 599278, 599279, 599280, 599306, 599307, 599308, 599311, 599312, 599313, 599314, 599315, 599316, 599317, 599318, 599319, 599320, 599321, 599322, 599323, 599324, 599325, 599327, 599328, 599329, 599330, 599349, 599353, 599355, 599356, 599357, 599358, 599359, 599360, 599361, 599362, 599363, 599364, 599369, 599371, 599372, 599373, 599376, 599378, 599379, 599382, 599384, 599386, 599387, 599388, 599389, 599390, 599391, 599392, 599393, 599394, 599395, 599396, 599397, 599398, 599399, 599400, 599401, 599402, 599403, 599404, 599405, 599406, 599407, 599408, 599409, 599410, 599412, 599413, 599414, 599415, 599416, 599417, 599418, 599419, 599420, 599421, 599422, 599423, 599424, 599425, 599433, 599434, 599435, 599436, 599437, 599438, 599439, 599440, 599441, 599442, 599443, 599444, 599445, 599446, 599447, 599448, 599456, 599467, 599468, 599471, 599472, 599473, 599474, 599475, 599476, 599477, 599478, 599479, 599480, 599481, 599482, 599483, 599484, 599485, 599486, 599487, 599488, 599489, 599490, 599491, 599492, 599493, 599494, 599495, 599496, 599497, 599498, 599499, 599500, 599501, 599502, 599503, 599504, 599505, 599506, 599507, 599508, 599512, 599531, 599547, 599548, 599549, 599552, 599553, 599554,

599555, 599557, 599558, 599562, 599563, 599564, 599565, 599566, 599567, 599568, 599569, 599570, 599577, 599578, 599579, 599580, 599581, 599582, 599584, 599585, 599586, 599587, 599588, 599589, 599590, 599591, 599592, 599593, 599594, 599595, 601323, 601327, 601329, 601332, 601333, 601333, 601334, 601335, 601336, 601338, 601339, 601341, 601342, 601343, 601344, 601345, 601346, 601347, 601348, 601349, 601368, 601369, 601371, 601372, 601374, 601375, 601377, 601378, 601380, 601381, 601382, 601383, 601384, 601385, 601386, 601387, and 601388.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 60% inhibition of a CFB mRNA, SEQ ID NOs: 12, 33, 84, 85, 86, 87, 198, 228, 237, 238, 239, 317, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 472, 473, 513, 514, 515, 531, 537, 541, 542, 543, 544, 545, 546, 547, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 564, 565, 569, 570, 577, 590, 592, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 682, 683, 684, 685, 686, 687, 688, 689, 700, 704, 706, 707, 708, 709, 711, 712, 713, 714, 715, 716, 717, 720, 721, 722, 723, 724, 725, 726, 727, 727, 728, 729, 730, 731, 732, 733, 734, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 758, 759, 760, 761, 767, 768, 770, 772, 773, 774, 775, 775, 776, 776, 777, 777, 778, 779, 780, 781, 782, 783, 783, 784, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 813, 833, 834, 841, 846, 849, and 850.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 70% inhibition of a CFB mRNA, ISIS NOs: 516350, 532614, 532686, 532687, 532688, 532770, 532800, 532809, 532810, 532811, 532917, 532952, 588512, 588513, 588514, 588515, 588516, 588517, 588518, 588524, 588529, 588530, 588531, 588532, 588533, 588534, 588535, 588536, 588537, 588538, 588539, 588540, 588541, 588542, 588543, 588544, 588545, 588546, 588547, 588548, 588549, 588550, 588551, 588552, 588553, 588554, 588555, 588556, 588557, 588558, 588559, 588560, 588561, 588562, 588563, 588564, 588565, 588568, 588569, 588570, 588571, 588572, 588573, 588574, 588575, 588577, 588636, 588638, 588640, 588696, 588698, 588807, 588814, 588815, 588819, 588842, 588847, 588848, 588849, 588850, 588851, 588852, 588853, 588856, 588857, 588858, 588859, 588860, 588861, 588862, 588863, 588866, 588867, 588870, 588871, 588872, 588873, 588874, 588875, 588876, 588877, 588878, 588879, 588880, 588881, 588882, 588883, 588884, 599000, 599001, 599003, 599004, 599005, 599008, 599009, 599010, 599011, 599014, 599015, 599024, 599025, 599027, 599028, 599029, 599030, 599031, 599032, 599033, 599034, 599072, 599077, 599080, 599085, 599086, 599087, 599088, 599089, 599090, 599091, 599093, 599094, 599095, 599096, 599097, 599125, 599126, 599134,

599138, 599139, 599148, 599149, 599150, 599151, 599152, 599154, 599155, 599156, 599157, 599158, 599187, 599188, 599193, 599195, 599196, 599197, 599198, 599199, 599200, 599201, 599202, 599203, 599204, 599205, 599206, 599207, 599208, 599210, 599211, 599212, 599213, 599214, 599215, 599216, 599217, 599218, 599219, 599220, 599221, 599222, 599223, 599224, 599225, 599226, 599227, 599228, 599229, 599230, 599231, 599232, 599233, 599234, 599235, 599236, 599266, 599272, 599272, 599273, 599274, 599275, 599277, 599278, 599279, 599280, 599280, 599306, 599311, 599312, 599313, 599314, 599315, 599316, 599317, 599318, 599319, 599320, 599321, 599322, 599323, 599325, 599327, 599328, 599329, 599330, 599355, 599357, 599358, 599359, 599360, 599361, 599362, 599363, 599364, 599369, 599371, 599372, 599373, 599378, 599379, 599382, 599384, 599386, 599387, 599388, 599389, 599390, 599391, 599392, 599393, 599394, 599395, 599396, 599397, 599398, 599399, 599400, 599401, 599402, 599403, 599404, 599405, 599406, 599407, 599408, 599409, 599410, 599413, 599414, 599415, 599416, 599417, 599418, 599419, 599420, 599421, 599422, 599423, 599424, 599433, 599434, 599435, 599436, 599437, 599438, 599439, 599440, 599441, 599442, 599443, 599445, 599446, 599447, 599448, 599472, 599473, 599474, 599475, 599476, 599477, 599478, 599479, 599480, 599481, 599482, 599483, 599484, 599485, 599486, 599487, 599488, 599489, 599490, 599491, 599492, 599493, 599494, 599495, 599496, 599497, 599498, 599499, 599500, 599501, 599502, 599503, 599504, 599505, 599506, 599507, 599508, 599512, 599547, 599548, 599552, 599553, 599554, 599555, 599558, 599562, 599563, 599564, 599566, 599567, 599568, 599569, 599570, 599577, 599578, 599579, 599580, 599581, 599582, 599585, 599586, 599587, 599588, 599589, 599590, 599591, 599592, 599593, 599594, 599595, 601332, 601335, 601341, 601343, 601344, 601345, 601346, 601347, 601348, 601349, 601371, 601372, 601380, 601382, 601383, 601384, 601385, 601386, and 601387.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 70% inhibition of a CFB mRNA, SEQ ID NOs: 12, 84, 85, 86, 198, 228, 237, 238, 239, 317, 395, 396, 397, 398, 399, 402, 403, 404, 405, 407, 408, 410, 411, 412, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 464, 465, 472, 473, 513, 514, 515, 541, 542, 543, 544, 545, 546, 547, 549, 550, 551, 552, 553, 554, 555, 556, 557, 564, 565, 569, 592, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 645, 646, 647, 648, 649, 650, 653, 654, 655, 656, 659, 660, 662, 663, 664, 665, 666, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 677, 678, 679, 680, 682, 683, 684, 686, 687, 688, 689, 706, 708, 709, 711, 712, 713, 714, 715, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 767, 768, 773, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 793, 794, 795, 797, 798, 799, 813, 833, 834, 841, 846, 849, 867, and 873.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least an 80% inhibition of a CFB mRNA, ISIS NOs: 532686, 532809, 532810, 532811, 532917, 532952, 588512, 588517, 588518, 588533, 588534, 588535, 588536, 588537, 588538, 588539, 588540, 588542, 588543, 588544, 588545, 588546, 588547, 588548, 588549, 588550, 588551, 588552, 588553, 588554, 588555, 588556, 588557, 588558, 588559, 588560, 588561, 588562, 588563, 588564, 588565, 588571, 588638, 588640, 588696, 588698, 588807, 588814, 588849, 588850, 588851, 588853, 588857, 588858, 588859, 588860, 588861, 588862, 588863, 588866, 588867, 588871, 588872, 588873, 588874, 588875, 588876, 588877, 588878, 588879, 588880, 588881, 588882, 588883, 599001, 599024, 599025, 599033, 599086, 599087, 599088, 599089, 599093, 599094, 599095, 599096, 599134, 599139, 599148, 599149, 599151, 599154, 599155, 599156, 599158, 599188, 599195, 599196, 599198, 599201, 599202, 599203, 599204, 599205, 599206, 599207, 599212, 599213, 599215, 599216, 599217, 599218, 599219, 599220, 599221, 599222, 599223, 599224, 599225, 599226, 599227, 599228, 599229, 599230, 599231, 599232, 599233, 599234, 599235, 599236, 599272, 599273, 599275, 599277, 599278, 599279, 599280, 599311, 599313, 599314, 599316, 599317, 599318, 599320, 599321, 599322, 599323, 599327, 599328, 599329, 599330, 599355, 599357, 599358, 599359, 599360, 599361, 599362, 599363, 599364, 599371, 599372, 599373, 599378, 599379, 599382, 599384, 599386, 599387, 599388, 599389, 599390, 599391, 599392, 599393, 599397, 599398, 599399, 599400, 599401, 599403, 599404, 599405, 599407, 599408, 599409, 599410, 599413, 599414, 599415, 599416, 599417, 599418, 599419, 599420, 599421, 599422, 599423, 599424, 599433, 599434, 599435, 599436, 599437, 599438, 599439, 599440, 599441, 599445, 599446, 599447, 599448, 599474, 599476, 599477, 599479, 599481, 599482, 599483, 599485, 599486, 599487, 599488, 599489, 599490, 599491, 599492, 599494, 599495, 599496, 599497, 599498, 599499, 599500, 599502, 599503, 599504, 599505, 599506, 599507, 599508, 599547, 599552, 599553, 599554, 599558, 599563, 599567, 599568, 599569, 599570, 599577, 599578, 599581, 599582, 599585, 599587, 599588, 599590, 599591, 599592, 599593, 599594, 601332, 601344, 601345, 601382, 601383, and 601385.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 80% inhibition of a CFB mRNA, SEQ ID NOs: 84, 237, 238, 239, 317, 395, 397, 411, 412, 413, 414, 415, 417, 418, 419, 420, 421, 422, 423, 425, 426, 427, 429, 430, 431, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 472, 473, 514, 515, 542, 543, 544, 545, 546, 547, 550, 551, 552, 553, 554, 555, 556, 557, 564, 595, 599, 600, 601, 602, 603, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 646, 655, 660, 662, 663, 666, 669, 670, 671, 672, 673, 675, 676, 677, 678, 679, 682, 684, 686, 687, 688, 689, 706, 708, 709, 711, 712, 713, 714, 715, 720, 722, 723, 724, 725, 726, 727, 729, 730, 731, 732, 733, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756,

768, 775, 776, 778, 781, 782, 783, 784, 785, 787, 788, 789, 790, 791, 792, 793, 794, 799, 813, 833, 834, 841, 849, 867, and 873.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 90% inhibition of a CFB mRNA, ISIS NOs: 532686, 532811, 532917, 588536, 588537, 588538, 588539, 588544, 588545, 588546, 588548, 588551, 588552, 588553, 588554, 588555, 588556, 588557, 588558, 588559, 588560, 588561, 588562, 588564, 588638, 588640, 588696, 588698, 588849, 588850, 588851, 588860, 588866, 588867, 588872, 588873, 588874, 588876, 588877, 588878, 588879, 588881, 588883, 599149, 599188, 599203, 599206, 599220, 599221, 599222, 599223, 599224, 599225, 599226, 599227, 599228, 599229, 599235, 599236, 599279, 599280, 599314, 599321, 599362, 599378, 599390, 599391, 599398, 599399, 599404, 599413, 599414, 599416, 599419, 599420, 599422, 599435, 599437, 599438, 599441, 599483, 599494, 599508, 599552, 599553, 599554, 599568, 599570, 599577, 599581, 599591, 599592, and 599593.

In certain embodiments, the following antisense compounds or oligonucleotides target a region of a CFB nucleic acid and effect at least a 90% inhibition of a CFB mRNA, SEQ ID NOs: 84, 238, 239, 317, 412, 413, 420, 421, 426, 434, 436, 437, 438, 439, 440, 442, 443, 444, 445, 446, 448, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 464, 465, 472, 473, 514, 515, 542, 543, 544, 545, 546, 551, 553, 555, 556, 599, 600, 601, 602, 610, 616, 617, 618, 662, 666, 670, 676, 677, 678, 688, 689, 713, 723, 729, 730, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 755, 756, 768, 783, 793, 833, and 867.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 10 to 30 linked nucleosides complementary within nucleotides 2193-2212, 2195-2210, 2457-2476, 2571-2590, 2584-2603, 2588-2607, 2592-2611, 2594-2613, 2597-2616, 2600-2619, or 2596-2611 of SEQ ID NO: 1.

In certain embodiments, a compound comprises a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598.

In certain embodiments, a compound comprises a modified oligonucleotide having a nucleobase sequence consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises at least one modified internucleoside linkage, at least one modified sugar, and/or at least one modified nucleobase.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises at least one modified sugar. In certain embodiments, at least one modified sugar comprises a 2'-O-methoxyethyl group. In certain embodiments, at least one modified sugar is a bicyclic sugar, such as a 4'-$CH(CH_3)$-O-2' group, a 4'-CH_2-O-2' group, or a 4'-$(CH_2)_2$-O-2'group.

In certain embodiments, the modified oligonucleotide comprises at least one modified internucleoside linkage, such as a phosphorothioate internucleoside linkage.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises at least one modified nucleobase, such as 5-methylcytosine.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the oligonucleotide consists of 10 to 30 linked nucleosides having a nucleobase sequence comprising the sequence recited in SEQ ID NO: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, or 598.

In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising the sequence recited in SEQ ID NO: 198, 228, 237, 440, 444, 448, 450, 453, or 455, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

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

In certain embodiments, a compound comprises or consists of a single-stranded modified oligonucleotide consisting of 20 linked nucleosides having a nucleobase sequence consisting of the sequence recited in SEQ ID NO: 198, 228, 237, 440, 444, 448, 450, 453, or 455, wherein the oligonucleotide comprises:

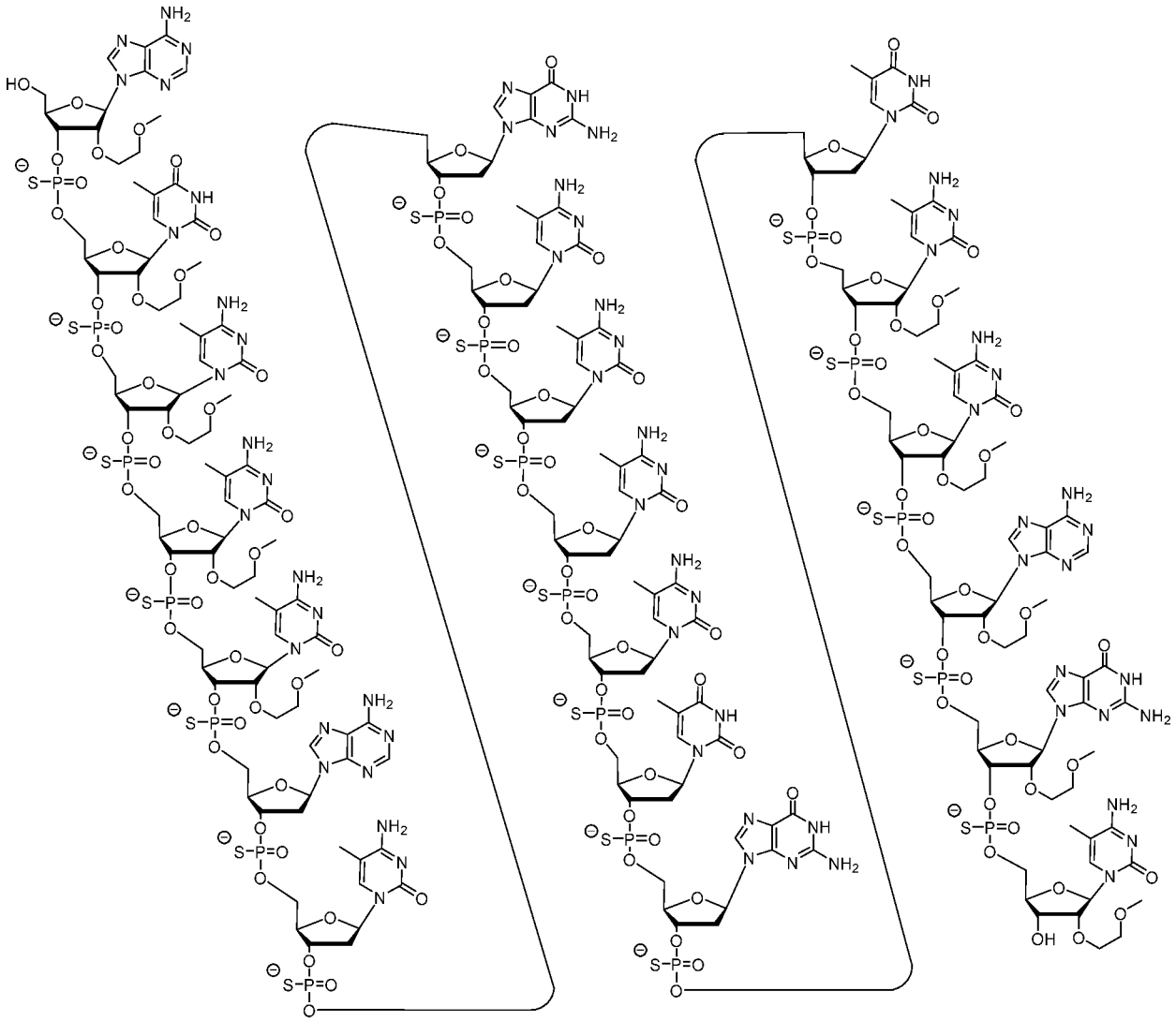
a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

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

In certain embodiments, a compound comprises ISIS 588540. In certain embodiments, a compound consists of ISIS 588540. In certain embodiments, ISIS 588540 has the following chemical structure:



In certain embodiments, a compound comprises or consists of a single-stranded modified oligonucleotide consisting of 16 linked nucleosides having a nucleobase sequence consisting of the sequence recited in SEQ ID NO: 549, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three 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 cEt sugar; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

In certain embodiments, a compound comprises or consists of a single-stranded modified oligonucleotide consisting of 16 linked nucleosides having a nucleobase sequence comprising the sequence recited in SEQ ID NO: 598, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein the 5' wing segment comprises a 2'-O-methoxyethyl sugar, 2'-O-methoxyethyl sugar, and cEt sugar in the 5' to 3' direction; wherein the 3' wing segment comprises a cEt sugar, cEt sugar, and 2'-O-methoxyethyl sugar in the 5' to 3' direction; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

In any of the foregoing embodiments, the compound or oligonucleotide can be at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% complementary to a nucleic acid encoding CFB.

In any of the foregoing embodiments, the compound or oligonucleotide can be single-stranded.

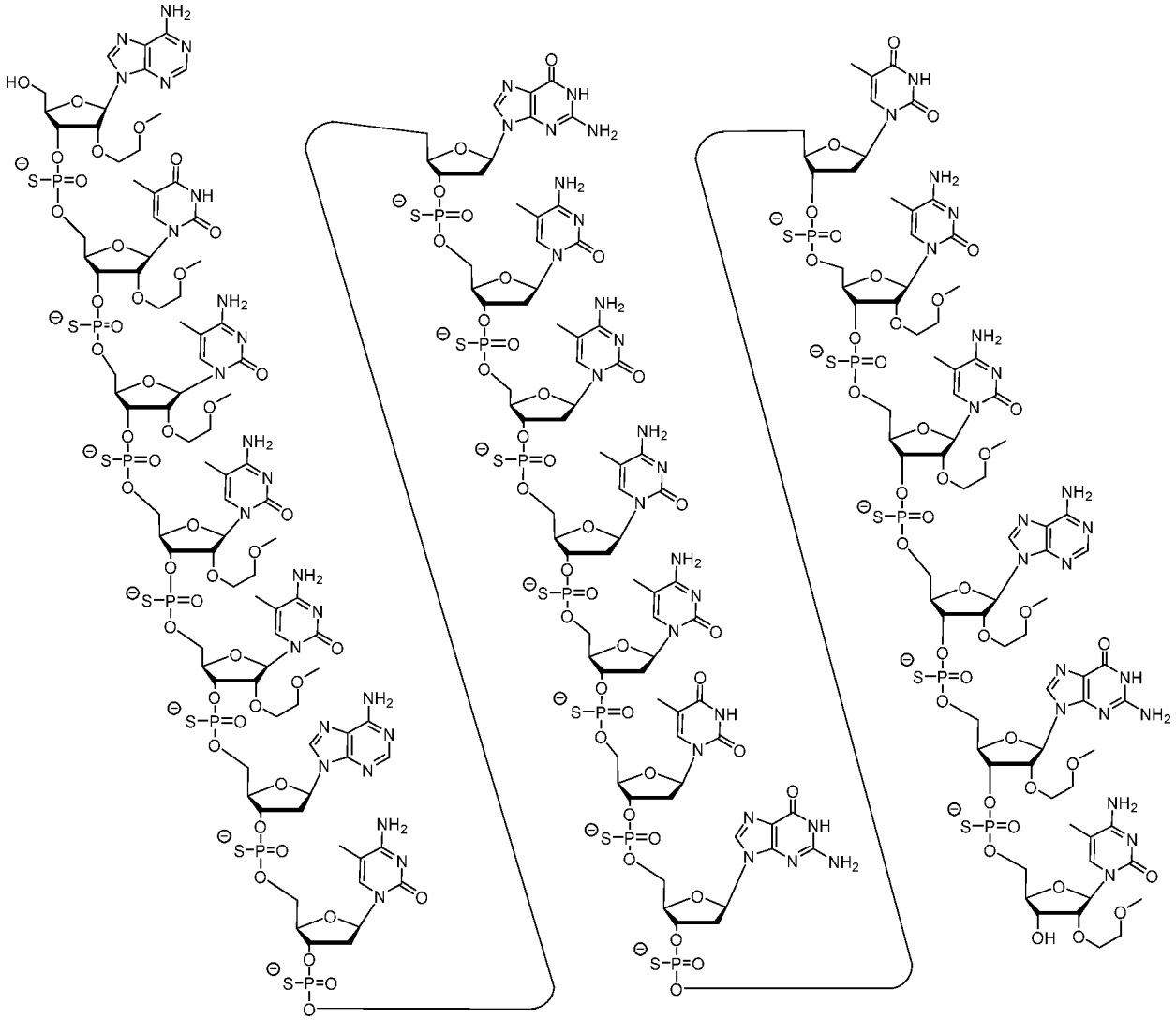
In certain embodiments, the compounds or compositions as described herein are efficacious by virtue of having at least one of an *in vitro* IC_{50} of less than 250 nM, less than 200 nM, less than 150 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 65 nM, less than 60 nM, less than 55 nM, less than 50 nM, less than 45 nM, less than 40 nM, less than 35 nM, less than 30 nM, less than 25 nM, or less than 20 nM.

In certain embodiments, the compounds or compositions as described herein are highly tolerable as demonstrated by having at least one of an increase an ALT or AST value of no more than 4 fold, 3 fold, or 2 fold over saline treated animals or an increase in liver, spleen, or kidney weight of no more than 30%, 20%, 15%, 12%, 10%, 5%, or 2%. In certain embodiments, the compounds or compositions as described herein are highly tolerable as demonstrated by having no increase of ALT or AST over saline treated animals. In certain embodiments, the compounds or compositions as described herein are highly tolerable as demonstrated by having no increase in liver, spleen, or kidney weight over saline treated animals.

Certain embodiments provide a composition comprising the compound of any of the aforementioned embodiments or salt thereof and at least one of a pharmaceutically acceptable carrier or diluent. In certain embodiments, the composition has a viscosity less than about 40 centipoise (cP), less than about 30 centipose

(cP), less than about 20 centipose (cP), less than about 15 centipose (cP), or less than about 10 centipose (cP). In certain embodiments, the composition having any of the aforementioned viscosities comprises a compound provided herein at a concentration of about 100 mg/mL, about 125 mg/mL, about 150 mg/mL, about 175 mg/mL, about 200 mg/mL, about 225 mg/mL, about 250 mg/mL, about 275 mg/mL, or about 300 mg/mL. In certain embodiments, the composition having any of the aforementioned viscosities and/or compound concentrations has a temperature of room temperature or about 20°C, about 21°C, about 22°C, about 23°C, about 24°C, about 25°C, about 26°C, about 27°C, about 28°C, about 29°C, or about 30°C.

In certain embodiments, a method of treating, preventing, or ameliorating a disease associated with dysregulation of the complement alternative pathway in a subject comprises administering to the subject a specific inhibitor of Complement Factor B (CFB), thereby treating, preventing, or ameliorating the disease. In certain embodiments, the complement alternative pathway is activated greater than normal. In certain embodiments, the CFB specific inhibitor is an antisense compound targeted to CFB, such as an antisense oligonucleotide targeted to CFB. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 588540, which has the following chemical structure:



In certain embodiments, the disease is macular degeneration, such as age related macular degeneration (AMD), which can be wet AMD or dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, the disease is a kidney disease such as lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof.

In certain embodiments, a method of treating, preventing, or ameliorating macular degeneration, such as age-related macular degeneration (AMD) in a subject comprises administering to the subject a CFB specific inhibitor, thereby treating, preventing, or ameliorating AMD, such as wet AMD and dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. Geographic Atrophy is considered an advanced form of dry AMD involving degeneration of the retina. In certain embodiments, the subject has a complement alternative pathway that is activated greater than normal. In certain embodiments, administering the antisense compound reduces or inhibits accumulation of ocular C3 levels, such as C3 protein levels. In certain embodiments, administering the antisense compound reduces the level of ocular C3 deposits or

inhibits accumulation of ocular C3 deposits. In certain embodiments, the CFB specific inhibitor is an antisense compound targeted to CFB, such as an antisense oligonucleotide targeted to CFB. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430. In certain embodiments, the compound is administered to the subject parenterally.

In certain embodiments, a method of treating, preventing, or ameliorating a kidney disease associated with dysregulation of the complement alternative pathway in a subject comprises administering to the subject a specific inhibitor of Complement Factor B (CFB), thereby treating, preventing, or ameliorating the kidney disease. In certain embodiments, the complement alternative pathway is activated greater than normal. In certain embodiments, the CFB specific inhibitor is an antisense compound targeted to CFB, such as an antisense oligonucleotide targeted to CFB. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430. In certain embodiments, the compound is administered to the subject parenterally. In certain embodiments, the kidney disease is lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof. In certain embodiments, the kidney disease is associated with C3 deposits, such as C3 deposits in the glomerulus. In certain embodiments, the kidney disease is associated with lower than normal circulating C3 levels, such as serum or plasma C3 levels. In certain embodiments, administering the compound reduces or inhibits accumulation of

C3 levels in the kidney, such as C3 protein levels. In certain embodiments, administering the compound reduces the level of kidney C3 deposits or inhibits accumulation of kidney C3 deposits, such as C3 levels in the glomerulus. In certain embodiments, the subject is identified as having or at risk of having a disease associated with dysregulation of the complement alternative pathway, for example by detecting complement levels or membrane-attack complex levels in the subject's blood and/or performing a genetic test for gene mutations of complement factors associated with the disease.

In certain embodiments, a method of inhibiting expression of Complement Factor B (CFB) in a subject having, or at risk of having, a disease associated with dysregulation of the complement alternative pathway comprises administering a Complement Factor B (CFB) specific inhibitor to the subject, thereby inhibiting expression of CFB in the subject. In certain embodiments, administering the inhibitor inhibits expression of CFB in the eye. In certain embodiments, the subject has, or is at risk of having, age related macular degeneration (AMD), such as wet AMD and dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, administering the inhibitor inhibits expression of CFB in the kidney, such as in the glomerulus. In certain embodiments, the subject has, or is at risk of having, lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430. In certain embodiments, the compound is administered to the subject parenterally.

In certain embodiments, a method of reducing or inhibiting accumulation of C3 deposits in the eye of a subject having, or at risk of having, a disease associated with dysregulation of the complement alternative pathway comprises administering a Complement Factor B (CFB) specific inhibitor to the subject, thereby reducing or inhibiting accumulation of C3 deposits in the eye of the subject. In certain embodiments, the subject has, or is at risk of having, age related macular degeneration (AMD), such as wet AMD and dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, the inhibitor is an antisense compound targeted to CFB. In certain embodiments, the CFB specific inhibitor is a

compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430. In certain embodiments, the compound is administered to the subject parenterally.

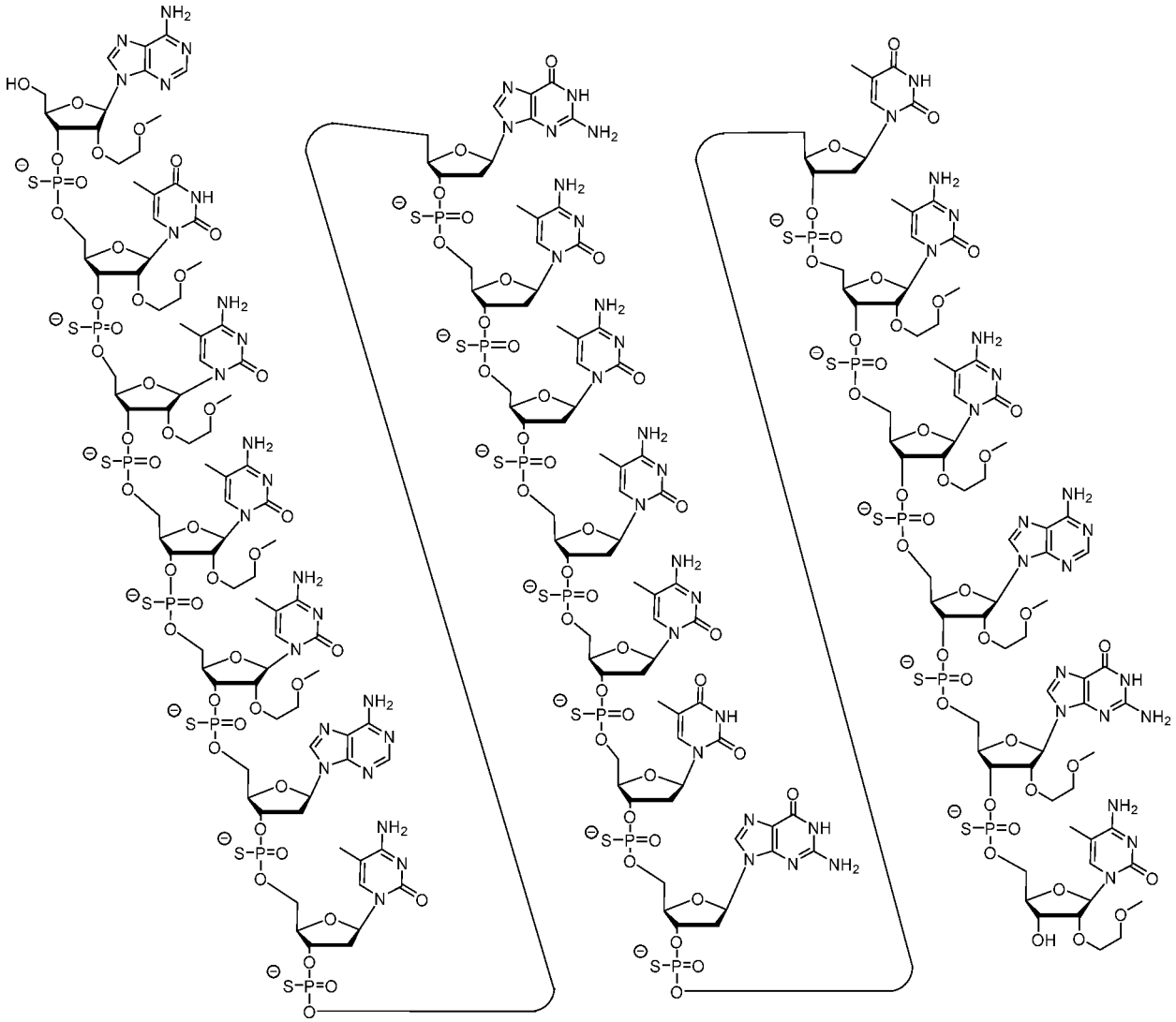
In certain embodiments, a method of reducing or inhibiting accumulation of C3 deposits in the kidney of a subject having, or at risk of having, a disease associated with dysregulation of the complement alternative pathway comprises administering a Complement Factor B (CFB) specific inhibitor to the subject, thereby reducing or inhibiting accumulation of C3 deposits in the kidney of the subject. In certain embodiments, the subject has, or is at risk of having, lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof. In certain embodiments, the inhibitor is an antisense compound targeted to CFB. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598. In certain embodiments, the CFB specific inhibitor is a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430. In certain embodiments, the compound is administered to the subject parenterally.

Certain embodiments are drawn to a compound or composition described herein for use in therapy. Certain embodiments are drawn to a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808 for use in therapy. Certain embodiments are drawn to a compound comprising or consisting of a modified oligonucleotide consisting of

10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808 for use in therapy. Certain embodiments are drawn to a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598, for use in therapy. Certain embodiments are drawn to a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430 for use in therapy.

Certain embodiments are drawn to a compound or composition described herein for use in treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808 for use in treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808 for use in treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598, for use in treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430 for use in treating a disease associated with dysregulation of the complement alternative pathway. In certain embodiments, the complement alternative pathway is activated greater than normal. In certain embodiments, the disease is macular degeneration, such as age related macular degeneration (AMD), which can be wet AMD or dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, the disease is a kidney disease such as lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof.

Certain embodiments are drawn to a compound comprising or consisting of ISIS 588540, which has the following chemical structure:

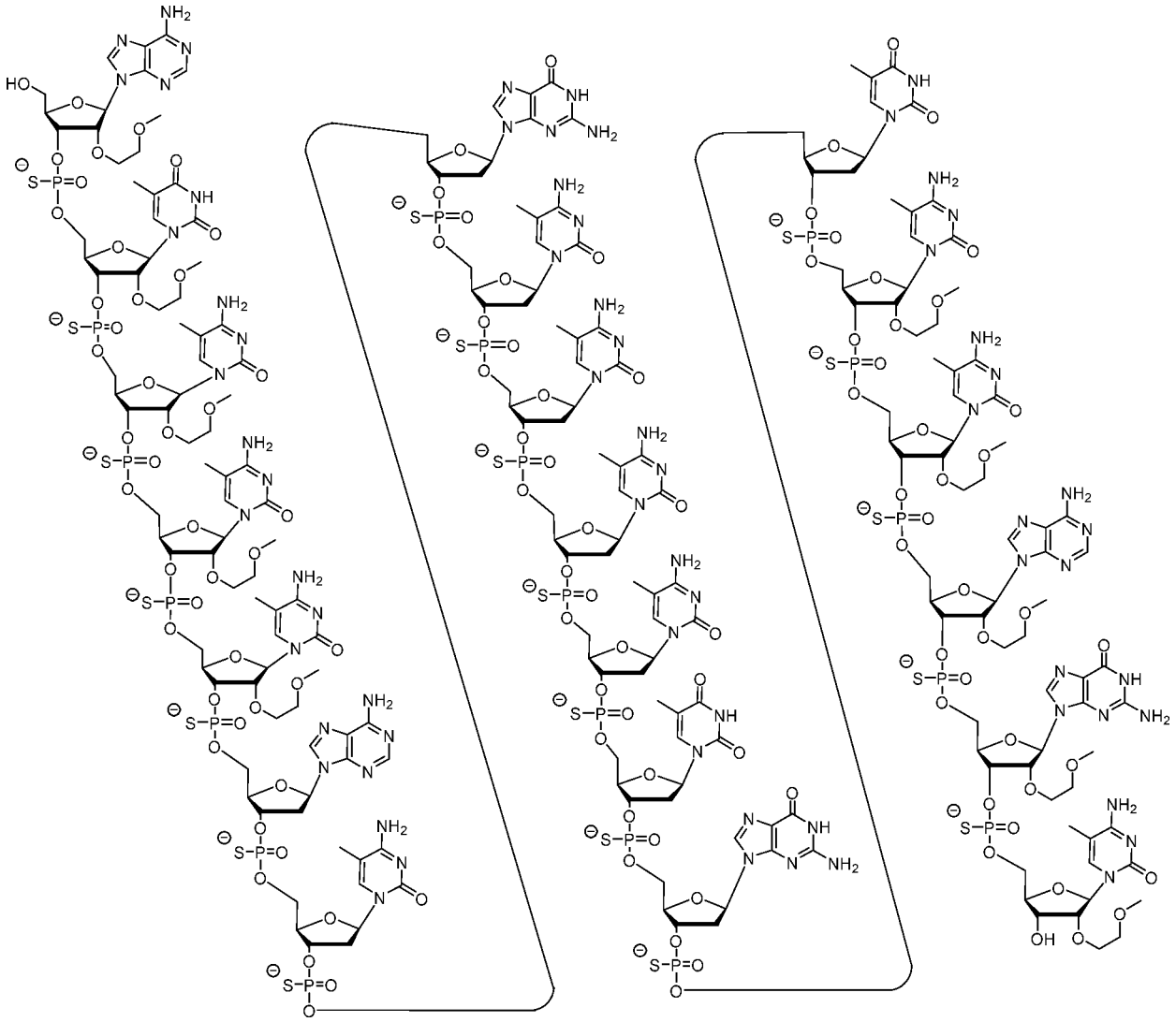


, for use in treating a disease associated with dysregulation of the complement alternative pathway. In certain embodiments, the complement alternative pathway is activated greater than normal. In certain embodiments, the disease is macular degeneration, such as age related macular degeneration (AMD), which can be wet AMD or dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, the disease is a kidney disease such as lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof.

Certain embodiments are drawn to use of a compound or composition described herein for the manufacture of a medicament for treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to use of a compound comprising or consisting of modified oligonucleotide consisting of 10 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 6-808 for

the manufacture of a medicament for treating disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to use of a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 6-808 for the manufacture of a medicament for treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to use of a compound comprising or consisting of a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising or consisting of any one of SEQ ID NOs: 198, 228, 237, 440, 444, 448, 450, 453, 455, 549, and 598, for the manufacture of a medicament for treating a disease associated with dysregulation of the complement alternative pathway. Certain embodiments are drawn to use of a compound comprising or consisting of ISIS 532770, 532800, 532809, 588540, 588544, 588548, 588550, 588553, 588555, 588848, or 594430 for the manufacture of a medicament for treating a disease associated with dysregulation of the complement alternative pathway. In certain embodiments, the complement alternative pathway is activated greater than normal. In certain embodiments, the disease is macular degeneration, such as age related macular degeneration (AMD), which can be wet AMD or dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, the disease is a kidney disease such as lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof.

Certain embodiments are drawn to use of a compound comprising or consisting of ISIS 588540, which has the following chemical structure:



, for the manufacture of a medicament for treating a disease associated with dysregulation of the complement alternative pathway. In certain embodiments, the complement alternative pathway is activated greater than normal. In certain embodiments, the disease is macular degeneration, such as age related macular degeneration (AMD), which can be wet AMD or dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. In certain embodiments, the disease is a kidney disease such as lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof.

In any of the foregoing embodiments, the CFB specific inhibitor can be an antisense compound targeted to CFB. In certain embodiments, the antisense compound comprises an antisense oligonucleotide, for example an antisense oligonucleotide consisting of 8 to 80 linked nucleosides, 12 to 30 linked nucleosides, or 20 linked nucleosides. In certain embodiments, the antisense oligonucleotide is at least 80%, 85%, 90%, 95% or 100% complementary to any of the nucleobase sequences recited in SEQ ID NOs: 1-5. In certain embodiments, the antisense oligonucleotide comprises at least one modified internucleoside linkage, at least

one modified sugar and/or at least one modified nucleobase. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage, the modified sugar is a bicyclic sugar or a 2'-O-methoxyethyl, and the modified nucleobase is a 5-methylcytosine. In certain embodiments, the modified oligonucleotide comprises a gap segment consisting of linked deoxynucleosides; a 5' wing segment consisting of linked nucleosides; and a 3' wing segment consisting of linked nucleosides, wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar. In certain embodiments, the antisense oligonucleotide is administered parenterally. For example, in certain embodiments the antisense oligonucleotide can be administered through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration.

Antisense compounds

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 is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

In certain embodiments, 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 embodiments, an antisense compound is 10 to 30 subunits in length. In certain embodiments, an antisense compound is 12 to 30 subunits in length. In certain embodiments, an antisense compound is 12 to 22 subunits in length. In certain embodiments, an antisense compound is 14 to 30 subunits in length. In certain embodiments, an antisense compound is 14 to 20 subunits in length. In certain embodiments, an antisense compoun is 15 to 30 subunits in length. In certain embodiments, an antisense compound is 15 to 20 subunits in length. In certain embodiments, an antisense compound is 16 to 30 subunits in length. In certain embodiments, an antisense compound is 16 to 20 subunits in length. In certain embodiments, an antisense compound is 17 to 30 subunits in length. In certain embodiments, an antisense compound is 17 to 20 subunits in length. In certain embodiments, an antisense compound is 18 to 30 subunits in length. In certain embodiments, an antisense compound is 18 to 21 subunits in length. In certain embodiments, an antisense compound is 18 to 20 subunits in length. In certain embodiments, an antisense compound is 20 to 30 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits, 14 to 30 linked subunits, 14 to 20 subunits, 15 to 30 subunits, 15 to 20 subunits, 16 to 30 subunits,

16 to 20 subunits, 17 to 30 subunits, 17 to 20 subunits, 18 to 30 subunits, 18 to 20 subunits, 18 to 21 subunits, 20 to 30 subunits, or 12 to 22 linked subunits, respectively. In certain embodiments, an antisense compound is 14 subunits in length. In certain embodiments, an antisense compound is 16 subunits in length. In certain embodiments, an antisense compound is 17 subunits in length. In certain embodiments, an antisense compound is 18 subunits in length. In certain embodiments, an antisense compound is 19 subunits in length. In certain embodiments, an antisense compound is 20 subunits in length. In other embodiments, 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. In certain such embodiments, 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 embodiments the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleotides.

In certain embodiments antisense oligonucleotides 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 an CFB 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.

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.

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.

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*.

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.

Certain Antisense Compound Motifs and Mechanisms

In certain embodiments, antisense compounds 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.

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 confer another desired property e.g., serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

Antisense activity may result from any mechanism involving the hybridization of the antisense compound (e.g., oligonucleotide) with a target nucleic acid, wherein the hybridization ultimately results in a biological effect. In certain embodiments, the amount and/or activity of the target nucleic acid is modulated. In certain embodiments, the amount and/or activity of the target nucleic acid is reduced. In certain embodiments, hybridization of the antisense compound to the target nucleic acid ultimately results in target nucleic acid degradation. In certain embodiments, hybridization of the antisense compound to the target nucleic acid does not result in target nucleic acid degradation. In certain such embodiments, the presence of the antisense compound hybridized with the target nucleic acid (occupancy) results in a modulation of antisense activity. In certain embodiments, antisense compounds having a particular chemical motif or pattern of chemical modifications are particularly suited to exploit one or more mechanisms. In certain embodiments, antisense compounds function through more than one mechanism and/or through mechanisms that have not been elucidated. Accordingly, the antisense compounds described herein are not limited by particular mechanism.

Antisense mechanisms include, without limitation, RNase H mediated antisense; RNAi mechanisms, which utilize the RISC pathway and include, without limitation, siRNA, ssRNA and microRNA mechanisms;

and occupancy based mechanisms. Certain antisense compounds may act through more than one such mechanism and/or through additional mechanisms.

RNase H-Mediated Antisense

In certain embodiments, antisense activity results at least in part from degradation of target RNA by RNase H. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-stranded antisense compounds which are "DNA-like" elicit RNase H activity in mammalian cells. Accordingly, antisense compounds comprising at least a portion of DNA or DNA-like nucleosides may activate RNase H, resulting in cleavage of the target nucleic acid. In certain embodiments, antisense compounds that utilize RNase H comprise one or more modified nucleosides. In certain embodiments, such antisense compounds comprise at least one block of 1-8 modified nucleosides. In certain such embodiments, the modified nucleosides do not support RNase H activity. In certain embodiments, such antisense compounds are gapmers, as described herein. In certain such embodiments, the gap of the gapmer comprises DNA nucleosides. In certain such embodiments, the gap of the gapmer comprises DNA-like nucleosides. In certain such embodiments, the gap of the gapmer comprises DNA nucleosides and DNA-like nucleosides.

Certain 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. In certain embodiments, 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-CH_3, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides may include those having a constrained ethyl). In certain embodiments, nucleosides in the wings may include several modified sugar moieties, including, for example 2'-MOE and bicyclic sugar moieties such as constrained ethyl or LNA. In certain embodiments, wings may include several modified and unmodified sugar moieties. In certain embodiments, wings may include various combinations of 2'-MOE nucleosides, bicyclic sugar moieties such as constrained ethyl nucleosides or LNA nucleosides, and 2'-deoxynucleosides.

Each distinct region may comprise uniform sugar moieties, variant, 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 embodiments, "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 embodiments, "X" and "Z" are the same; in other embodiments they are different. In certain embodiments, "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.

In certain embodiments, the antisense compound targeted to a CFB nucleic acid has a gapmer motif in which the gap consists of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 linked nucleosides.

In certain embodiments, 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;

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.

RNAi Compounds

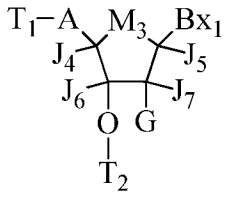
In certain embodiments, antisense compounds are interfering RNA compounds (RNAi), which include double-stranded RNA compounds (also referred to as short-interfering RNA or siRNA) and single-stranded RNAi compounds (or ssRNA). Such compounds work at least in part through the RISC pathway to degrade and/or sequester a target nucleic acid (thus, include microRNA/microRNA-mimic compounds). In certain embodiments, antisense compounds comprise modifications that make them particularly suited for such mechanisms.

i. ssRNA compounds

In certain embodiments, antisense compounds including those particularly suited for use as single-stranded RNAi compounds (ssRNA) comprise a modified 5'-terminal end. In certain such embodiments, the 5'-terminal end comprises a modified phosphate moiety. In certain embodiments, such modified phosphate is

stabilized (e.g., resistant to degradation/cleavage compared to unmodified 5'-phosphate). In certain embodiments, such 5'-terminal nucleosides stabilize the 5'-phosphorous moiety. Certain modified 5'-terminal nucleosides may be found in the art, for example in WO/2011/139702.

In certain embodiments, the 5'-nucleoside of an ssRNA compound has Formula IIc:



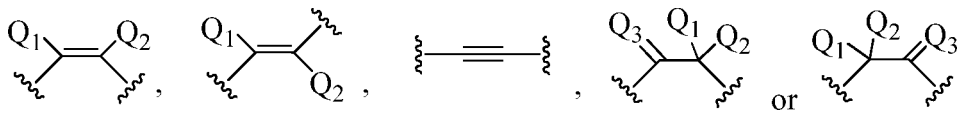
IIc

wherein:

T_1 is an optionally protected phosphorus moiety;

T_2 is an internucleoside linking group linking the compound of Formula IIc to the oligomeric compound;

A has one of the formulas:



Q_1 and Q_2 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_2-C_6 alkynyl or $N(R_3)(R_4)$;

Q_3 is O, S, $N(R_5)$ or $C(R_6)(R_7)$;

each R_3, R_4 R_5, R_6 and R_7 is, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl or C_1-C_6 alkoxy;

M_3 is O, S, NR_{14}, $C(R_{15})(R_{16})$, $C(R_{15})(R_{16})C(R_{17})(R_{18})$, $C(R_{15})=C(R_{17})$, $OC(R_{15})(R_{16})$ or $OC(R_{15})(Bx_2)$;

R_{14} is H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

R_{15}, R_{16}, R_{17} and R_{18} are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

Bx_1 is a heterocyclic base moiety;

or if Bx_2 is present then Bx_2 is a heterocyclic base moiety and Bx_1 is H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

J_4, J_5, J_6 and J_7 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

or J_4 forms a bridge with one of J_5 or J_7 wherein said bridge comprises from 1 to 3 linked biradical groups selected from O, S, NR_{19}, $C(R_{20})(R_{21})$, $C(R_{20})=C(R_{21})$, $C[=C(R_{20})(R_{21})]$ and C(=O) and the other two of J_5, J_6 and J_7 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

each R_{19}, R_{20} and R_{21} is, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

G is H, OH, halogen or $O\text{-}[C(R_8)(R_9)]_n\text{-}[(C=O)_m\text{-}X_1]_j\text{-}Z$;

each R_8 and R_9 is, independently, H, halogen, C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

X_1 is O, S or $N(E_1)$;

Z is H, halogen, 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, substituted C_2-C_6 alkynyl or $N(E_2)(E_3)$;

E_1, E_2 and E_3 are each, independently, H, C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

n is from 1 to about 6;

m is 0 or 1;

j is 0 or 1;

each substituted group comprises one or more optionally protected substituent groups independently selected from halogen, OJ_1, $N(J_1)(J_2)$, $=NJ_1$, SJ_1, N_3, CN, $OC(=X_2)J_1$, $OC(=X_2)N(J_1)(J_2)$ and $C(=X_2)N(J_1)(J_2)$;

X_2 is O, S or NJ_3;

each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl;

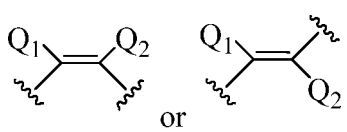
when j is 1 then Z is other than halogen or $N(E_2)(E_3)$; and

wherein said oligomeric compound comprises from 8 to 40 monomeric subunits and is hybridizable to at least a portion of a target nucleic acid.

In certain embodiments, M_3 is O, CH=CH, OCH_2 or $OC(H)(Bx_2)$. In certain embodiments, M_3 is O.

In certain embodiments, J_4, J_5, J_6 and J_7 are each H. In certain embodiments, J_4 forms a bridge with one of J_5 or J_7.

In certain embodiments, A has one of the formulas:

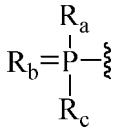


or

wherein:

Q_1 and Q_2 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy or substituted C_1-C_6 alkoxy. In certain embodiments, Q_1 and Q_2 are each H. In certain embodiments, Q_1 and Q_2 are each, independently, H or halogen. In certain embodiments, Q_1 and Q_2 is H and the other of Q_1 and Q_2 is F, CH_3 or OCH_3.

In certain embodiments, T_1 has the formula:



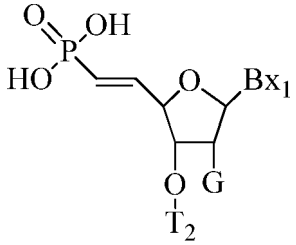
wherein:

R_a and R_c are each, independently, protected hydroxyl, protected thiol, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, protected amino or substituted amino; and

R_b is O or S. In certain embodiments, R_b is O and R_a and R_c are each, independently, OCH_3, OCH_2CH_3 or $CH(CH_3)_2$.

In certain embodiments, G is halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-SCH_3, $O(CH_2)_2$-OCF_3, $O(CH_2)_3$-$N(R_{10})(R_{11})$, $O(CH_2)_2$-$ON(R_{10})(R_{11})$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_{10})(R_{11})$, $OCH_2C(=O)$-$N(R_{10})(R_{11})$, $OCH_2C(=O)$-$N(R_{12})$-$(CH_2)_2$-$N(R_{10})(R_{11})$ or $O(CH_2)_2$-$N(R_{12})$-$C(=NR_{13})[N(R_{10})(R_{11})]$ wherein R_{10}, R_{11}, R_{12} and R_{13} are each, independently, H or C_1-C_6 alkyl. In certain embodiments, G is halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$ or OCH_2-$N(H)$-$C(=NH)NH_2$. In certain embodiments, G is F, OCH_3 or $O(CH_2)_2$-OCH_3. In certain embodiments, G is $O(CH_2)_2$-OCH_3.

In certain embodiments, the 5'-terminal nucleoside has Formula IIe:



IIe

In certain embodiments, antisense compounds, including those particularly suitable for ssRNA comprise one or more type of modified sugar moieties and/or naturally occurring sugar moieties arranged along an oligonucleotide or region thereof in a defined pattern or sugar modification motif. Such motifs may include any of the sugar modifications discussed herein and/or other known sugar modifications.

In certain embodiments, the oligonucleotides comprise or consist of a region having uniform sugar modifications. In certain such embodiments, each nucleoside of the region comprises the same RNA-like sugar modification. In certain embodiments, each nucleoside of the region is a 2'-F nucleoside. In certain

embodiments, each nucleoside of the region is a 2'-OMe nucleoside. In certain embodiments, each nucleoside of the region is a 2'-MOE nucleoside. In certain embodiments, each nucleoside of the region is a cEt nucleoside. In certain embodiments, each nucleoside of the region is an LNA nucleoside. In certain embodiments, the uniform region constitutes all or essentially all of the oligonucleotide. In certain embodiments, the region constitutes the entire oligonucleotide except for 1-4 terminal nucleosides.

In certain embodiments, oligonucleotides comprise one or more regions of alternating sugar modifications, wherein the nucleosides alternate between nucleotides having a sugar modification of a first type and nucleotides having a sugar modification of a second type. In certain embodiments, nucleosides of both types are RNA-like nucleosides. In certain embodiments the alternating nucleosides are selected from: 2'-OMe, 2'-F, 2'-MOE, LNA, and cEt. In certain embodiments, the alternating modificatios are 2'-F and 2'-OMe. Such regions may be contiguous or may be interupted by differently modified nucleosides or conjugated nucleosides.

In certain embodiments, the alternating region of alternating modifications each consist of a single nucleoside (i.e., the patern is $(AB)_xA_y$ wheren A is a nucleoside having a sugar modification of a first type and B is a nucleoside having a sugar modification of a second type; x is 1-20 and y is 0 or 1). In certan embodiments, one or more alternating regions in an alternating motif includes more than a single nucleoside of a type. For example, oligonucleotides may include one or more regions of any of the following nucleoside motifs:

AABBAA;
ABBABB;
AABAAB;
ABBABAABB;
ABABAA;
AABABAB;
ABABAA;
ABBAABBABABAA;
BABBAABBABABAA; or
ABABBAABBABABAA;

wherein A is a nucleoside of a first type and B is a nucleoside of a second type. In certain embodiments, A and B are each selected from 2'-F, 2'-OMe, BNA, and MOE.

In certain embodiments, oligonucleotides having such an alternating motif also comprise a modified 5' terminal nucleoside, such as those of formula IIc or IIe.

In certain embodiments, oligonucleotides comprise a region having a 2-2-3 motif. Such regions comprises the following motif:

$-(A)_2-(B)_x-(A)_2-(C)_y-(A)_3-$

wherein: A is a first type of modifed nucleosde;

B and C, are nucleosides that are differently modified than A, however, B and C may have the same or different modifications as one another;

x and y are from 1 to 15.

In certain embodiments, A is a 2'-OMe modified nucleoside. In certain embodiments, B and C are both 2'-F modified nucleosides. In certain embodiments, A is a 2'-OMe modified nucleoside and B and C are both 2'-F modified nucleosides.

In certain embodiments, oligonucleosides have the following sugar motif:

5'- (Q)- $(AB)_xA_y$-$(D)_z$

wherein:

Q is a nucleoside comprising a stabilized phosphate moiety. In certain embodiments, Q is a nucleoside having Formula IIc or IIe;

A is a first type of modifed nucleoside;

B is a second type of modified nucleoside;

D is a modified nucleoside comprising a modification different from the nucleoside adjacent to it. Thus, if y is 0, then D must be differently modified than B and if y is 1, then D must be differently modified than A. In certain embodiments, D differs from both A and B.

X is 5-15;

Y is 0 or 1;

Z is 0-4.

In certain embodiments, oligonucleosides have the following sugar motif:

5'- (Q)- $(A)_x$-$(D)_z$

wherein:

Q is a nucleoside comprising a stabilized phosphate moiety. In certain embodiments, Q is a nucleoside having Formula IIc or IIe;

A is a first type of modifed nucleoside;

D is a modified nucleoside comprising a modification different from A.

X is 11-30;

Z is 0-4.

In certain embodiments A, B, C, and D in the above motifs are selected from: 2'-OMe, 2'-F, 2'-MOE, LNA, and cEt. In certain embodiments, D represents terminal nucleosides. In certain embodiments, such terminal nucleosides are not designed to hybridize to the target nucleic acid (though one or more might hybridize by chance). In certiain embodiments, the nucleobase of each D nucleoside is adenine, regardless of the identity of the nucleobase at the corresponding position of the target nucleic acid. In certain embodiments the nucleobase of each D nucleoside is thymine.

In certain embodiments, antisense compounds, including those particularly suited for use as ssRNA comprise modified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or modified internucleoside linkage motif. In certain embodiments, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides comprise a region of uniformly modified internucleoside linkages. In certain such embodiments, the oligonucleotide comprises a region that is uniformly linked by phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide is uniformly linked by phosphorothioate internucleoside linkages. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate and at least one internucleoside linkage is phosphorothioate.

In certain embodiments, the oligonucleotide comprises at least 6 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 6 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 8 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 10 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least one 12 consecutive phosphorothioate internucleoside linkages. In certain such embodiments, at least one such block is located at the 3' end of the oligonucleotide. In certain such embodiments, at least one such block is located within 3 nucleosides of the 3' end of the oligonucleotide.

Oligonucleotides having any of the various sugar motifs described herein, may have any linkage motif. For example, the oligonucleotides, including but not limited to those described above, may have a linkage motif selected from non-limiting the table below:

5' most linkage	Central region	3'-region
PS	Alternating PO/PS	6 PS
PS	Alternating PO/PS	7 PS
PS	Alternating PO/PS	8 PS

ii. siRNA compounds

In certain embodiments, antisense compounds are double-stranded RNAi compounds (siRNA). In such embodiments, one or both strands may comprise any modification motif described above for ssRNA. In

certain embodiments, ssRNA compounds may be unmodified RNA. In certain embodiments, siRNA compounds may comprise unmodified RNA nucleosides, but modified internucleoside linkages.

Several embodiments relate to double-stranded compositions wherein each strand comprises a motif defined by the location of one or more modified or unmodified nucleosides. In certain embodiments, compositions are provided comprising a first and a second oligomeric compound that are fully or at least partially hybridized to form a duplex region and further comprising a region that is complementary to and hybridizes to a nucleic acid target. It is suitable that such a composition comprise a first oligomeric compound that is an antisense strand having full or partial complementarity to a nucleic acid target and a second oligomeric compound that is a sense strand having one or more regions of complementarity to and forming at least one duplex region with the first oligomeric compound.

The compositions of several embodiments modulate gene expression by hybridizing to a nucleic acid target resulting in loss of its normal function. In certain embodiments, the degradation of the targeted CFB is facilitated by an activated RISC complex that is formed with compositions of the invention.

Several embodiments are directed to double-stranded compositions wherein one of the strands is useful in, for example, influencing the preferential loading of the opposite strand into the RISC (or cleavage) complex. The compositions are useful for targeting selected nucleic acid molecules and modulating the expression of one or more genes. In some embodiments, the compositions of the present invention hybridize to a portion of a target RNA resulting in loss of normal function of the target RNA.

Certain embodiments are drawn to double-stranded compositions wherein both the strands comprises a hemimer motif, a fully modified motif, a positionally modified motif or an alternating motif. Each strand of the compositions of the present invention can be modified to fulfil a particular role in for example the siRNA pathway. Using a different motif in each strand or the same motif with different chemical modifications in each strand permits targeting the antisense strand for the RISC complex while inhibiting the incorporation of the sense strand. Within this model, each strand can be independently modified such that it is enhanced for its particular role. The antisense strand can be modified at the 5'-end to enhance its role in one region of the RISC while the 3'-end can be modified differentially to enhance its role in a different region of the RISC.

The double-stranded oligonucleotide molecules can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The double-stranded oligonucleotide molecules can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense

strand form a duplex or double-stranded structure, for example wherein the double-stranded region is about 15 to about 30, e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs; the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof (e.g., about 15 to about 25 or more nucleotides of the double-stranded oligonucleotide molecule are complementary to the target nucleic acid or a portion thereof). Alternatively, the double-stranded oligonucleotide is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siRNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s).

The double-stranded oligonucleotide can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The double-stranded oligonucleotide can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide can be processed either in vivo or in vitro to generate an active siRNA molecule capable of mediating RNAi.

In certain embodiments, the double-stranded oligonucleotide comprises separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the double-stranded oligonucleotide comprises nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the double-stranded oligonucleotide interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene.

As used herein, double-stranded oligonucleotides need not be limited to those molecules containing only RNA, but further encompasses chemically modified nucleotides and non-nucleotides. In certain embodiments, the short interfering nucleic acid molecules lack 2'-hydroxy (2'-OH) containing nucleotides. In certain embodiments short interfering nucleic acids optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such double-stranded oligonucleotides that do not require the presence of ribonucleotides within the molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups.

Optionally, double-stranded oligonucleotides can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. As used herein, the term siRNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, double-stranded oligonucleotides can be used to epigenetically silence genes at both the post-transcriptional level and the pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siRNA molecules of the invention can result from siRNA mediated modification of chromatin structure or methylation pattern to alter gene expression (see, for example, Verdel et al., 2004, Science, 303, 672-676; Pal-Bhadra et al., 2004, Science, 303, 669-672; Allshire, 2002, Science, 297, 1818-1819; Volpe et al., 2002, Science, 297, 1833-1837; Jenuwein, 2002, Science, 297, 2215-2218; and Hall et al., 2002, Science, 297, 2232-2237).

It is contemplated that compounds and compositions of several embodiments provided herein can target CFB by a dsRNA-mediated gene silencing or RNAi mechanism, including, e.g., "hairpin" or stem-loop double-stranded RNA effector molecules in which a single RNA strand with self-complementary sequences is capable of assuming a double-stranded conformation, or duplex dsRNA effector molecules comprising two separate strands of RNA. In various embodiments, the dsRNA consists entirely of ribonucleotides or consists of a mixture of ribonucleotides and deoxynucleotides, such as the RNA/DNA hybrids disclosed, for example, by WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999. The dsRNA or dsRNA effector molecule may be a single molecule with a region of self-complementarity such that nucleotides in one segment of the molecule base pair with nucleotides in another segment of the molecule. In various embodiments, a dsRNA that consists of a single molecule consists entirely of ribonucleotides or includes a region of ribonucleotides that is complementary to a region of deoxyribonucleotides. Alternatively, the dsRNA may include two different strands that have a region of complementarity to each other.

In various embodiments, both strands consist entirely of ribonucleotides, one strand consists entirely of ribonucleotides and one strand consists entirely of deoxyribonucleotides, or one or both strands contain a mixture of ribonucleotides and deoxyribonucleotides. In certain embodiments, the regions of complementarity are at least 70, 80, 90, 95, 98, or 100% complementary to each other and to a target nucleic acid sequence. In certain embodiments, the region of the dsRNA that is present in a double-stranded conformation includes at least 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 50, 75,100, 200, 500, 1000, 2000 or 5000 nucleotides or includes all of the nucleotides in a cDNA or other target nucleic acid sequence being represented in the dsRNA. In some embodiments, the dsRNA does not contain any single stranded regions,

such as single stranded ends, or the dsRNA is a hairpin. In other embodiments, the dsRNA has one or more single stranded regions or overhangs. In certain embodiments, RNA/DNA hybrids include a DNA strand or region that is an antisense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% complementarity to a target nucleic acid) and an RNA strand or region that is a sense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% identity to a target nucleic acid), and vice versa.

In various embodiments, the RNA/DNA hybrid is made in vitro using enzymatic or chemical synthetic methods such as those described herein or those described in WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999. In other embodiments, a DNA strand synthesized in vitro is complexed with an RNA strand made in vivo or in vitro before, after, or concurrent with the transformation of the DNA strand into the cell. In yet other embodiments, the dsRNA is a single circular nucleic acid containing a sense and an antisense region, or the dsRNA includes a circular nucleic acid and either a second circular nucleic acid or a linear nucleic acid (see, for example, WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999.) Exemplary circular nucleic acids include lariat structures in which the free 5' phosphoryl group of a nucleotide becomes linked to the 2' hydroxyl group of another nucleotide in a loop back fashion.

In other embodiments, the dsRNA includes one or more modified nucleotides in which the 2' position in the sugar contains a halogen (such as fluorine group) or contains an alkoxy group (such as a methoxy group) which increases the half-life of the dsRNA in vitro or in vivo compared to the corresponding dsRNA in which the corresponding 2' position contains a hydrogen or an hydroxyl group. In yet other embodiments, the dsRNA includes one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramide, phosphorothioate, and phosphorodithioate linkages. The dsRNAs may also be chemically modified nucleic acid molecules as taught in U.S. Pat. No. 6,673,661. In other embodiments, the dsRNA contains one or two capped strands, as disclosed, for example, by WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999.

In other embodiments, the dsRNA can be any of the at least partially dsRNA molecules disclosed in WO 00/63364, as well as any of the dsRNA molecules described in U.S. Provisional Application 60/399,998; and U.S. Provisional Application 60/419,532, and PCT/US2003/033466, the teaching of which is hereby incorporated by reference. Any of the dsRNAs may be expressed in vitro or in vivo using the methods described herein or standard methods, such as those described in WO 00/63364.

Occupancy

In certain embodiments, antisense compounds are not expected to result in cleavage or the target nucleic acid via RNase H or to result in cleavage or sequestration through the RISC pathway. In certain such embodiments, antisense activity may result from occupancy, wherein the presence of the hybridized antisense

compound disrupts the activity of the target nucleic acid. In certain such embodiments, the antisense compound may be uniformly modified or may comprise a mix of modifications and/or modified and unmodified nucleosides.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

Nucleotide sequences that encode Complement Factor B (CFB) include, without limitation, the following: GENBANK Accession No. NM_001710.5 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No NW_001116486.1 truncated from nucleotides 536000 to 545000 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. XM_001113553.2 (incorporated herein as SEQ ID NO: 4), or GENBANK Accession No. NM_008198.2 (incorporated herein as SEQ ID NO: 5).

Hybridization

In some embodiments, hybridization occurs between an antisense compound disclosed herein and a CFB 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.

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.

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

Complementarity

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 CFB nucleic acid).

Non-complementary nucleobases between an antisense compound and a CFB 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 CFB nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

In certain embodiments, 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 CFB 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.

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).

In certain embodiments, the antisense compounds provided herein, or specified portions thereof, are fully complementary (i.e. 100% complementary) to a target nucleic acid, or specified portion thereof. For example, an antisense compound may be fully complementary to a CFB 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.

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.

In certain embodiments, 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 CFB nucleic acid, or specified portion thereof.

In certain embodiments, 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 CFB nucleic acid, or specified portion thereof.

The antisense compounds provided also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an antisense compound. In certain embodiments, the antisense compounds, are complementary to at least an 8 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 9 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 10 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least an 11 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 12 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 13 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 14 nucleobase portion of a target segment. In certain embodiments, 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

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.

In certain embodiments, the antisense compounds, or portions thereof, are, or 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.

In certain embodiments, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain embodiments, 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.

In certain embodiments, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain embodiments, 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

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.

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.

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

The naturally occuring 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.

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

In certain embodiments, antisense compounds targeted to a CFB nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

Modified Sugar Moieties

Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substitutent 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 $C(R_1)(R_2)$ (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (see PCT International Application WO 2008/101157 Published on 8/21/08 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923, published on June 16, 2005) or alternatively 5'-substitution of a BNA (see PCT International Application WO 2007/134181 Published on 11/22/07 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (*R* or *S*), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F and 2'-$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-$N(R_m)(R_n)$, O-CH_2-C(=O)-$N(R_m)(R_n)$, and O-CH_2-C(=O)-$N(R_l)$-$(CH_2)_2$-$N(R_m)(R_n)$, where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein

include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)-S-2'; 4'-(CH_2)$_2$-O-2' (ENA); 4'-CH(CH_3)-O-2' (also referred to as constrained ethyl or cEt) and 4'-CH(CH_2OCH_3)-O-2' (and analogs thereof see U.S. Patent 7,399,845, issued on July 15, 2008); 4'-C(CH_3)(CH_3)-O-2' (and analogs thereof see published International Application WO/2009/006478, published January 8, 2009); 4'-CH_2-N(OCH_3)-2' (and analogs thereof see published International Application WO/2008/150729, published December 11, 2008); 4'-CH_2-O-N(CH_3)-2' (see published U.S. Patent Application US2004-0171570, published September 2, 2004); 4'-CH_2-N(R)-O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Patent 7,427,672, issued on September 23, 2008); 4'-CH_2-C(H)(CH_3)-2' (see Chattopadhyaya *et al., J. Org. Chem.,* 2009, *74*, 118-134); and 4'-CH_2-C(=CH_2)-2' (and analogs thereof see published International Application WO 2008/154401, published on December 8, 2008).

Further reports related to bicyclic nucleosides can also be found in published literature (see for example: Singh *et al., Chem. Commun.*, 1998, *4*, 455-456; Koshkin *et al., Tetrahedron*, 1998, *54*, 3607-3630; Wahlestedt *et al., Proc. Natl. Acad. Sci. U. S. A.*, 2000, *97*, 5633-5638; Kumar *et al., Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222; Singh *et al., J. Org. Chem.*, 1998, *63*, 10035-10039; Srivastava *et al., J. Am. Chem. Soc.*, 2007, *129(26)* 8362-8379; Elayadi *et al., Curr. Opinion Invest. Drugs,* 2001, *2*, 558-561; Braasch *et al., Chem. Biol.,* 2001, *8*, 1-7; and Orum *et al., Curr. Opinion Mol. Ther.,* 2001, *3*, 239-243; U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Serial Nos. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on March 25, 1999 as WO 99/14226).

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

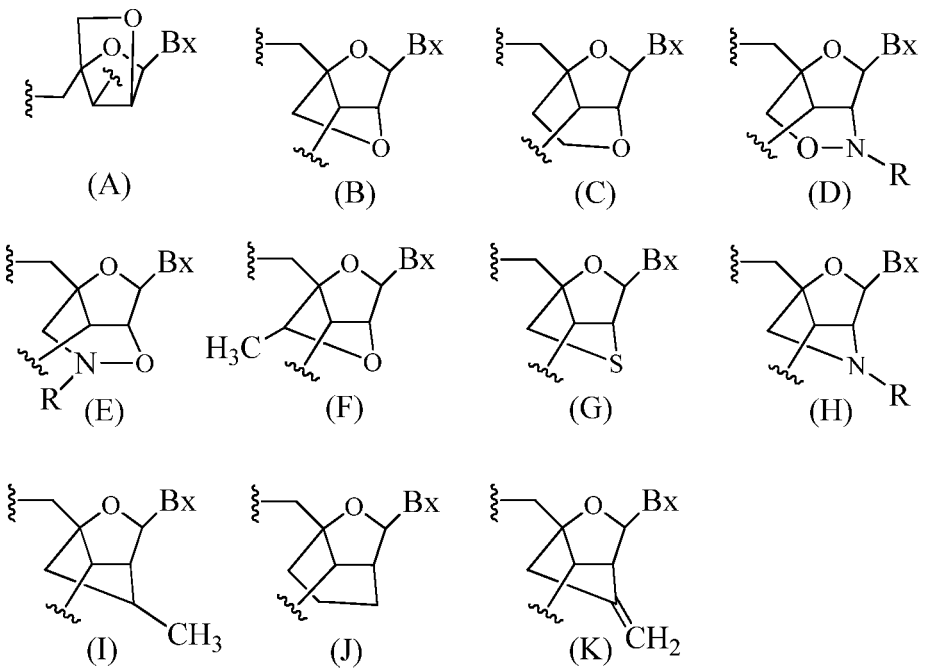
C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl ($S(=O)$-J_1); and

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 (C(=O)-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.

In certain embodiments, the bridge of a bicyclic sugar moiety is $-[C(R_a)(R_b)]_n$-, $-[C(R_a)(R_b)]_n$-O-, $-C(R_aR_b)$-N(R)-O- or $-C(R_aR_b)$-O-N(R)-. In certain embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R)-2' and 4'-CH_2-N(R)-O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl.

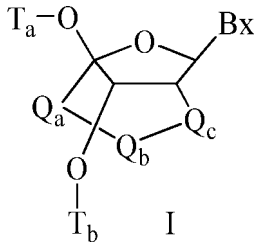
In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2-O-2') BNA's have been incorporated into antisense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

In certain embodiments, bicyclic nucleosides include, but are not limited to, (A) α-L-methyleneoxy (4'-CH_2-O-2') BNA , (B) β-D-methyleneoxy (4'-CH_2-O-2') BNA , (C) ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA , (D) aminooxy (4'-CH_2-O-N(R)-2') BNA, (E) oxyamino (4'-CH_2-N(R)-O-2') BNA, and (F) methyl(methyleneoxy) (4'-$CH(CH_3)$-O-2') BNA, (G) methylene-thio (4'-CH_2-S-2') BNA, (H) methylene-amino (4'-CH_2-N(R)-2') BNA, (I) methyl carbocyclic (4'-CH_2-$CH(CH_3)$-2') BNA, (J) propylene carbocyclic (4'-$(CH_2)_3$-2') BNA and (K) vinyl BNA as depicted below:



wherein Bx is the base moiety and R is independently H, a protecting group, C_1-C_{12} alkyl or C_1-C_{12} alkoxy.

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



I

wherein:

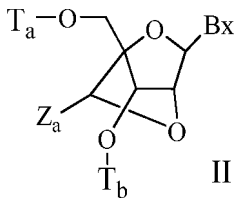
Bx is a heterocyclic base moiety;

$-Q_a-Q_b-Q_c-$ is $-CH_2-N(R_c)-CH_2-$, $-C(=O)-N(R_c)-CH_2-$, $-CH_2-O-N(R_c)-$, $-CH_2-N(R_c)-O-$ or $-N(R_c)-O-CH_2$;

R_c is C_1-C_{12} 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.

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



II

wherein:

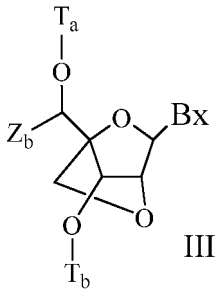
Bx is a heterocyclic base moiety;

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

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

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

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



III

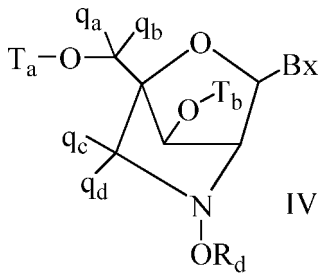
wherein:

Bx is a heterocyclic base moiety;

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

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

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



IV

wherein:

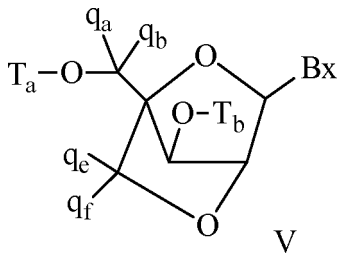
Bx is a heterocyclic base moiety;

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

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

each q_a, q_b, q_c and q_d is, independently, H, halogen, 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, C_1-C_6 alkoxyl, substituted C_1-C_6 alkoxyl, acyl, substituted acyl, C_1-C_6 aminoalkyl or substituted C_1-C_6 aminoalkyl;

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



V

wherein:

Bx is a heterocyclic base moiety;

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

q_a, q_b, q_e and q_f are each, independently, hydrogen, halogen, 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, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O\text{-}C(=O)NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)NJ_jJ_k$ or $N(H)C(=S)NJ_jJ_k$;

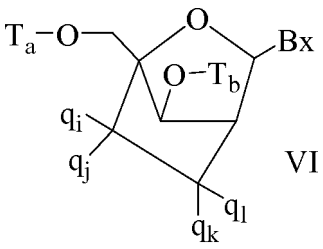
or q_e and q_f together are $=C(q_g)(q_h)$;

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

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 (Koshkin *et al.*, *Tetrahedron*, 1998, *54*, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

Analogs of methyleneoxy (4'-CH_2-O-2') BNA and 2'-thio-BNAs, have also been prepared (Kumar *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222). Preparation of locked nucleoside analogs comprising oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel *et al.*, WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel comformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh *et al.*, *J. Org. Chem.*, 1998, *63*, 10035-10039). In addition, 2'-amino- and 2'-methylamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

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



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} alkoxyl, substituted C_1-C_{12} alkoxyl, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O\text{-}C(=O)NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)NJ_jJ_k$ or $N(H)C(=S)NJ_jJ_k$; and

q_i and q_j or q_l and q_k together are $=C(q_g)(q_h)$, wherein q_g and q_h are each, independently, H, halogen, C_1-C_{12} alkyl or substituted C_1-C_{12} alkyl.

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 (Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443 and Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (Srivastava *et al., J. Am. Chem. Soc.*, 2007, *129(26)*, 8362-8379).

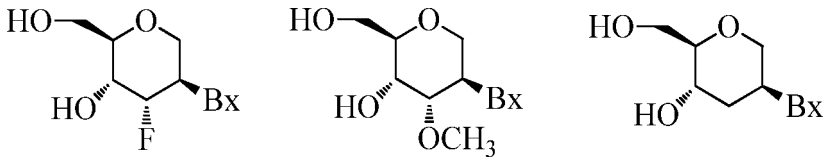
As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2' carbon atom and the 4' carbon atom of the sugar ring.

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

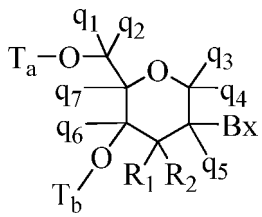
As used herein, "2'-modified sugar" means a furanosyl sugar modified at the 2' position. In certain embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In certain embodiments, 2' modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nF$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, 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, F, 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, or a group for improving the pharmacodynamic properties of an antisense compound, and other substituents having similar properties. In certain embodiments, modifed nucleosides comprise a 2'-MOE side chain (Baker *et al., J. Biol. Chem.*, 1997, *272*, 11944-12000). Such 2'-MOE substitution have been described as having improved

binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2'- *O*-methyl, *O*-propyl, and *O*-aminopropyl. Oligonucleotides having the 2'-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for *in vivo* use (Martin, *Helv. Chim. Acta*, 1995, *78*, 486-504; Altmann *et al.*, *Chimia*, 1996, *50*, 168-176; Altmann *et al.*, *Biochem. Soc. Trans.*, 1996, *24*, 630-637; and Altmann *et al.*, *Nucleosides Nucleotides*, 1997, *16*, 917-926).

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



In certain embodiments, sugar surrogates are selected having Formula VII:



VII

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

Bx is a heterocyclic base moiety;

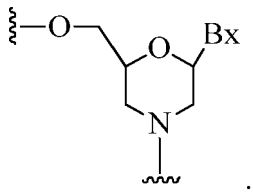
T_a and T_b are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_a and T_b is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_a and T_b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

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 each of R_1 and R_2 is selected from hydrogen, hydroxyl, halogen, subsitituted 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 C_1-C_6 alkyl.

In certain embodiments, the modified THP nucleosides of Formula VII are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, THP

nucleosides of Formula VII are provided wherein one of R_1 and R_2 is fluoro. In certain embodiments, R_1 is fluoro and R_2 is H; R_1 is methoxy and R_2 is H, and R_1 is methoxyethoxy and R_2 is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example nucleosides comprising morpholino sugar moieties and their use in oligomeric compounds has been reported (see for example: Braasch *et al.*, *Biochemistry*, 2002, *41*, 4503-4510; and U.S. Patents 5,698,685; 5,166,315; 5,185,444; and 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following formula:

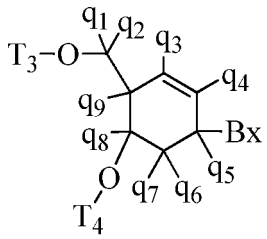


In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as "modifed morpholinos."

Combinations of modifications are also provided without limitation, such as 2'-F-5'-methyl substituted nucleosides (see PCT International Application WO 2008/101157 published on 8/21/08 for other disclosed 5', 2'-bis substituted nucleosides) and replacement of the ribosyl ring oxygen atom with S and 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 bicyclic nucleic acid (see PCT International Application WO 2007/134181, published on 11/22/07 wherein a 4'-CH_2-O-2' bicyclic nucleoside is further substituted at the 5' position with a 5'-methyl or a 5'-vinyl group). 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).

In certain embodiments, antisense compounds comprise one or more modified cyclohexenyl nucleosides, which is a nucleoside having a six-membered cyclohexenyl in place of the pentofuranosyl residue in naturally occurring nucleosides. Modified cyclohexenyl nucleosides include, but are not limited to those described in the art (see for example commonly owned, published PCT Application WO 2010/036696, published on April 10, 2010, Robeyns *et al., J. Am. Chem. Soc.,* 2008, *130(6)*, 1979-1984; Horváth *et al., Tetrahedron Letters,* 2007, *48*, 3621-3623; Nauwelaerts *et al., J. Am. Chem. Soc.*, 2007, *129(30)*, 9340-9348; Gu *et al.,, Nucleosides, Nucleotides & Nucleic Acids*, 2005, *24(5-7)*, 993-998; Nauwelaerts *et al., Nucleic Acids Research,* 2005, *33(8)*, 2452-2463; Robeyns et al., *Acta Crystallographica, Section F: Structural Biology and Crystallization Communications,* 2005, *F61(6)*, 585-586; Gu *et al., Tetrahedron*, 2004, *60(9)*, 2111-2123; Gu *et al., Oligonucleotides*, 2003, *13(6)*, 479-489; Wang *et al., J. Org. Chem.,* 2003, *68*, 4499-4505; Verbeure *et al., Nucleic Acids Research*, 2001, *29(24)*, 4941-4947; Wang *et al., J. Org. Chem.,* 2001, *66*, 8478-82; Wang *et al., Nucleosides, Nucleotides & Nucleic Acids*, 2001, *20(4-7)*, 785-788; Wang *et al., J.*

Am. Chem., 2000, *122*, 8595-8602; Published PCT application, WO 06/047842; and Published PCT Application WO 01/049687; the text of each is incorporated by reference herein, in their entirety). Certain modified cyclohexenyl nucleosides have Formula X.



X

wherein independently for each of said at least one cyclohexenyl 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 cyclohexenyl nucleoside analog to an antisense compound or one of T_3 and T_4 is an internucleoside linking group linking the tetrahydropyran nucleoside analog to an 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; and

q_1, q_2, q_3, q_4, q_5, q_6, q_7, q_8 and q_9 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, substituted C_2-C_6 alkynyl or other sugar substituent group.

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-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-O$(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-$N(R_m)(R_n)$, or O-CH_2-C(=O)-$N(R_m)(R_n)$, where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. 2'-modifed nucleosides may further comprise other modifications, for example at other positions of the sugar and/or at the nucleobase.

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

As used herein, "2'-OMe" or "2'-OCH_3" or "2'-O-methyl" each refers to a nucleoside comprising a sugar comprising an -OCH_3 group at the 2' position of the sugar ring.

As used herein, "MOE" or "2'-MOE" or "2'-$OCH_2CH_2OCH_3$" or "2'-O-methoxyethyl" each refers to a nucleoside comprising a sugar comprising a -$OCH_2CH_2OCH_3$ group at the 2' position of the sugar ring.

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

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

Methods for the preparations of modified sugars are well known to those skilled in the art. Some representative U.S. patents that teach the preparation of such modified sugars include without limitation, U.S.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,670,633; 5,700,920; 5,792,847 and 6,600,032 and International Application PCT/US2005/019219, filed June 2, 2005 and published as WO 2005/121371 on December 22, 2005, and each of which is herein incorporated by reference in its entirety.

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.

In certain embodiments, antisense compounds comprise one or more nucleosides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE. In certain embodiments, the 2'-MOE modified nucleosides are arranged in a gapmer motif. In certain embodiments, the modified sugar moiety is a bicyclic nucleoside having a (4'-$CH(CH_3)$-O-2') bridging group. In certain embodiments, the (4'-$CH(CH_3)$-O-2') modified nucleosides are arranged throughout the wings of a gapmer motif.

Modified Nucleobases

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

Additional modified nucleobases include 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH3) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl

and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

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

In certain embodiments, antisense compounds targeted to a CFB nucleic acid comprise one or more modified nucleobases. In certain embodiments, shortened or gap-widened antisense oligonucleotides targeted to a CFB nucleic acid comprise one or more modified nucleobases. In certain embodiments, the modified nucleobase is 5-methylcytosine. In certain embodiments, each cytosine is a 5-methylcytosine.

Conjugated Antisense compounds

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.

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.

In certain embodiments, antisense compounds, including, but not limited to those particularly suited for use as ssRNA, are modified by attachment of one or more conjugate groups. In general, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, cellular distribution, cellular uptake, charge and clearance. Conjugate groups are routinely used in the chemical arts and are linked directly or via an optional conjugate linking moiety or conjugate linking group to a parent compound such as an oligonucleotide. Conjugate groups includes without limitation, intercalators, reporter molecules, polyamines,

polyamides, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins and dyes. Certain conjugate groups have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Let., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937).

For additional conjugates including those useful for ssRNA and their placement within antisense compounds, see e.g., US Application No.; 61/583,963.

In vitro testing of antisense oligonucleotides

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

Cells may be treated with antisense oligonucleotides when the cells reach approximately 60-80% confluency in culture.

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

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

Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation.

Yet another technique used to introduce antisense oligonucleotides into cultured cells includes free uptake of the oligonucleotides by the cells.

Cells are treated with antisense oligonucleotides by routine methods. Cells may be harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein. In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

The concentration of antisense oligonucleotide used varies from cell line to cell line. Methods to determine the optimal antisense oligonucleotide concentration for a particular cell line are well known in the art. Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM when transfected with LIPOFECTAMINE. Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using electroporation.

RNA Isolation

RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. RNA is prepared using methods well known in the art, for example, using the TRIZOL Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocols.

Certain Indications

Certain embodiments provided herein relate to methods of treating, preventing, or ameliorating a disease associated with dysregulation of the complement alternative pathway in a subject by administration of a CFB specific inhibitor, such as an antisense compound targeted to CFB.

Examples of renal diseases associated with dysregulation of the complement alternative pathway treatable, preventable, and/or ameliorable with the methods provided herein include C3 glomerulopathy, atypical hemolytic uremic syndrome (aHUS), dense deposit disease (DDD; also known as MPGN Type II or C3Neph), and CFHR5 nephropathy.

Additional renal diseases associated with dysregulation of the complement alternative pathway treatable, preventable, and/or ameliorable with the methods provided herein include IgA nephropathy; mesangiocapillary (membranoproliferative) glomerulonephritis (MPGN); autoimmune disorders including lupus nephritis and systemic lupus erythematosus (SLE); infection-induced glomerulonephritis (also known as Postinfectious glomerulonephritis); and renal ischemia-reperfusion injury, for example post-transplant renal ischemia-reperfusion injury.

Examples of non-renal disorders associated with dysregulation of the complement alternative pathway treatable and/or preventable with the methods provided herein include ocular diseases such as macular degeneration, for example age-related macular degeneration (AMD), including wet AMD and dry AMD, such as Geographic Atrophy; neuromyelitis optica; corneal disease, such as corneal inflammation; autoimmune uveitis; and diabetic retinopathy. It has been reported that complement system is involved in ocular diseases. Jha P, et al., *Mol Immunol* (2007) 44(16): 3901-3908. Additional examples of non-renal disorders associated with dysregulation of the complement alternative pathway treatable and/or preventable with the methods provided herein include ANCA-assocaited vasculitis, antiphospholipid syndrome (also known as antiphospholipid antibody syndrome (APS)), asthma, rheumatoid arthritis, Myasthenia Gravis, and multiple sclerosis.

Certain embodiments provided herein relate to methods of treating, preventing, or ameliorating a renal disease associated with dysregulation of the complement alternative pathway in a subject by administration of a CFB specific inhibitor, such as an antisense compound targeted to CFB. In certain embodiments, the renal disease is lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS), or any combination thereof.

Certain embodiments provided herein relate to methods of treating, preventing, or ameliorating macular degeneration, such as age-related macular degeneration (AMD), in a subject by administration of a CFB specific inhibitor, such as an antisense compound targeted to CFB. In certain embodiments, the AMD is wet AMD or dry AMD. In certain embodiments, dry AMD can be Geographic Atrophy. Studies have demonstrated the association of complement alternative pathway dysregulation and AMD. Complement components are common constituents of ocular drusen, the extracellular material that accumulates in the macula of AMD patients. Furthermore, it has been reported that CFH and CFB variants account for nearly 75% of AMD cases in northern Europe and North America. It has also been found that a specific CFB polymorphism confers protection against AMD. Patel, N. et al., *Eye* (2008) 22(6):768-76. Additionally, CFB homozygous null mice have lower complement pathway activity, exhibit smaller ocular lesions, and choroidal neovascularization (CNV) after laser photocoagulation. Rohrer, B. et al., *Invest Ophthalmol Vis Sci.* (2009) 50(7):3056-64. Furthermore, CFB siRNA treatment protects mice from laser induced CNV. Bora, NS et al., *J Immunol.* (2006) 177(3):1872-8. Studies have also shown that the kidney and eye share developmental pathways and structural features including basement membrane collagen IV protomer composition and vascularity. Savige et al., *J Am Soc Nephrol.* (2011) 22(8):1403-15. There is evidence that the complement pathway is involved in renal and ocular diseases. For instance, inherited complement regulatory protein deficiency causes predisposition to atypical hemolytic uremic syndrome and AMD. Richards A et al., *Adv Immunol.* (2007) 96:141-77. Additionally, chronic kidney disease has been associated

with AMD. Nitsch, D. et al., *Ophthalmic Epidemiol.* (2009) 16(3):181-6; Choi, J. et al, *Ophthalmic Epidemiol.* (2011) 18(6):259-63. Dense deposit disease (DDD), a kidney disease associated with dysregulated complement alternative pathway, is characterized by acute nephritic syndrome and ocular drusen. Cruz and Smith, *GeneReviews* (2007) Jul 20. Moreover, mice harboring genetic deletion of a component of the complement alternative pathway have coexisting renal and ocular disease phenotypes. It has been reported that CFH homozygous null mice develop DDD and present retinal abnormalities and visual dysfunction. Pickering et al., *Nat Genet.* (2002) 31(4):424-8. Mouse models of renal diseases associated with dysregulation of the complement alternative pathway are also accepted as models of AMD. Pennesi ME et al., *Mol Apects Med* (2012) 33:487-509. CFH null mice, for example, are an accepted model for renal diseases, such as DDD, and AMD. Furthermore, it has been reported that AMD is associated with the systemic source of complement factors, which accumulate locally in the eye to drive alternative pathway complement activation. Loyet et al., *Invest Ophthalmol Vis Sci.* (2012) 53(10):6628-37.

EXAMPLES

Non-limiting disclosure and incorporation by reference

While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references recited in the present application is incorporated herein by reference in its entirety.

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

Example 1: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells by MOE gapmers

Antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 4,500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 (forward sequence AGTCTCTGTGGCATGGTTTGG, designated

herein as SEQ ID NO: 810; reverse sequence GGGCGAATGACTGAGATCTTG, designated herein as SEQ ID NO: 811; probe sequence TACCGATTACCACAAGCAACCATGGCA, designated herein as SEQ ID NO: 812) was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 5-10-5 MOE gapmers. The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity.

Table 1

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	SEQ ID NO:
532608	20	39	Exon 1	GCTGAGCTGCCAGTCAAGGA	36	1741	1760	6
532609	26	45	Exon 1	GGCCCCGCTGAGCTGCCAGT	16	1747	1766	7
532610	45	64	Exon 1	CGGAACATCCAAGCGGGAGG	11	1766	1785	8
532611	51	70	Exon 1	CTTTCCCGGAACATCCAAGC	26	1772	1791	9
532612	100	119	Exon 1	ATCTGTGTTCTGGCACCTGC	25	1821	1840	10
532613	148	167	Exon 1	GTCACATTCCCTTCCCCTGC	39	1869	1888	11
532614	154	173	Exon 1	GACCTGGTCACATTCCCTTC	71	1875	1894	12
532615	160	179	Exon 1	GACCTAGACCTGGTCACATT	35	1881	1900	13
532616	166	185	Exon 1	ACTCCAGACCTAGACCTGGT	39	1887	1906	14
532617	172	191	Exon 1	GCTGAAACTCCAGACCTAGA	27	1893	1912	15
532618	178	197	Exon 1	GTCCAAGCTGAAACTCCAGA	29	1899	1918	16
532619	184	203	Exon 1	CTCAGTGTCCAAGCTGAAAC	21	1905	1924	17
532620	246	265	Exon 1	AGGAGAGAAGCTGGGCCTGG	31	1967	1986	18

532621	252	271	Exon 1	GAAGGCAGGAGAGAAGCTGG	25	1973	1992	19
532622	336	355	Exon 1-2 Junction	GTGGTGGTCACACCTCCAGA	28	n/a	n/a	20
532623	381	400	Exon 2	CCCTCCAGAGAGCAGGATCC	22	2189	2208	21
532624	387	406	Exon 2	TCTACCCCCTCCAGAGAGCA	37	2195	2214	22
532625	393	412	Exon 2	TTGATCTCTACCCCCTCCAG	30	2201	2220	23
532626	417	436	Exon 2	TGGAGAAGTCGGAAGGAGCC	35	2225	2244	24
532627	423	442	Exon 2	CCCTCTTGGAGAAGTCGGAA	37	2231	2250	25
532628	429	448	Exon 2	GCCTGGCCCTCTTGGAGAAG	0	2237	2256	26
532629	435	454	Exon 2	TCCAGTGCCTGGCCCTCTTG	26	2243	2262	27
532630	458	477	Exon 2	AGAAGCCAGAAGGACACACG	30	2266	2285	28
532631	464	483	Exon 2	ACGGGTAGAAGCCAGAAGGA	43	2272	2291	29
532632	480	499	Exon 2	CGTGTCTGCACAGGGTACGG	57	2288	2307	30
532633	513	532	Exon 2	AGGGTGCTCCAGGACCCCGT	27	2321	2340	31
532634	560	579	Exon 2-3 Junction	TTGCTCTGCACTCTGCCTTC	41	n/a	n/a	32
532635	600	619	Exon 3	TATTCCCCGTTCTCGAAGTC	67	2808	2827	33
532636	626	645	Exon 3	CATTGTAGTAGGGAGACCGG	24	2834	2853	34
532637	632	651	Exon 3	CACTCACATTGTAGTAGGGA	49	2840	2859	35
532638	638	657	Exon 3	TCTCATCACTCACATTGTAG	50	2846	2865	36
532639	644	663	Exon 3	AAGAGATCTCATCACTCACA	52	2852	2871	37
532640	650	669	Exon 3	AGTGGAAAGAGATCTCATCA	34	2858	2877	38
532641	656	675	Exon 3	CATAGCAGTGGAAAGAGATC	32	2864	2883	39
532642	662	681	Exon 3	AACCGTCATAGCAGTGGAAA	45	2870	2889	40
532643	668	687	Exon 3	GAGTGTAACCGTCATAGCAG	36	2876	2895	41
532644	674	693	Exon 3	CCCGGAGAGTGTAACCGTCA	30	2882	2901	42
532645	680	699	Exon 3	CAGAGCCCCGGAGAGTGTAA	27	2888	2907	43
532646	686	705	Exon 3	GATTGGCAGAGCCCCGGAGA	20	2894	2913	44
532647	692	711	Exon 3	AGGTGCGATTGGCAGAGCCC	28	2900	2919	45
532648	698	717	Exon 3	CTTGGCAGGTGCGATTGGCA	24	2906	2925	46
532649	704	723	Exon 3	CATTCACTTGGCAGGTGCGA	28	2912	2931	47
532650	729	748	Exon 3	ATCGCTGTCTGCCCACTCCA	44	2937	2956	48
532651	735	754	Exon 3	TCACAGATCGCTGTCTGCCC	44	2943	2962	49
532652	741	760	Exon 3	CCGTTGTCACAGATCGCTGT	27	2949	2968	50
532653	747	766	Exon 3-4 Junction	CCCGCTCCGTTGTCACAGAT	28	n/a	n/a	51
532654	753	772	Exon 3-4 Junction	CAGTACCCCGCTCCGTTGTC	13	n/a	n/a	52
532655	759	778	Exon 3-4 Junction	TTGGAGCAGTACCCCGCTCC	8	n/a	n/a	53

532656	789	808	Exon 4	ACCTTCCTTGTGCCAATGGG	40	3152	3171	54
532657	795	814	Exon 4	CTGCCCACCTTCCTTGTGCC	41	3158	3177	55
532658	818	837	Exon 4	CGCTGTCTTCAAGGCGGTAC	33	3181	3200	56
532659	835	854	Exon 4	GCTGCAGTGGTAGGTGACGC	32	3198	3217	57
532660	841	860	Exon 4	CCCCCGGCTGCAGTGGTAGG	17	3204	3223	58
532661	847	866	Exon 4	GGTAAGCCCCCGGCTGCAGT	28	3210	3229	59
532662	853	872	Exon 4	ACGCAGGGTAAGCCCCCGGC	13	3216	3235	60
532663	859	878	Exon 4	GGAGCCACGCAGGGTAAGCC	33	3222	3241	61
532664	866	885	Exon 4	GCCGCTGGGAGCCACGCAGG	10	3229	3248	62
532665	891	910	Exon 4	CAAGAGCCACCTTCCTGACA	17	3254	3273	63
532666	897	916	Exon 4	CCGCTCCAAGAGCCACCTTC	25	3260	3279	64
532667	903	922	Exon 4	TCCGTCCCGCTCCAAGAGCC	29	3266	3285	65
532668	909	928	Exon 4	GAAGGCTCCGTCCCGCTCCA	14	3272	3291	66
532669	915	934	Exon 4	TGGCAGGAAGGCTCCGTCCC	18	3278	3297	67
532670	921	940	Exon 4-5 Junction	GAGTCTTGGCAGGAAGGCTC	20	n/a	n/a	68
532671	927	946	Exon 4-5 Junction	ATGAAGGAGTCTTGGCAGGA	14	n/a	n/a	69
532672	956	975	Exon 5	CTTCGGCCACCTCTTGAGGG	45	3539	3558	70
532673	962	981	Exon 5	GGAAAGCTTCGGCCACCTCT	37	3545	3564	71
532674	968	987	Exon 5	AAGACAGGAAAGCTTCGGCC	28	3551	3570	72
532675	974	993	Exon 5	TCAGGGAAGACAGGAAAGCT	16	3557	3576	73
532676	996	1015	Exon 5	TCGACTCCTTCTATGGTCTC	31	3579	3598	74
532677	1033	1052	Exon 5-6 Junction	CTTCTGTTGTTCCCCTGGGC	36	n/a	n/a	75
532678	1068	1087	Exon 6	TTCATGGAGCCTGAAGGGTC	19	3752	3771	76
532679	1074	1093	Exon 6	TAGATGTTCATGGAGCCTGA	24	3758	3777	77
532680	1080	1099	Exon 6	ACCAGGTAGATGTTCATGGA	13	3764	3783	78
532681	1086	1105	Exon 6	TCTAGCACCAGGTAGATGTT	20	3770	3789	79
532682	1092	1111	Exon 6	GATCCATCTAGCACCAGGTA	33	3776	3795	80
532683	1098	1117	Exon 6	CTGTCTGATCCATCTAGCAC	44	3782	3801	81
532684	1104	1123	Exon 6	CCAATGCTGTCTGATCCATC	29	3788	3807	82
532685	1129	1148	Exon 6	TTTGGCTCCTGTGAAGTTGC	40	3813	3832	83

Table 2

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 and 2

ISIS No	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	SEQ ID NO:
532686	1135	1154	Exon 6	ACACTTTTTGGCTCCTGTGA	91	3819	3838	84

532687	1141	1160	Exon 6	GACTAGACACTTTTTGGCTC	77	3825	3844	85
532688	1147	1166	Exon 6	TAAGTTGACTAGACACTTTT	70	3831	3850	86
532689	1153	1172	Exon 6	CTCAATTAAGTTGACTAGAC	61	3837	3856	87
532690	1159	1178	Exon 6-7 Junction	CACCTTCTCAATTAAGTTGA	57	3843	3862	88
532691	1165	1184	Exon 6-7 Junction	ACTTGCCACCTTCTCAATTA	56	n/a	n/a	89
532692	1171	1190	Exon 6-7 Junction	ACCATAACTTGCCACCTTCT	56	n/a	n/a	90
532693	1177	1196	Exon 7	CTTCACACCATAACTTGCCA	56	4153	4172	91
532694	1183	1202	Exon 7	TCTTGGCTTCACACCATAAC	55	4159	4178	92
532695	1208	1227	Exon 7	ATGTGGCATATGTCACTAGA	55	4184	4203	93
532696	1235	1254	Exon 7	CAGACACTTTGACCCAAATT	55	4211	4230	94
532697	1298	1317	Exon 7-8 Junction	GGTCTTCATAATTGATTTCA	53	n/a	n/a	95
532698	1304	1323	Exon 7-8 Junction	ACTTGTGGTCTTCATAATTG	53	n/a	n/a	96
532699	1310	1329	Exon 7-8 Junction	ACTTCAACTTGTGGTCTTCA	52	n/a	n/a	97
532700	1316	1335	Exon 8	TCCCTGACTTCAACTTGTGG	52	4609	4628	98
532701	1322	1341	Exon 8	TGTTAGTCCCTGACTTCAAC	52	4615	4634	99
532702	1328	1347	Exon 8	TCTTGGTGTTAGTCCCTGAC	51	4621	4640	100
532703	1349	1368	Exon 8	TGTACACTGCCTGGAGGGCC	51	4642	4661	101
532704	1355	1374	Exon 8	TCATGCTGTACACTGCCTGG	51	4648	4667	102
532705	1393	1412	Exon 8	GTTCCAGCCTTCAGGAGGGA	50	4686	4705	103
532706	1399	1418	Exon 8	GGTGCGGTTCCAGCCTTCAG	50	4692	4711	104
532707	1405	1424	Exon 8	ATGGCGGGTGCGGTTCCAGC	50	4698	4717	105
532708	1411	1430	Exon 8	GATGACATGGCGGGTGCGGT	49	4704	4723	106
532709	1417	1436	Exon 8	GAGGATGATGACATGGCGGG	49	4710	4729	107
532710	1443	1462	Exon 8-9 Junction	CCCATGTTGTGCAATCCATC	48	n/a	n/a	108
532711	1449	1468	Exon 9	TCCCCGCCCATGTTGTGCAA	48	5023	5042	109
532712	1455	1474	Exon 9	ATTGGGTCCCCGCCCATGTT	48	5029	5048	110
532713	1461	1480	Exon 9	ACAGTAATTGGGTCCCCGCC	48	5035	5054	111
532714	1467	1486	Exon 9	TCAATGACAGTAATTGGGTC	47	5041	5060	112
532715	1473	1492	Exon 9	ATCTCATCAATGACAGTAAT	47	5047	5066	113
532716	1479	1498	Exon 9	TCCCGGATCTCATCAATGAC	46	5053	5072	114
532717	1533	1552	Exon 9-10 Junction	ACATCCAGATAATCCTCCCT	46	n/a	n/a	115
532718	1539	1558	Exon 9-10 Junction	ACATAGACATCCAGATAATC	46	n/a	n/a	116
532719	1545	1564	Exon 9-10 Junction	CCAAACACATAGACATCCAG	46	n/a	n/a	117
532720	1582	1601	Exon 10	AGCATTGATGTTCACTTGGT	46	5231	5250	118
532721	1588	1607	Exon 10	AGCCAAAGCATTGATGTTCA	45	5237	5256	119
532722	1594	1613	Exon 10	CTTGGAAGCCAAAGCATTGA	45	5243	5262	120

532723	1600	1619	Exon 10	GTCTTTCTTGGAAGCCAAAG	45	5249	5268	121
532724	1606	1625	Exon 10	CTCATTGTCTTTCTTGGAAG	44	5255	5274	122
532725	1612	1631	Exon 10	ATGTTGCTCATTGTCTTTCT	44	5261	5280	123
532726	1618	1637	Exon 10	GAACACATGTTGCTCATTGT	44	5267	5286	124
532727	1624	1643	Exon 10	GACTTTGAACACATGTTGCT	43	5273	5292	125
532728	1630	1649	Exon 10	ATCCTTGACTTTGAACACAT	43	5279	5298	126
532729	1636	1655	Exon 10	TTCCATATCCTTGACTTTGA	43	5285	5304	127
532730	1642	1661	Exon 10	CAGGTTTTCCATATCCTTGA	42	5291	5310	128
532731	1686	1705	Exon 11	CTCAGAGACTGGCTTTCATC	42	5827	5846	129
532732	1692	1711	Exon 11	CAGAGACTCAGAGACTGGCT	42	5833	5852	130
516252	1698	1717	Exon 11	ATGCCACAGAGACTCAGAGA	42	5839	5858	131
532733	1704	1723	Exon 11	CAAACCATGCCACAGAGACT	41	5845	5864	132
532734	1710	1729	Exon 11	TGTTCCCAAACCATGCCACA	41	5851	5870	133
532735	1734	1753	Exon 11	TTGTGGTAATCGGTACCCTT	41	5875	5894	134
532736	1740	1759	Exon 11	GGTTGCTTGTGGTAATCGGT	40	5881	5900	135
532737	1746	1765	Exon 11	TGCCATGGTTGCTTGTGGTA	40	5887	5906	136
532738	1752	1771	Exon 11	TTGGCCTGCCATGGTTGCTT	40	5893	5912	137
532739	1758	1777	Exon 11	GAGATCTTGGCCTGCCATGG	38	5899	5918	138
532740	1803	1822	Exon 12	ACAGCCCCCATACAGCTCTC	38	6082	6101	139
532741	1809	1828	Exon 12	GACACCACAGCCCCCATACA	38	6088	6107	140
532742	1815	1834	Exon 12	TACTCAGACACCACAGCCCC	38	6094	6113	141
532743	1821	1840	Exon 12	ACAAAGTACTCAGACACCAC	37	6100	6119	142
532744	1827	1846	Exon 12	GTCAGCACAAAGTACTCAGA	37	6106	6125	143
532745	1872	1891	Exon 12	TTGATTGAGTGTTCCTTGTC	36	6151	6170	144
532746	1878	1897	Exon 12	CTGACCTTGATTGAGTGTTC	35	6157	6176	145
532747	1909	1928	Exon 13	TATCTCCAGGTCCCGCTTCT	35	6403	6422	146
532748	1967	1986	Exon 13	GAATTCCTGCTTCTTTTTTC	32	6461	6480	147
532749	1973	1992	Exon 13	ATTCAGGAATTCCTGCTTCT	32	6467	6486	148
532750	1979	1998	Exon 13	CATAAAATTCAGGAATTCCT	32	6473	6492	149
532751	1985	2004	Exon 13	CATAGTCATAAAATTCAGGA	31	6479	6498	150
532752	2006	2025	Exon 13	TGAGCTTGATCAGGGCAACG	30	6500	6519	151
532753	2012	2031	Exon 13	TATTCTTGAGCTTGATCAGG	30	6506	6525	152
532754	2048	2067	Exon 13-14 Junction	GACAAATGGGCCTGATAGTC	30	n/a	n/a	153
532755	2070	2089	Exon 14	GTTGTTCCCTCGGTGCAGGG	29	6659	6678	154
532756	2076	2095	Exon 14	GCTCGAGTTGTTCCCTCGGT	28	6665	6684	155
532757	2082	2101	Exon 14	CTCAAAGCTCGAGTTGTTCC	28	6671	6690	156
532758	2088	2107	Exon 14	GGAAGCCTCAAAGCTCGAGT	25	6677	6696	157
532759	2094	2113	Exon 14	GTTGGAGGAAGCCTCAAAGC	23	6683	6702	158
532760	2100	2119	Exon 14	GTGGTAGTTGGAGGAAGCCT	23	6689	6708	159
532761	2106	2125	Exon 14	TGGCAAGTGGTAGTTGGAGG	18	6695	6714	160
532762	2112	2131	Exon 14	TGTTGCTGGCAAGTGGTAGT	14	6701	6720	161

Table 3

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	SEQ ID NO:
532812	n/a	n/a	Exon 1	TCCAGCTCACTCCCCTGTTG	19	1593	1612	162
532813	n/a	n/a	Exon 1	TAAGGATCCAGCTCACTCCC	40	1599	1618	163
532814	n/a	n/a	Exon 1	CAGAAATAAGGATCCAGCTC	39	1605	1624	164
532815	n/a	n/a	Exon 1	AGGGACCAGAAATAAGGATC	0	1611	1630	165
532816	n/a	n/a	Exon 1	CCACTTAGGGACCAGAAATA	27	1617	1636	166
532817	n/a	n/a	Exon 1	TCCAGGACTCTCCCCTTCAG	39	1682	1701	167
532818	n/a	n/a	Exon 1	AAGTCCCACCCTTTGCTGCC	15	1707	1726	168
532819	n/a	n/a	Exon 1	CTGCAGAAGTCCCACCCTTT	26	1713	1732	169
532820	n/a	n/a	Exon 1	CAGAAACTGCAGAAGTCCCA	8	1719	1738	170
532821	n/a	n/a	Exon 2 - Intron 2	AACCTCTGCACTCTGCCTTC	39	2368	2387	171
532822	n/a	n/a	Exon 2 - Intron 2	CCCTCAAACCTCTGCACTCT	3	2374	2393	172
532823	n/a	n/a	Exon 2 - Intron 2	TCATTGCCCTCAAACCTCTG	19	2380	2399	173
532824	n/a	n/a	Intron 2	CCACACTCATTGCCCTCAAA	37	2386	2405	174
532825	n/a	n/a	Intron 2	CACTGCCCACACTCATTGCC	23	2392	2411	175
532826	n/a	n/a	Intron 2	TTAGGCCACTGCCCACACTC	15	2398	2417	176
532827	n/a	n/a	Intron 2	CTAGTCCTGACCTTGCTGCC	28	2436	2455	177
532828	n/a	n/a	Intron 2	CTCATCCTAGTCCTGACCTT	25	2442	2461	178
532829	n/a	n/a	Intron 2	CCTAGTCTCATCCTAGTCCT	23	2448	2467	179
532830	n/a	n/a	Intron 2	ACCCTGCCTAGTCTCATCCT	30	2454	2473	180
532831	n/a	n/a	Intron 2	CTTGTCACCCTGCCTAGTCT	34	2460	2479	181
532832	n/a	n/a	Intron 2	GCCCACCTTGTCACCCTGCC	36	2466	2485	182
532833	n/a	n/a	Intron 2	CCTAAAACTGCTCCTACTCC	9	2492	2511	183
532834	n/a	n/a	Intron 4	GAGTCAGAAATGAGGTCAAA	19	3494	3513	184
532835	n/a	n/a	Intron 11	CCCTACTCCCATTTCACCTT	16	5971	5990	185
532836	n/a	n/a	Intron 8 - Exon 9	TGTTGTGCAATCCTGCAGAA	25	5013	5032	186
532837	n/a	n/a	Intron 1	AAAGGCTGATGAAGCCTGGC	18	2123	2142	187
532838	n/a	n/a	Intron 7	CCTTTGACCACAAAGTGGCC	21	4461	4480	188
532839	n/a	n/a	Intron 12	AGGTACCACCTCTTTGTGGG	29	6362	6381	189
532840	n/a	n/a	Intron 1	TGGTGGTCACACCTGAAGAG	34	2143	2162	190

			- Exon 2					
532763	2133	2152	Exon 14-15 Junction	GCAGGGAGCAGCTCTTCCTT	40	n/a	n/a	191
532764	2139	2158	Exon 15	TCCTGTGCAGGGAGCAGCTC	28	6927	6946	192
532765	2145	2164	Exon 15	TTGATATCCTGTGCAGGGAG	41	6933	6952	193
532766	2151	2170	Exon 15	AGAGCTTTGATATCCTGTGC	36	6939	6958	194
532767	2157	2176	Exon 15	ACAAACAGAGCTTTGATATC	33	6945	6964	195
532768	2163	2182	Exon 15	TCAGACACAAACAGAGCTTT	41	6951	6970	196
532769	2169	2188	Exon 15	TCCTCCTCAGACACAAACAG	49	6957	6976	197
532770	2193	2212	Exon 15	ACCTCCTTCCGAGTCAGCTT	61	6981	7000	198
532771	2199	2218	Exon 15	ATGTAGACCTCCTTCCGAGT	39	6987	7006	199
532772	2205	2224	Exon 15	TTCTTGATGTAGACCTCCTT	30	6993	7012	200
532773	2211	2230	Exon 15	TCCCCATTCTTGATGTAGAC	31	6999	7018	201
532774	2217	2236	Exon 15-16 Junction	TTCTTATCCCCATTCTTGAT	36	n/a	n/a	202
532775	2223	2242	Exon 15-16 Junction	CTGCCTTTCTTATCCCCATT	56	n/a	n/a	203
532776	2229	2248	Exon 15-16 Junction	TCACAGCTGCCTTTCTTATC	33	n/a	n/a	204
532777	2235	2254	Exon 16	TCTCTCTCACAGCTGCCTTT	38	7119	7138	205
532778	2241	2260	Exon 16	TGAGCATCTCTCTCACAGCT	51	7125	7144	206
532779	2247	2266	Exon 16	GCATATTGAGCATCTCTCTC	39	7131	7150	207
532780	2267	2286	Exon 16	TGACTTTGTCATAGCCTGGG	56	7151	7170	208
532781	2273	2292	Exon 16	TGTCCTTGACTTTGTCATAG	36	7157	7176	209
532782	2309	2328	Exon 16	CAGTACAAAGGAACCGAGGG	30	7193	7212	210
532783	2315	2334	Exon 16	CTCCTCCAGTACAAAGGAAC	21	7199	7218	211
532784	2321	2340	Exon 16	GACTCACTCCTCCAGTACAA	31	7205	7224	212
532785	2327	2346	Exon 16	CATAGGGACTCACTCCTCCA	30	7211	7230	213
532786	2333	2352	Exon 16	GGTCAGCATAGGGACTCACT	31	7217	7236	214
532787	2352	2371	Exon 16-17 Junction	TCACCTCTGCAAGTATTGGG	42	7236	7255	215
532788	2358	2377	Exon 16-17 Junction	CCAGAATCACCTCTGCAAGT	32	n/a	n/a	216
532789	2364	2383	Exon 16-17 Junction	GGGCCGCCAGAATCACCTCT	35	n/a	n/a	217
532790	2382	2401	Exon 17	CTCTTGTGAACTATCAAGGG	33	7347	7366	218
532791	2388	2407	Exon 17	CGACTTCTCTTGTGAACTAT	52	7353	7372	219
532792	2394	2413	Exon 17	ATGAAACGACTTCTCTTGTG	16	7359	7378	220
532793	2400	2419	Exon	ACTTGAATGAAACGACTTCT	45	7365	7384	221

			17-18 Junction					
532794	2406	2425	Exon 17-18 Junction	ACACCAACTTGAATGAAACG	18	n/a	n/a	222
532795	2427	2446	Exon 18	TCCACTACTCCCCAGCTGAT	30	7662	7681	223
532796	2433	2452	Exon 18	CAGACATCCACTACTCCCCA	38	7668	7687	224
532797	2439	2458	Exon 18	TTTTTGCAGACATCCACTAC	35	7674	7693	225
532798	2445	2464	Exon 18	TTCTGGTTTTTGCAGACATC	45	7680	7699	226
532799	2451	2470	Exon 18	TGCCGCTTCTGGTTTTTGCA	47	7686	7705	227
532800	2457	2476	Exon 18	TGCTTTTGCCGCTTCTGGTT	61	7692	7711	228
532801	2463	2482	Exon 18	GGTACCTGCTTTTGCCGCTT	47	7698	7717	229
532802	2469	2488	Exon 18	TGAGCAGGTACCTGCTTTTG	31	7704	7723	230
532803	2517	2536	Exon 18	TTCAGCCAGGGCAGCACTTG	41	7752	7771	231
532804	2523	2542	Exon 18	TTCTCCTTCAGCCAGGGCAG	44	7758	7777	232
532805	2529	2548	Exon 18	TGGAGTTTCTCCTTCAGCCA	46	7764	7783	233
532806	2535	2554	Exon 18	TCATCTTGGAGTTTCTCCTT	49	7770	7789	234
532807	2541	2560	Exon 18	AAATCCTCATCTTGGAGTTT	30	7776	7795	235
532808	2547	2566	Exon 18	AAACCCAAATCCTCATCTTG	20	7782	7801	236
532809	2571	2590	Exon 18	GTCCAGCAGGAAACCCCTTA	65	7806	7825	237
532810	2577	2596	Exon 18	GCCCCTGTCCAGCAGGAAAC	74	7812	7831	238
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	96	7834	7853	239

Table 4

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	% inhibition	SEQ ID NO:
532841	n/a	n/a	Intron 6-Exon 7	AACTTGCCACCTGTGGGTGA	4142	4161	11	240
532842	n/a	n/a	Exon 15 - Intron 15	TCACCTTATCCCCATTCTTG	7007	7026	16	241
532843	n/a	n/a	Intron 11	TCAACTTTCACAAACCACCA	6015	6034	19	242
532844	n/a	n/a	Intron 16 - Exon 17	CCGCCAGAATCACCTGCAAG	7326	7345	33	243
532845	n/a	n/a	Intron 10	AGGAGGAATGAAGAAGGCTT	5431	5450	29	244
532846	n/a	n/a	Intron 13	GCCTTTCCTCAGGGATCTGG	6561	6580	26	245
532847	n/a	n/a	Intron 4	AAATGTCTGGGAGTGTCAGG	3477	3496	18	246
532848	n/a	n/a	Intron 15	GCCTAGAGTGCCTCCTTAGG	7038	7057	20	247
532849	n/a	n/a	Intron 17	GGCATCTCCCCAGATAGGAA	7396	7415	16	248
532850	n/a	n/a	Intron 6	AGGGAGCTAGTCCTGGAAGA	3906	3925	14	249
532851	n/a	n/a	Intron 1 - Exon 2	ACACCTGAAGAGAAAGGCTG	2135	2154	6	250
532852	n/a	n/a	Intron 7	CCCTTTGACCACAAAGTGGC	4462	4481	25	251

532853	n/a	n/a	Intron 7	GCCCTCAAGGTAGTCTCATG	4354	4373	26	252
532854	n/a	n/a	Intron 6	AAGGGAAGGAGGACAGAATA	3977	3996	18	253
532855	n/a	n/a	Intron 1	AAAGGCCAAGGAGGGATGCT	2099	2118	9	254
532856	n/a	n/a	Exon 8 - Intron 8	AGAGGTCCCTTCTGACCATC	4736	4755	4	255
532857	n/a	n/a	Intron 8	GCTGGGACAGGAGAGAGGTC	4749	4768	0	256
532858	n/a	n/a	Intron 4	TCAAATGTCTGGGAGTGTCA	3479	3498	13	257
532859	n/a	n/a	Intron 10	AGAAGGAGAATGTGCTGAAA	5801	5820	20	258
532860	n/a	n/a	Intron 17	TGCTGACCACTTGGCATCTC	7408	7427	20	259
532861	n/a	n/a	Intron 11	CAACTTTCACAAACCACCAT	6014	6033	18	260
532862	n/a	n/a	Intron 10	AGCTCTGTGATTCTAAGGTT	5497	5516	15	261
532863	n/a	n/a	Intron 6-Exon 7	CCACCTGTGGGTGAGGAGAA	4136	4155	16	262
532864	n/a	n/a	Exon 17 - Intron 17	GAGGACTCACTTGAATGAAA	7373	7392	21	263
532865	n/a	n/a	Intron 6	TGGAATGATCAGGGAGCTAG	3916	3935	30	264
532866	n/a	n/a	Intron 5	GTCCCTTCTCCATTTTCCCC	3659	3678	26	265
532867	n/a	n/a	Intron 7	TCAACTTTTTAAGTTAATCA	4497	4516	14	266
532868	n/a	n/a	Intron 6	GGGTGAGGAGAACAAGGCGC	4128	4147	21	267
532869	n/a	n/a	Intron 7	CTTCCAAGCCATCTTTTAAC	4553	4572	5	268
532870	n/a	n/a	Exon 17 - Intron 17	AGGACTCACTTGAATGAAAC	7372	7391	18	269
532871	n/a	n/a	Intron 10	TTCCAGGCAACTAGAGCTTC	5412	5431	15	270
532872	n/a	n/a	Exon 1	CAGAGTCCAGCCACTGTTTG	1557	1576	13	271
532873	n/a	n/a	Intron 17 - Exon 18	CCAACCTGCAGAGGCAGTGG	7638	7657	23	272
532874	n/a	n/a	Intron 16	TGCAAGGAGAGGAGAAGCTG	7312	7331	10	273
532875	n/a	n/a	Exon 9 - Intron 9	CTAGGCAGGTTACTCACCCA	5120	5139	21	274
532876	n/a	n/a	Intron 6-Exon 7	CACCATAACTTGCCACCTGT	4148	4167	41	275
532877	n/a	n/a	Intron 12	TAGGTACCACCTCTTTGTGG	6363	6382	27	276
532878	n/a	n/a	Intron 11	CTTGACCTCACCTCCCCCAA	5954	5973	13	277
532879	n/a	n/a	Intron 12	CCACCTCTTTGTGGGCAGCT	6357	6376	33	278
532880	n/a	n/a	Intron 11	TTCACAAACCACCATCTCTT	6009	6028	8	279
532881	n/a	n/a	Exon 3 - Intron 3	TTCTCACCTCCGTTGTCACA	2958	2977	17	280
532882	n/a	n/a	Intron 12	GAAAGTGGGAGGTGTTGCCT	6225	6244	19	281
532883	n/a	n/a	Intron 1	ACAGCAGGAAGGGAAGGTTA	2075	2094	34	282
532884	n/a	n/a	Intron 17	CATGCTGACCACTTGGCATC	7410	7429	18	283
532885	n/a	n/a	Exon 4 - Intron 4	GGTCACCTTGGCAGGAAGGC	3286	3305	0	284
532886	n/a	n/a	Intron 8	GTATAGTGTTACAAGTGGAC	4804	4823	13	285
532887	n/a	n/a	Intron 7	GGACTTCCCTTTGACCACAA	4468	4487	18	286
532888	n/a	n/a	Intron 11	TCACCTTGACCTCACCTCCC	5958	5977	20	287
532889	n/a	n/a	Intron 15	TAGAGTGCCTCCTTAGGATG	7035	7054	27	288

532890	n/a	n/a	Intron 7	TGACTTCAACTTGTGGTCTG	4605	4624	16	289
532891	n/a	n/a	Intron 10	CAGAGAAGGAGAATGTGCTG	5804	5823	25	290
532892	n/a	n/a	Intron 14 - Exon 15	AGGGAGCAGCTCTTCCTCTG	6919	6938	47	291
532893	n/a	n/a	Intron 5 - Exon 6	TGTTCCCCTGGGTGCCAGGA	3710	3729	24	292
532894	n/a	n/a	Intron 10	GGCCTGGCTGTTTTCAAGCC	5612	5631	15	293
532895	n/a	n/a	Intron 10 - Exon 11	GACTGGCTTTCATCTGGCAG	5821	5840	25	294
532896	n/a	n/a	Intron 10	GAAGGCTTTCCAGGCAACTA	5419	5438	19	295
532897	n/a	n/a	Exon 17 - Intron 17	TCACTTGAATGAAACGACTT	7367	7386	11	296
532898	n/a	n/a	Intron 1	GGCCCCAAAAGGCCAAGGAG	2106	2125	5	297
532899	n/a	n/a	Intron 16 - Exon 17	AATCACCTGCAAGGAGAGGA	7319	7338	19	298
532900	n/a	n/a	Intron 12	GACCTTCAGTTGCATCCTTA	6183	6202	25	299
532901	n/a	n/a	Intron 1	TGATGAAGCCTGGCCCCAAA	2117	2136	0	300
532902	n/a	n/a	Intron 12	TAGAAAGTGGGAGGTGTTGC	6227	6246	0	301
532903	n/a	n/a	Intron 12	CCCATCCCTGACTGGTCTGG	6295	6314	14	302
532904	n/a	n/a	Intron 8	CCATGGGTATAGTGTTACAA	4810	4829	13	303
532905	n/a	n/a	Intron 2	GTGTTCTCTTGACTTCCAGG	2586	2605	23	304
532906	n/a	n/a	Intron 13	GGCCTGCTCCTCACCCCAGT	6597	6616	27	305
532907	n/a	n/a	Intron 10	GAGGCCTGGCTGTTTTCAAG	5614	5633	32	306
532908	n/a	n/a	Exon 1	GACTCTCCCCTTCAGTACCT	1677	1696	16	307
532909	n/a	n/a	Intron 8	CATGGGTATAGTGTTACAAG	4809	4828	10	308
532910	n/a	n/a	Intron 10	GAAGGAGAATGTGCTGAAAA	5800	5819	0	309
532911	n/a	n/a	Intron 7	TCACCTGGTCTTCCAAGCCA	4562	4581	0	310
532912	n/a	n/a	Intron 17	CTCCCCAGATAGGAAAGGGA	7391	7410	0	311
532913	n/a	n/a	Exon 17 - Intron 17	GGACTCACTTGAATGAAACG	7371	7390	0	312
532914	n/a	n/a	Intron 16 - Exon 17	GGCCGCCAGAATCACCTGCA	7328	7347	30	313
532915	n/a	n/a	Exon 17 - Intron 17	CTCACTTGAATGAAACGACT	7368	7387	22	314
532916	n/a	n/a	Intron 13	CTTTCCCAGCCTTTCCTCAG	6569	6588	28	315
532918	n/a	n/a	Intron 12	AGAAAGTGGGAGGTGTTGCC	6226	6245	3	316
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	7839	7858	90	317

Table 5

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	% inhibition	SEQ ID NO:
532919	n/a	n/a	Exon 1	CCAGGACTCTCCCCTTCAGT	1681	1700	4	318
532920	n/a	n/a	Intron 6	AGGGAAGGAGGACAGAATAG	3976	3995	25	319

532921	n/a	n/a	Intron 4	GAAATGAGGTCAAATGTCTG	3488	3507	30	320
532922	n/a	n/a	Intron 4	GGAGAGTCAGAAATGAGGTC	3497	3516	25	321
532923	n/a	n/a	Intron 12	GTAGAAAGTGGGAGGTGTTG	6228	6247	26	322
532924	n/a	n/a	Intron 10	TAGAAAGATCTCTGAAGTGC	5521	5540	24	323
532925	n/a	n/a	Intron 13	CTGCTCCTCACCCCAGTCCT	6594	6613	26	324
532926	n/a	n/a	Intron 11	CTACTGGGATTCTGTGCTTA	5927	5946	30	325
532927	n/a	n/a	Intron 1	CCCAAAAGGCCAAGGAGGGA	2103	2122	13	326
532928	n/a	n/a	Intron 17	TGACCACTTGGCATCTCCCC	7405	7424	27	327
532929	n/a	n/a	Intron 16 - Exon 17	CCTGCAAGGAGAGGAGAAGC	7314	7333	29	328
532930	n/a	n/a	Exon 16 - Intron 16	CTCTCACCTCTGCAAGTATT	7239	7258	44	329
532931	n/a	n/a	Intron 1	CCCCAAAAGGCCAAGGAGGG	2104	2123	21	330
532932	n/a	n/a	Intron 7	GTCTTCCAAGCCATCTTTTA	4555	4574	20	331
532933	n/a	n/a	Intron 8	GTTACAAGTGGACTTAAGGG	4797	4816	30	332
532934	n/a	n/a	Intron 8 - Exon 9	CCCATGTTGTGCAATCCTGC	5017	5036	30	333
532935	n/a	n/a	Intron 15	GAGGTGGGAAGCATGGAGAA	7091	7110	17	334
532936	n/a	n/a	Intron 14	TGCTCCCACCACTGTCATCT	6874	6893	21	335
532937	n/a	n/a	Exon 9 - Intron 9	AGGCAGGTTACTCACCCAGA	5118	5137	18	336
532938	n/a	n/a	Intron 11	TACTGGGATTCTGTGCTTAC	5926	5945	15	337
532939	n/a	n/a	Intron 13	GCCTTTCCCAGCCTTTCCTC	6571	6590	27	338
532940	n/a	n/a	Intron 8 - Exon 9	GTGCAATCCTGCAGAAGAGA	5009	5028	21	339
532941	n/a	n/a	Intron 8	ACAGGAGAGAGGTCCCTTCT	4743	4762	20	340
532942	n/a	n/a	Intron 10	CCCAAAAGGAGAAAGGGAAA	5717	5736	14	341
532943	n/a	n/a	Intron 2	AAGCCCAGGGTAAATGCTTA	2557	2576	32	342
532944	n/a	n/a	Intron 1	GATGAAGCCTGGCCCCAAAA	2116	2135	22	343
532945	n/a	n/a	Intron 10	TGGCAGAGAAGGAGAATGTG	5807	5826	22	344
532946	n/a	n/a	Intron 13	TTCCCAGCCTTTCCTCAGGG	6567	6586	35	345
532947	n/a	n/a	Intron 10	GGCAGAGAAGGAGAATGTGC	5806	5825	30	346
532948	n/a	n/a	Intron 10	ACAGTGCCAGGAAACAAGAA	5471	5490	25	347
532949	n/a	n/a	Exon 9 - Intron 9	TAGGCAGGTTACTCACCCAG	5119	5138	22	348
532950	n/a	n/a	Intron 2	TTCTCTTGACTTCCAGGGCT	2583	2602	22	349
532951	n/a	n/a	Intron 13	CCTGCTCCTCACCCCAGTCC	6595	6614	16	350
532953	n/a	n/a	Intron 7	TCCCACTAACCTCCATTGCC	4422	4441	14	351
532954	n/a	n/a	Intron 7	TTCCCTTTGACCACAAAGTG	4464	4483	16	352
532955	n/a	n/a	Intron 9	CTGGGTCCTAGGCAGGTTAC	5127	5146	30	353
532956	n/a	n/a	Intron 10	TCCAGGCAACTAGAGCTTCA	5411	5430	20	354
532957	n/a	n/a	Intron 8 - Exon 9	GCCCATGTTGTGCAATCCTG	5018	5037	45	355
532958	n/a	n/a	Intron 7	GGTTCCCACTAACCTCCATT	4425	4444	18	356
532959	n/a	n/a	Intron 3	AGGTAGAGAGCAAGAGTTAC	3052	3071	26	357

532960	n/a	n/a	Intron 7	CCACTAACCTCCATTGCCCA	4420	4439	10	358
532961	n/a	n/a	Intron 11	TCACAAACCACCATCTCTTA	6008	6027	40	359
532962	n/a	n/a	Exon 9 - Intron 9	TACTCACCCAGATAATCCTC	5110	5129	27	360
532963	n/a	n/a	Intron 13	TGCTCCTCACCCCAGTCCTC	6593	6612	24	361
532964	n/a	n/a	Intron 15 - Exon 16	TCTCACAGCTGCCTTTCTGT	7115	7134	25	362
532965	n/a	n/a	Exon 17 - Intron 17	GAAAGGGAGGACTCACTTGA	7379	7398	11	363
532966	n/a	n/a	Intron 7	CCATCTTTTAACCCCAGAGA	4545	4564	18	364
532967	n/a	n/a	Intron 13	TCCTCACCCCAGTCCTCCAG	6590	6609	27	365
532968	n/a	n/a	Intron 10	CTGGCAGAGAAGGAGAATGT	5808	5827	15	366
532969	n/a	n/a	Intron 17	TCTCCCCAGATAGGAAAGGG	7392	7411	23	367
532970	n/a	n/a	Intron 14	ACTTCAGCTGCTCCCACCAC	6882	6901	18	368
532971	n/a	n/a	Intron 1	GACAGCAGGAAGGGAAGGTT	2076	2095	13	369
532972	n/a	n/a	Intron 13 - Exon 14	GGAGACAAATGGGCCTATAA	6640	6659	33	370
532973	n/a	n/a	Intron 14	CTGCTCCCACCACTGTCATC	6875	6894	11	371
532974	n/a	n/a	Intron 10	AGGAATGAAGAAGGCTTTCC	5428	5447	21	372
532975	n/a	n/a	Intron 14	GGGATCTCATCCTTATCCTC	6741	6760	31	373
532976	n/a	n/a	Intron 9	GTGCTGGGTCCTAGGCAGGT	5130	5149	16	374
532977	n/a	n/a	Intron 1	CAAAAGGCCAAGGAGGGATG	2101	2120	14	375
532978	n/a	n/a	Intron 17	CCATGCTGACCACTTGGCAT	7411	7430	20	376
532979	n/a	n/a	Intron 8	GGAGGCTGGGACAGGAGAGA	4753	4772	25	377
532980	n/a	n/a	Intron 14 - Exon 15	GGAGCAGCTCTTCCTCTGGA	6917	6936	36	378
532981	n/a	n/a	Exon 3 - Intron 3	TCTCACCTCCGTTGTCACAG	2957	2976	20	379
532982	n/a	n/a	Intron 13	CAGTCCTCCAGCCTTTCCCA	6581	6600	21	380
532983	n/a	n/a	Intron 13	AGTCCTCCAGCCTTTCCCAG	6580	6599	22	381
532984	n/a	n/a	Intron 4 - Exon 5	TGAAGGAGTCTGGGAGAGTC	3509	3528	12	382
532985	n/a	n/a	Intron 16 - Exon 17	CAGAATCACCTGCAAGGAGA	7322	7341	20	383
532986	n/a	n/a	Exon 17 - Intron 17	TAGGAAAGGGAGGACTCACT	7382	7401	3	384
532987	n/a	n/a	Exon 4 - Intron 4	ACCTTGGCAGGAAGGCTCCG	3282	3301	12	385
532988	n/a	n/a	Intron 13 - Exon 14	GAGACAAATGGGCCTATAAA	6639	6658	15	386
532989	n/a	n/a	Intron 1	CTGAAGAGAAAGGCTGATGA	2131	2150	17	387
532990	n/a	n/a	Intron 6	AATGATCAGGGAGCTAGTCC	3913	3932	30	388
532991	n/a	n/a	Intron 17	CTTAGCTGACCTAAAGGAAT	7557	7576	22	389
532992	n/a	n/a	Intron 8	TGGGTATAGTGTTACAAGTG	4807	4826	17	390
532993	n/a	n/a	Intron 1	TGAAGAGAAAGGCTGATGAA	2130	2149	19	391
532994	n/a	n/a	Intron 8	GTGTTACAAGTGGACTTAAG	4799	4818	25	392

532995	n/a	n/a	Intron 6	ACCTGTGGGTGAGGAGAACA	4134	4153	24	393
532996	n/a	n/a	Exon 9 - Intron 9	TCACCCAGATAATCCTCCCT	5107	5126	36	394
532952	2608	2627	Exon 18	TGTTGTCGCAGCTGTTTTAA	7843	7862	90	395

Example 2: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells by MOE gapmers

Additional antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 4,500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3460_MGB (forward sequence CGAAGCAGCTCAATGAAATCAA, designated herein as SEQ ID NO: 813; reverse sequence TGCCTGGAGGGCCTTCTT, designated herein as SEQ ID NO: 814; probe sequence AGACCACAAGTTGAAGTC, designated herein as SEQ ID NO: 815) was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 5-10-5 MOE gapmers. The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000) , or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity.

Table 6

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1	SEQ ID NO:1	Target region	Sequence	% inhibition	SEQ ID NO: 2	SEQ ID NO: 2	SEQ ID NO:

	start site	stop site				start site	stop site	
532686	1135	1154	Exon 6	ACACTTTTTGGCTCCTGTGA	48	3819	3838	84
532687	1141	1160	Exon 6	GACTAGACACTTTTTGGCTC	63	3825	3844	85
532688	1147	1166	Exon 6	TAAGTTGACTAGACACTTTT	47	3831	3850	86
532689	1153	1172	Exon 6	CTCAATTAAGTTGACTAGAC	57	3837	3856	87
532690	1159	1178	Exon 6-7 Junction	CACCTTCTCAATTAAGTTGA	49	3843	3862	88
532691	1165	1184	Exon 6-7 Junction	ACTTGCCACCTTCTCAATTA	33	n/a	n/a	89
532692	1171	1190	Exon 6-7 Junction	ACCATAACTTGCCACCTTCT	67	n/a	n/a	90
532693	1177	1196	Exon 7	CTTCACACCATAACTTGCCA	56	4153	4172	91
532694	1183	1202	Exon 7	TCTTGGCTTCACACCATAAC	50	4159	4178	92
532695	1208	1227	Exon 7	ATGTGGCATATGTCACTAGA	53	4184	4203	93
532696	1235	1254	Exon 7	CAGACACTTTGACCCAAATT	52	4211	4230	94
532697	1298	1317	Exon 7-8 Juncion	GGTCTTCATAATTGATTTCA	59	n/a	n/a	95
532698	1304	1323	Exon 7-8 Juncion	ACTTGTGGTCTTCATAATTG	52	n/a	n/a	96
532699	1310	1329	Exon 7-8 Juncion	ACTTCAACTTGTGGTCTTCA	85	n/a	n/a	97
532700	1316	1335	Exon 8	TCCCTGACTTCAACTTGTGG	96	4609	4628	98
532701	1322	1341	Exon 8	TGTTAGTCCCTGACTTCAAC	56	4615	4634	99
532702	1328	1347	Exon 8	TCTTGGTGTTAGTCCCTGAC	86	4621	4640	100
532703	1349	1368	Exon 8	TGTACACTGCCTGGAGGGCC	35	4642	4661	101
532704	1355	1374	Exon 8	TCATGCTGTACACTGCCTGG	12	4648	4667	102
532705	1393	1412	Exon 8	GTTCCAGCCTTCAGGAGGGA	27	4686	4705	103
532706	1399	1418	Exon 8	GGTGCGGTTCCAGCCTTCAG	67	4692	4711	104
532707	1405	1424	Exon 8	ATGGCGGGTGCGGTTCCAGC	26	4698	4717	105
532708	1411	1430	Exon 8	GATGACATGGCGGGTGCGGT	28	4704	4723	106
532709	1417	1436	Exon 8	GAGGATGATGACATGGCGGG	6	4710	4729	107
532710	1443	1462	Exon 8-9 Junction	CCCATGTTGTGCAATCCATC	35	n/a	n/a	108
532711	1449	1468	Exon 9	TCCCCGCCCATGTTGTGCAA	28	5023	5042	109
532712	1455	1474	Exon 9	ATTGGGTCCCCGCCCATGTT	19	5029	5048	110
532713	1461	1480	Exon 9	ACAGTAATTGGGTCCCCGCC	29	5035	5054	111
532714	1467	1486	Exon 9	TCAATGACAGTAATTGGGTC	49	5041	5060	112
532715	1473	1492	Exon 9	ATCTCATCAATGACAGTAAT	45	5047	5066	113
532716	1479	1498	Exon 9	TCCCGGATCTCATCAATGAC	54	5053	5072	114
532717	1533	1552	Exon 9-10 Junction	ACATCCAGATAATCCTCCCT	22	n/a	n/a	115
532718	1539	1558	Exon 9-10 Junction	ACATAGACATCCAGATAATC	8	n/a	n/a	116
532719	1545	1564	Exon 9-	CCAAACACATAGACATCCAG	30	n/a	n/a	117

			10 Junction					
532720	1582	1601	Exon 10	AGCATTGATGTTCACTTGGT	62	5231	5250	118
532721	1588	1607	Exon 10	AGCCAAAGCATTGATGTTCA	46	5237	5256	119
532722	1594	1613	Exon 10	CTTGGAAGCCAAAGCATTGA	35	5243	5262	120
532723	1600	1619	Exon 10	GTCTTTCTTGGAAGCCAAAG	43	5249	5268	121
532724	1606	1625	Exon 10	CTCATTGTCTTTCTTGGAAG	40	5255	5274	122
532725	1612	1631	Exon 10	ATGTTGCTCATTGTCTTTCT	49	5261	5280	123
532726	1618	1637	Exon 10	GAACACATGTTGCTCATTGT	68	5267	5286	124
532727	1624	1643	Exon 10	GACTTTGAACACATGTTGCT	54	5273	5292	125
532728	1630	1649	Exon 10	ATCCTTGACTTTGAACACAT	61	5279	5298	126
532729	1636	1655	Exon 10	TTCCATATCCTTGACTTTGA	55	5285	5304	127
532730	1642	1661	Exon 10	CAGGTTTTCCATATCCTTGA	51	5291	5310	440
532731	1686	1705	Exon 10-11 Junction	CTCAGAGACTGGCTTTCATC	41	5827	5846	129
532732	1692	1711	Exon 11	CAGAGACTCAGAGACTGGCT	59	5833	5852	130
516252	1698	1717	Exon 11	ATGCCACAGAGACTCAGAGA	57	5839	5858	131
532733	1704	1723	Exon 11	CAAACCATGCCACAGAGACT	34	5845	5864	132
532734	1710	1729	Exon 11	TGTTCCCAAACCATGCCACA	51	5851	5870	133
532735	1734	1753	Exon 11	TTGTGGTAATCGGTACCCTT	50	5875	5894	134
532736	1740	1759	Exon 11	GGTTGCTTGTGGTAATCGGT	64	5881	5900	135
532737	1746	1765	Exon 11	TGCCATGGTTGCTTGTGGTA	40	5887	5906	136
532738	1752	1771	Exon 11	TTGGCCTGCCATGGTTGCTT	49	5893	5912	137
532739	1758	1777	Exon 11	GAGATCTTGGCCTGCCATGG	47	5899	5918	138
532740	1803	1822	Exon 12	ACAGCCCCCATACAGCTCTC	48	6082	6101	139
532741	1809	1828	Exon 12	GACACCACAGCCCCCATACA	40	6088	6107	140
532742	1815	1834	Exon 12	TACTCAGACACCACAGCCCC	33	6094	6113	141
532743	1821	1840	Exon 12	ACAAAGTACTCAGACACCAC	39	6100	6119	142
532744	1827	1846	Exon 12	GTCAGCACAAAGTACTCAGA	45	6106	6125	143
532745	1872	1891	Exon 12	TTGATTGAGTGTTCCTTGTC	42	6151	6170	144
532746	1878	1897	Exon 12	CTGACCTTGATTGAGTGTTC	53	6157	6176	145
532747	1909	1928	Exon 13	TATCTCCAGGTCCCGCTTCT	31	6403	6422	146
532748	1967	1986	Exon 13	GAATTCCTGCTTCTTTTTTC	30	6461	6480	147
532749	1973	1992	Exon 13	ATTCAGGAATTCCTGCTTCT	40	6467	6486	148
532750	1979	1998	Exon 13	CATAAAATTCAGGAATTCCT	45	6473	6492	149
532751	1985	2004	Exon 13	CATAGTCATAAAATTCAGGA	43	6479	6498	150
532752	2006	2025	Exon 13	TGAGCTTGATCAGGGCAACG	61	6500	6519	151
532753	2012	2031	Exon 13	TATTCTTGAGCTTGATCAGG	47	6506	6525	152
532754	2048	2067	Exon 13-14 Junction	GACAAATGGGCCTGATAGTC	35	n/a	n/a	153
532755	2070	2089	Exon 14	GTTGTTCCCTCGGTGCAGGG	43	6659	6678	154
532756	2076	2095	Exon 14	GCTCGAGTTGTTCCCTCGGT	51	6665	6684	155

532757	2082	2101	Exon 14	CTCAAAGCTCGAGTTGTTCC	36	6671	6690	156
532758	2088	2107	Exon 14	GGAAGCCTCAAAGCTCGAGT	54	6677	6696	157
532759	2094	2113	Exon 14	GTTGGAGGAAGCCTCAAAGC	52	6683	6702	158
532760	2100	2119	Exon 14	GTGGTAGTTGGAGGAAGCCT	22	6689	6708	159
532761	2106	2125	Exon 14	TGGCAAGTGGTAGTTGGAGG	34	6695	6714	160
532762	2112	2131	Exon 14	TGTTGCTGGCAAGTGGTAGT	52	6701	6720	161

Example 3: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells by MOE gapmers

Additional antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 5,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000) , or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity. In case the sequence alignment for a target gene in a particular table is not shown, it is understood that none of the oligonucleotides presented in that table align with 100% complementarity with that target gene.

Table 7

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO:
588570	150	169	Exon 1	TGGTCACATTCCCTTCCCCT	54	396
588571	152	171	Exon 1	CCTGGTCACATTCCCTTCCC	63	397
532614	154	173	Exon 1	GACCTGGTCACATTCCCTTC	64	12
588572	156	175	Exon 1	TAGACCTGGTCACATTCCCT	62	398
588573	158	177	Exon 1	CCTAGACCTGGTCACATTCC	53	399
588566	2189	2208	Exon 15	CCTTCCGAGTCAGCTTTTTC	60	400
588567	2191	2210	Exon 15	CTCCTTCCGAGTCAGCTTTT	61	401
532770	2193	2212	Exon 15	ACCTCCTTCCGAGTCAGCTT	77	198
588568	2195	2214	Exon 15	AGACCTCCTTCCGAGTCAGC	72	402
588569	2197	2216	Exon 15	GTAGACCTCCTTCCGAGTCA	46	403
588574	2453	2472	Exon 18	TTTGCCGCTTCTGGTTTTTG	46	404
588575	2455	2474	Exon 18	CTTTTGCCGCTTCTGGTTTT	41	405
532800	2457	2476	Exon 18	TGCTTTTGCCGCTTCTGGTT	69	228
588576	2459	2478	Exon 18	CCTGCTTTTGCCGCTTCTGG	61	406
588577	2461	2480	Exon 18	TACCTGCTTTTGCCGCTTCT	51	407
516350	2550	2569	Exon 18	AGAAAACCCAAATCCTCATC	71	408
588509	2551	2570	Exon 18	TAGAAAACCCAAATCCTCAT	58	409
588510	2552	2571	Exon 18	ATAGAAAACCCAAATCCTCA	57	410
588511	2553	2572	Exon 18	TATAGAAAACCCAAATCCTC	57	411
588512	2554	2573	Exon 18	TTATAGAAAACCCAAATCCT	44	412
588513	2555	2574	Exon 18	CTTATAGAAAACCCAAATCC	37	413
588514	2556	2575	Exon 18	CCTTATAGAAAACCCAAATC	50	414
588515	2557	2576	Exon 18	CCCTTATAGAAAACCCAAAT	45	415
588516	2558	2577	Exon 18	CCCCTTATAGAAAACCCAAA	60	416
588517	2559	2578	Exon 18	ACCCCTTATAGAAAACCCAA	67	417
588518	2560	2579	Exon 18	AACCCCTTATAGAAAACCCA	57	418
588519	2561	2580	Exon 18	AAACCCCTTATAGAAAACCC	61	419
588520	2562	2581	Exon 18	GAAACCCCTTATAGAAAACC	27	420
588521	2563	2582	Exon 18	GGAAACCCCTTATAGAAAAC	25	421
588522	2564	2583	Exon 18	AGGAAACCCCTTATAGAAAA	36	422
588523	2565	2584	Exon 18	CAGGAAACCCCTTATAGAAA	36	423
588524	2566	2585	Exon 18	GCAGGAAACCCCTTATAGAA	46	424
588525	2567	2586	Exon 18	AGCAGGAAACCCCTTATAGA	38	425
588526	2568	2587	Exon 18	CAGCAGGAAACCCCTTATAG	47	426
588527	2569	2588	Exon 18	CCAGCAGGAAACCCCTTATA	68	427
588528	2570	2589	Exon 18	TCCAGCAGGAAACCCCTTAT	63	428
532809	2571	2590	Exon 18	GTCCAGCAGGAAACCCCTTA	85	237
588529	2572	2591	Exon 18	TGTCCAGCAGGAAACCCCTT	76	429
588530	2573	2592	Exon 18	CTGTCCAGCAGGAAACCCCT	74	430

588531	2574	2593	Exon 18	CCTGTCCAGCAGGAAACCCC	75	431
588532	2575	2594	Exon 18	CCCTGTCCAGCAGGAAACCC	73	432
588533	2576	2595	Exon 18	CCCCTGTCCAGCAGGAAACC	82	433
532810	2577	2596	Exon 18	GCCCCTGTCCAGCAGGAAAC	88	238
588534	2578	2597	Exon 18	CGCCCCTGTCCAGCAGGAAA	86	434
588535	2579	2598	Exon 18	ACGCCCCTGTCCAGCAGGAA	86	435
588536	2580	2599	Exon 18	CACGCCCCTGTCCAGCAGGA	93	436
588537	2581	2600	Exon 18	CCACGCCCCTGTCCAGCAGG	92	437
588538	2582	2601	Exon 18	CCCACGCCCCTGTCCAGCAG	94	438
588539	2583	2602	Exon 18	TCCCACGCCCCTGTCCAGCA	96	439
588540	2584	2603	Exon 18	ATCCCACGCCCCTGTCCAGC	88	440
588541	2585	2604	Exon 18	AATCCCACGCCCCTGTCCAG	79	441
588542	2586	2605	Exon 18	CAATCCCACGCCCCTGTCCA	83	442
588543	2587	2606	Exon 18	TCAATCCCACGCCCCTGTCC	86	443
588544	2588	2607	Exon 18	TTCAATCCCACGCCCCTGTC	90	444
588545	2589	2608	Exon 18	ATTCAATCCCACGCCCCTGT	92	445
588546	2590	2609	Exon 18	AATTCAATCCCACGCCCCTG	92	446
588547	2591	2610	Exon 18	TAATTCAATCCCACGCCCCT	88	447
588548	2592	2611	Exon 18	TTAATTCAATCCCACGCCCC	93	448
588549	2593	2612	Exon 18	TTTAATTCAATCCCACGCCC	88	449
588550	2594	2613	Exon 18	TTTTAATTCAATCCCACGCC	89	450
588551	2595	2614	Exon 18	GTTTTAATTCAATCCCACGC	94	451
588552	2596	2615	Exon 18	TGTTTTAATTCAATCCCACG	93	452
588553	2597	2616	Exon 18	CTGTTTTAATTCAATCCCAC	96	453
588554	2598	2617	Exon 18	GCTGTTTTAATTCAATCCCA	98	454
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	97	239
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	95	239
588555	2600	2619	Exon 18	CAGCTGTTTTAATTCAATCC	93	455
588556	2601	2620	Exon 18	GCAGCTGTTTTAATTCAATC	96	456
588557	2602	2621	Exon 18	CGCAGCTGTTTTAATTCAAT	98	457
588558	2603	2622	Exon 18	TCGCAGCTGTTTTAATTCAA	95	458
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	97	317
588559	2605	2624	Exon 18	TGTCGCAGCTGTTTTAATTC	95	459
588560	2606	2625	Exon 18	TTGTCGCAGCTGTTTTAATT	92	460
588561	2607	2626	Exon 18	GTTGTCGCAGCTGTTTTAAT	93	461
532952	2608	2627	Exon 18	TGTTGTCGCAGCTGTTTTAA	88	395
588562	2609	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTTTA	90	462
588563	2610	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTTTT	89	463
588564	2611	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGTTT	92	464
588565	2612	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTGTT	88	465

Table 8

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO:1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO 2: start site	SEQ ID NO: 2 stop site	SEQ ID NO:
588685	n/a	n/a	Exon 1	GGATCCAGCTCACTCCCCTG	48	1596	1615	466
588686	n/a	n/a	Exon 1	AAATAAGGATCCAGCTCACT	29	1602	n/a	467
588688	n/a	n/a	Exon 1	GACCAGAAATAAGGATCCAG	58	1608	1627	468
588690	n/a	n/a	Exon 1	CTTAGGGACCAGAAATAAGG	45	1614	1633	469
588692	n/a	n/a	Exon 1	CACCCACTTAGGGACCAGAA	36	1620	1639	470
588694	n/a	n/a	Exon 1	ACCACCCACTTAGGGACCAG	47	1622	1641	471
588696	n/a	n/a	Exon 1	AGGTCCAGGACTCTCCCCTT	96	1685	1704	472
588698	n/a	n/a	Exon 1	AAGGTCCAGGACTCTCCCCT	96	1686	1705	473
588700	n/a	n/a	Exon 1	AAACTGCAGAAGTCCCACCC	2	1716	1735	474
588586	30	49	Exon 1	GGAGGGCCCCGCTGAGCTGC	59	1751	1770	475
588587	48	67	Exon 1	TCCCGGAACATCCAAGCGGG	45	1769	1788	476
588588	56	75	Exon 1	CATCACTTTCCCGGAACATC	39	1777	n/a	477
588589	151	170	Exon 1	CTGGTCACATTCCCTTCCCC	29	1872	1891	478
588590	157	176	Exon 1	CTAGACCTGGTCACATTCCC	47	1878	1897	479
588591	339	358	Exon 1-2 Junction	GGAGTGGTGGTCACACCTCC	44	n/a	n/a	480
588592	384	403	Exon 2	ACCCCCTCCAGAGAGCAGGA	43	2192	2211	481
588593	390	409	Exon 2	ATCTCTACCCCCTCCAGAGA	34	2198	2217	482
588594	467	486	Exon 2	GGTACGGGTAGAAGCCAGAA	17	2275	2294	483
588595	671	690	Exon 3	GGAGAGTGTAACCGTCATAG	37	2879	2898	484
588596	689	708	Exon 3	TGCGATTGGCAGAGCCCCGG	18	2897	2916	485
588597	695	714	Exon 3	GGCAGGTGCGATTGGCAGAG	32	2903	2922	486
588598	707	726	Exon 3	GGCCATTCACTTGGCAGGTG	45	2915	2934	487
588599	738	757	Exon 3	TTGTCACAGATCGCTGTCTG	52	2946	2965	488
588600	924	943	Exon 4-5 Junction	AAGGAGTCTTGGCAGGAAGG	39	n/a	n/a	489
588601	931	950	Exon 4-5 Junction	GTACATGAAGGAGTCTTGGC	37	n/a	n/a	490
588602	959	978	Exon 5	AAGCTTCGGCCACCTCTTGA	21	3542	3561	491
588603	1089	1108	Exon 6	CCATCTAGCACCAGGTAGAT	22	3773	3792	492
588604	1108	1127	Exon 6	GGCCCCAATGCTGTCTGATC	21	3792	3811	493
588606	1150	1169	Exon 6	AATTAAGTTGACTAGACACT	56	3834	3853	494
588608	1162	1181	Exon 6-7 Junction	TGCCACCTTCTCAATTAAGT	50		19	495
588578	1167	1186	Exon 6-7 Junction	TAACTTGCCACCTTCTCAAT	23	n/a	n/a	496
588579	1169	1188	Exon 6-7 Junction	CATAACTTGCCACCTTCTCA	23	n/a	n/a	497

532692	1171	1190	Exon 6-7 Junction	ACCATAACTTGCCACCTTCT	15	n/a	n/a	90
588580	1173	1192	Exon 6-7 Junction	ACACCATAACTTGCCACCTT	16	n/a	n/a	498
588581	1175	1194	Exon 6-7 Junction	TCACACCATAACTTGCCACC	14	4151	4170	499
588610	1319	1338	Exon 8	TAGTCCCTGACTTCAACTTG	50	4612	4631	500
588612	1325	1344	Exon 8	TGGTGTTAGTCCCTGACTTC	47	4618	4637	501
588614	1396	1415	Exon 8	GCGGTTCCAGCCTTCAGGAG	47	4689	4708	502
588616	1421	1440	Exon 8	TCATGAGGATGATGACATGG	51	4714	4733	503
588618	1446	1465	Exon 9	CCGCCCATGTTGTGCAATCC	18	5020	5039	504
588620	1458	1477	Exon 9	GTAATTGGGTCCCCGCCCAT	40	5032	5051	505
588623	1482	1501	Exon 9	AAGTCCCGGATCTCATCAAT	40	5056	5075	506
588624	1542	1561	Exon 9-10 Junction	AACACATAGACATCCAGATA	45	n/a	n/a	507
588626	1585	1604	Exon 10	CAAAGCATTGATGTTCACTT	43	5234	5253	508
588628	1621	1640	Exon 10	TTTGAACACATGTTGCTCAT	45	5270	5289	509
588631	1646	1665	Exon 10	CTTCCAGGTTTTCCATATCC	53	5295	5314	510
588632	1647	1666	Exon 10	TCTTCCAGGTTTTCCATATC	56	5296	5315	511
588634	1689	1708	Exon 11	AGACTCAGAGACTGGCTTTC	35	5830	5849	512
588636	1749	1768	Exon 11	GCCTGCCATGGTTGCTTGTG	55	5890	5909	513
588638	1763	1782	Exon 11	TGACTGAGATCTTGGCCTGC	78	5904	5923	514
588640	1912	1931	Exon 13	TTCTATCTCCAGGTCCCGCT	95	6406	6425	515
588642	1982	2001	Exon 13	AGTCATAAAATTCAGGAATT	44	6476	6495	516
588645	2073	2092	Exon 14	CGAGTTGTTCCCTCGGTGCA	40	6662	6681	517
588646	2085	2104	Exon 14	AGCCTCAAAGCTCGAGTTGT	57	6674	6693	518
588648	2091	2110	Exon 14	GGAGGAAGCCTCAAAGCTCG	48	6680	6699	519
588651	2097	2116	Exon 14	GTAGTTGGAGGAAGCCTCAA	40	6686	6705	520
588652	2103	2122	Exon 14	CAAGTGGTAGTTGGAGGAAG	43	6692	6711	521
588654	2166	2185	Exon 15	TCCTCAGACACAAACAGAGC	13	6954	6973	522
588656	2172	2191	Exon 15	TTCTCCTCCTCAGACACAAA	55	6960	6979	523
588658	2196	2215	Exon 15	TAGACCTCCTTCCGAGTCAG	44	6984	7003	524
588660	2202	2221	Exon 15	TTGATGTAGACCTCCTTCCG	50	6990	7009	525
588582	2219	2238	Exon 15-16 Junction	CTTTCTTATCCCCATTCTTG	19	n/a	n/a	526
588583	2221	2240	Exon 15-16 Junction	GCCTTTCTTATCCCCATTCT	14	n/a	n/a	527
532775	2223	2242	Exon 15-16 Junction	CTGCCTTTCTTATCCCCATT	3	n/a	n/a	203
588584	2225	2244	Exon 15-16 Junction	AGCTGCCTTTCTTATCCCCA	18	n/a	n/a	528

588662	2226	2245	Exon 15-16 Junction	CAGCTGCCTTTCTTATCCCC	27	n/a	n/a	529
588585	2227	2246	Exon 15-16 Junction	ACAGCTGCCTTTCTTATCCC	59	n/a	n/a	530
588664	2238	2257	Exon 16	GCATCTCTCTCACAGCTGCC	49	7122	7141	531
588666	2276	2295	Exon 16	AGATGTCCTTGACTTTGTCA	41	7160	7179	532
588668	2330	2349	Exon 16	CAGCATAGGGACTCACTCCT	41	7214	7233	533
588670	2361	2380	Exon 16-17 Junction	CCGCCAGAATCACCTCTGCA	43	n/a	n/a	534
588672	2397	2416	Exon 17	TGAATGAAACGACTTCTCTT	52	7362	7381	535
588674	2430	2449	Exon 18	ACATCCACTACTCCCCAGCT	39	7665	7684	536
588676	2448	2467	Exon 18	CGCTTCTGGTTTTTGCAGAC	69	7683	7702	537
588678	2454	2473	Exon 18	TTTTGCCGCTTCTGGTTTTT	46	7689	7708	538
588680	2466	2485	Exon 18	GCAGGTACCTGCTTTTGCCG	47	7701	7720	539
588682	2532	2551	Exon 18	TCTTGGAGTTTCTCCTTCAG	58	7767	7786	540
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	10	7834	7853	239
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	11	7839	7858	317

Example 4: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells by MOE gapmers

Antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 3,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 4-8-5 MOE, 5-9-5 MOE, 5-10-5 MOE, 3-10-4 MOE, 3-10-7 MOE, 6-7-6- MOE, 6-8-6 MOE, or 5-7-5 MOE gapmers, or as deoxy, MOE, and cEt oligonucleotides.

The 4-8-5 MOE gapmers are 17 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising four and five nucleosides respectively. The 5-9-5 MOE gapmers are 19 nucleosides in length,

wherein the central gap segment comprises of nine 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 5-7-5 MOE gapmers are 17 nucleosides in length, wherein the central gap segment comprises of seven 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 3-10-4 MOE gapmers are 17 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising three and four nucleosides respectively. The 3-10-7 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising three and seven nucleosides respectively. The 6-7-6 MOE gapmers are 19 nucleosides in length, wherein the central gap segment comprises of seven 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising six nucleosides each. The 6-8-6 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising six nucleosides each. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

The deoxy, MOE and cEt oligonucleotides are 16 nucleosides in length wherein the nucleoside have either a MOE sugar modification, an cEt sugar modification, or a deoxy modification. The 'Chemistry' column describes the sugar modifications of each oligonucleotide. 'k' indicates an cEt sugar modification; 'd' indicates deoxyribose; and 'e' indicates a MOE modification.

"Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity.

Table 9

Inhibition of CFB mRNA by deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 Start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 Start site	SEQ ID NO: 2 Stop site	Motif	SEQ ID NO:
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	10	7834	7853	eeeeeddddddddddeeeee	239
588884	48	63	Exon 1	GGAACATCCAAGCGGG	79	1769	1784	eekddddddddddkke	541
588872	154	169	Exon 1	TGGTCACATTCCCTTC	91	1875	1890	eekddddddddddkke	542
588873	156	171	Exon 1	CCTGGTCACATTCCCT	91	1877	1892	eekddddddddddkke	543
588874	158	173	Exon 1	GACCTGGTCACATTCC	91	1879	1894	eekddddddddddkke	544
588878	1171	1186	Exon 6-7 Junction	TAACTTGCCACCTTCT	92	n/a	n/a	eekddddddddddkke	545
588879	1173	1188	Exon 6-7 Junction	CATAACTTGCCACCTT	94	n/a	n/a	eekddddddddddkke	546
588880	1175	1190	Exon 6-7 Junction	ACCATAACTTGCCACC	89	4151	4166	eekddddddddddkke	547
588869	2193	2208	Exon 15	CCTTCCGAGTCAGCTT	17	6981	6996	eekddddddddddkke	548
588870	2195	2210	Exon 15	CTCCTTCCGAGTCAGC	78	6983	6998	eekddddddddddkke	549
588871	2197	2212	Exon 15	ACCTCCTTCCGAGTCA	80	6985	7000	eekddddddddddkke	550
588881	2223	2238	Exon 15-16 Junction	CTTTCTTATCCCCATT	93	n/a	n/a	eekddddddddddkke	551
588882	2225	2240	Exon 15-16 Junction	GCCTTTCTTATCCCCA	88	n/a	n/a	eekddddddddddkke	552
588883	2227	2242	Exon 15-16 Junction	CTGCCTTTCTTATCCC	90	n/a	n/a	eekddddddddddkke	553
588875	2457	2472	Exon 18	TTTGCCGCTTCTGGTT	81	7692	7707	eekddddddddddkke	554
588876	2459	2474	Exon 18	CTTTTGCCGCTTCTGG	95	7694	7709	eekddddddddddkke	555
588877	2461	2476	Exon 18	TGCTTTTGCCGCTTCT	91	7696	7711	eekddddddddddkke	556
588807	2551	2566	Exon 18	AAACCCAAATCCTCAT	82	7786	7801	eekddddddddddkke	557
588808	2553	2568	Exon 18	GAAAACCCAAATCCTC	69	7788	7803	eekddddddddddkke	558
588809	2555	2570	Exon 18	TAGAAAACCCAAATCC	51	7790	7805	eekddddddddddkke	559
588810	2556	2571	Exon 18	ATAGAAAACCCAAATC	23	7791	7806	eekddddddddddkke	560
588811	2559	2574	Exon 18	CTTATAGAAAACCCAA	13	7794	7809	eekddddddddddkke	561
588812	2560	2575	Exon 18	CCTTATAGAAAACCCA	29	7795	7810	eekddddddddddkke	562
588813	2561	2576	Exon 18	CCCTTATAGAAAACCC	53	7796	7811	eekddddddddddkke	563
588814	2562	2577	Exon 18	CCCCTTATAGAAAACC	86	7797	7812	eekddddddddddkke	564
588815	2563	2578	Exon 18	ACCCCTTATAGAAAAC	76	7798	7813	eekddddddddddkke	565
588816	2564	2579	Exon 18	AACCCCTTATAGAAAA	33	7799	7814	eekddddddddddkke	566
588817	2565	2580	Exon 18	AAACCCCTTATAGAAA	48	7800	7815	eekddddddddddkke	567
588818	2566	2581	Exon 18	GAAACCCCTTATAGAA	44	7801	7816	eekddddddddddkke	568
588819	2567	2582	Exon 18	GGAAACCCCTTATAGA	74	7802	7817	eekddddddddddkke	569
588820	2568	2583	Exon 18	AGGAAACCCCTTATAG	68	7803	7818	eekddddddddddkke	570
588821	2569	2584	Exon 18	CAGGAAACCCCTTATA	45	7804	7819	eekddddddddddkke	571

588822	2570	2585	Exon 18	GCAGGAAACCCCTTAT	50	7805	7820	eekddddddddddkke	572
588823	2571	2586	Exon 18	AGCAGGAAACCCCTTA	54	7806	7821	eekddddddddddkke	573
588824	2572	2587	Exon 18	CAGCAGGAAACCCCTT	35	7807	7822	eekddddddddddkke	574
588825	2573	2588	Exon 18	CCAGCAGGAAACCCCT	11	7808	7823	eekddddddddddkke	575
588826	2574	2589	Exon 18	TCCAGCAGGAAACCCC	19	7809	7824	eekddddddddddkke	576
588827	2575	2590	Exon 18	GTCCAGCAGGAAACCC	42	7810	7825	eekddddddddddkke	577
588828	2576	2591	Exon 18	TGTCCAGCAGGAAACC	0	7811	7826	eekddddddddddkke	578
588829	2577	2592	Exon 18	CTGTCCAGCAGGAAAC	49	7812	7827	eekddddddddddkke	579
588830	2578	2593	Exon 18	CCTGTCCAGCAGGAAA	11	7813	7828	eekddddddddddkke	580
588831	2579	2594	Exon 18	CCCTGTCCAGCAGGAA	20	7814	7829	eekddddddddddkke	581
588832	2580	2595	Exon 18	CCCCTGTCCAGCAGGA	19	7815	7830	eekddddddddddkke	582
588833	2581	2596	Exon 18	GCCCCTGTCCAGCAGG	12	7816	7831	eekddddddddddkke	583
588834	2582	2597	Exon 18	CGCCCCTGTCCAGCAG	10	7817	7832	eekddddddddddkke	584
588835	2583	2598	Exon 18	ACGCCCCTGTCCAGCA	13	7818	7833	eekddddddddddkke	585
588836	2584	2599	Exon 18	CACGCCCCTGTCCAGC	13	7819	7834	eekddddddddddkke	586
588837	2585	2600	Exon 18	CCACGCCCCTGTCCAG	39	7820	7835	eekddddddddddkke	587
588838	2586	2601	Exon 18	CCCACGCCCCTGTCCA	54	7821	7836	eekddddddddddkke	588
588839	2587	2602	Exon 18	TCCCACGCCCCTGTCC	51	7822	7837	eekddddddddddkke	589
588840	2588	2603	Exon 18	ATCCCACGCCCCTGTC	65	7823	7838	eekddddddddddkke	590
588841	2589	2604	Exon 18	AATCCCACGCCCCTGT	59	7824	7839	eekddddddddddkke	591
588842	2590	2605	Exon 18	CAATCCCACGCCCCTG	70	7825	7840	eekddddddddddkke	592
588843	2591	2606	Exon 18	TCAATCCCACGCCCCT	0	7826	7841	eekddddddddddkke	593
588844	2592	2607	Exon 18	TTCAATCCCACGCCCC	48	7827	7842	eekddddddddddkke	594
588845	2593	2608	Exon 18	ATTCAATCCCACGCCC	46	7828	7843	eekddddddddddkke	595
588846	2594	2609	Exon 18	AATTCAATCCCACGCC	67	7829	7844	eekddddddddddkke	596
588847	2595	2610	Exon 18	TAATTCAATCCCACGC	75	7830	7845	eekddddddddddkke	597
588848	2596	2611	Exon 18	TTAATTCAATCCCACG	76	7831	7846	eekddddddddddkke	598
588849	2597	2612	Exon 18	TTTAATTCAATCCCAC	94	7832	7847	eekddddddddddkke	599
588850	2598	2613	Exon 18	TTTTAATTCAATCCCA	91	7833	7848	eekddddddddddkke	600
588851	2599	2614	Exon 18	GTTTTAATTCAATCCC	91	7834	7849	eekddddddddddkke	601
588852	2600	2615	Exon 18	TGTTTTAATTCAATCC	78	7835	7850	eekddddddddddkke	602
588853	2601	2616	Exon 18	CTGTTTTAATTCAATC	81	7836	7851	eekddddddddddkke	603
588854	2602	2617	Exon 18	GCTGTTTTAATTCAAT	63	7837	7852	eekddddddddddkke	604
588855	2603	2618	Exon 18	AGCTGTTTTAATTCAA	65	7838	7853	eekddddddddddkke	605
588856	2604	2619	Exon 18	CAGCTGTTTTAATTCA	76	7839	7854	eekddddddddddkke	606
588857	2605	2620	Exon 18	GCAGCTGTTTTAATTC	89	7840	7855	eekddddddddddkke	607
588858	2606	2621	Exon 18	CGCAGCTGTTTTAATT	89	7841	7856	eekddddddddddkke	608
588859	2607	2622	Exon 18	TCGCAGCTGTTTTAAT	89	7842	7857	eekddddddddddkke	609
588860	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	76	7843	7858	eekddddddddddkke	610
588861	2609	2624	Exon 18	TGTCGCAGCTGTTTTA	87	7844	7859	eekddddddddddkke	611
588862	2610	2625	Exon 18	TTGTCGCAGCTGTTTT	85	7845	7860	eekddddddddddkke	612
588863	2611	2626	Exon 18	GTTGTCGCAGCTGTTT	87	7846	7861	eekddddddddddkke	613
588864	2612	2627	Exon 18	TGTTGTCGCAGCTGTT	67	7847	7862	eekddddddddddkke	614

588865	2613	2628	Exon 18	TTGTTGTCGCAGCTGT	51	n/a	n/a	eekddddddddddkke	615
588866	2614	2629	Exon 18	TTTGTTGTCGCAGCTG	95	n/a	n/a	eekddddddddddkke	616
588867	2615	2630	Exon 18	TTTTGTTGTCGCAGCT	92	n/a	n/a	eekddddddddddkke	617
588868	2616	2631	Exon 18	TTTTTGTTGTCGCAGC	66	n/a	n/a	eekddddddddddkke	618

Table 10

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	SEQ ID NO:
588685	n/a	n/a	Exon 1	GGATCCAGCTCACTCCCCTG	14	1596	1615	466
588686	n/a	n/a	Exon 1	AAATAAGGATCCAGCTCACT	2	1602	1621	467
588688	n/a	n/a	Exon 1	GACCAGAAATAAGGATCCAG	3	1608	1627	468
588690	n/a	n/a	Exon 1	CTTAGGGACCAGAAATAAGG	10	1614	1633	469
588692	n/a	n/a	Exon 1	CACCCACTTAGGGACCAGAA	23	1620	1639	470
588694	n/a	n/a	Exon 1	ACCACCCACTTAGGGACCAG	23	1622	1641	471
588696	n/a	n/a	Exon 1	AGGTCCAGGACTCTCCCCTT	15	1685	1704	472
588698	n/a	n/a	Exon 1	AAGGTCCAGGACTCTCCCCT	19	1686	1705	473
588700	n/a	n/a	Exon 1	AAACTGCAGAAGTCCCACCC	16	1716	1735	474
588586	30	49	Exon 1	GGAGGGCCCCGCTGAGCTGC	11	1751	1770	475
588587	48	67	Exon 1	TCCCGGAACATCCAAGCGGG	14	1769	1788	476
588588	56	75	Exon 1	CATCACTTTCCCGGAACATC	18	1777	1796	477
588589	151	170	Exon 1	CTGGTCACATTCCCTTCCCC	59	1872	1891	478
588590	157	176	Exon 1	CTAGACCTGGTCACATTCCC	59	1878	1897	479
588591	339	358	Exon 1-2 Junction	GGAGTGGTGGTCACACCTCC	45	n/a	n/a	480
588592	384	403	Exon 2	ACCCCCTCCAGAGAGCAGGA	39	2192	2211	481
588593	390	409	Exon 2	ATCTCTACCCCCTCCAGAGA	29	2198	2217	482
588594	467	486	Exon 2	GGTACGGGTAGAAGCCAGAA	47	2275	2294	483
588595	671	690	Exon 3	GGAGAGTGTAACCGTCATAG	44	2879	2898	484
588596	689	708	Exon 3	TGCGATTGGCAGAGCCCCGG	43	2897	2916	638
588597	695	714	Exon 3	GGCAGGTGCGATTGGCAGAG	34	2903	2922	486
588598	707	726	Exon 3	GGCCATTCACTTGGCAGGTG	17	2915	2934	487
588599	738	757	Exon 3	TTGTCACAGATCGCTGTCTG	37	2946	2965	488
588600	924	943	Exon 3-4 Junction	AAGGAGTCTTGGCAGGAAGG	18	n/a	n/a	489
588601	931	950	Exon 3-4 Junction	GTACATGAAGGAGTCTTGGC	32	n/a	n/a	490
588602	959	978	Exon 5	AAGCTTCGGCCACCTCTTGA	45	3542	3561	491
588603	1089	1108	Exon 6	CCATCTAGCACCAGGTAGAT	52	3773	3792	492
588604	1108	1127	Exon 6	GGCCCCAATGCTGTCTGATC	39	3792	3811	493
588606	1150	1169	Exon 6	AATTAAGTTGACTAGACACT	37	3834	3853	494

588608	1162	1181	Exon 6-7 Junction	TGCCACCTTCTCAATTAAGT	21	n/a	n/a	648
588578	1167	1186	Exon 6-7 Junction	TAACTTGCCACCTTCTCAAT	22	n/a	n/a	496
588579	1169	1188	Exon 6-7 Junction	CATAACTTGCCACCTTCTCA	21	n/a	n/a	497
532692	1171	1190	Exon 6-7 Junction	ACCATAACTTGCCACCTTCT	56	n/a	n/a	90
588580	1173	1192	Exon 6-7 Junction	ACACCATAACTTGCCACCTT	50	n/a	n/a	498
588581	1175	1194	Exon 7	TCACACCATAACTTGCCACC	50	4151	4170	499
588610	1319	1338	Exon 8	TAGTCCCTGACTTCAACTTG	47	4612	4631	500
588612	1325	1344	Exon 8	TGGTGTTAGTCCCTGACTTC	47	4618	4637	501
588614	1396	1415	Exon 8	GCGGTTCCAGCCTTCAGGAG	51	4689	4708	502
588616	1421	1440	Exon 8	TCATGAGGATGATGACATGG	18	4714	4733	503
588618	1446	1465	Exon 9	CCGCCCATGTTGTGCAATCC	40	5020	5039	504
588620	1458	1477	Exon 9	GTAATTGGGTCCCCGCCCAT	40	5032	5051	505
588623	1482	1501	Exon 9	AAGTCCCGGATCTCATCAAT	45	5056	5075	506
588624	1542	1561	Exon 9-10 Junction	AACACATAGACATCCAGATA	43	n/a	n/a	507
588626	1585	1604	Exon 10	CAAAGCATTGATGTTCACTT	45	5234	5253	508
588628	1621	1640	Exon 10	TTTGAACACATGTTGCTCAT	53	5270	5289	509
588631	1646	1665	Exon 10	CTTCCAGGTTTTCCATATCC	56	5295	5314	510
588632	1647	1666	Exon 10	TCTTCCAGGTTTTCCATATC	35	5296	5315	511
588634	1689	1708	Exon 11	AGACTCAGAGACTGGCTTTC	55	5830	5849	512
588636	1749	1768	Exon 11	GCCTGCCATGGTTGCTTGTG	78	5890	5909	513
588638	1763	1782	Exon 11	TGACTGAGATCTTGGCCTGC	95	5904	5923	514
588640	1912	1931	Exon 13	TTCTATCTCCAGGTCCCGCT	44	6406	6425	515
588642	1982	2001	Exon 13	AGTCATAAAATTCAGGAATT	40	6476	6495	516
588645	2073	2092	Exon 14	CGAGTTGTTCCCTCGGTGCA	57	6662	6681	517
588646	2085	2104	Exon 14	AGCCTCAAAGCTCGAGTTGT	48	6674	6693	518
588648	2091	2110	Exon 14	GGAGGAAGCCTCAAAGCTCG	40	6680	6699	519
588651	2097	2116	Exon 14	GTAGTTGGAGGAAGCCTCAA	43	6686	6705	520
588652	2103	2122	Exon 14	CAAGTGGTAGTTGGAGGAAG	13	6692	6711	521
588654	2166	2185	Exon 15	TCCTCAGACACAAACAGAGC	55	6954	6973	522
588656	2172	2191	Exon 15	TTCTCCTCCTCAGACACAAA	44	6960	6979	523
588658	2196	2215	Exon 15	TAGACCTCCTTCCGAGTCAG	50	6984	7003	524
588660	2202	2221	Exon 15	TTGATGTAGACCTCCTTCCG	27	6990	7009	525
588582	2219	2238	Exon 15-16 Junction	CTTTCTTATCCCCATTCTTG	49	n/a	n/a	526
588583	2221	2240	Exon 15-16 Junction	GCCTTTCTTATCCCCATTCT	41	n/a	n/a	527
532775	2223	2242	Exon 15-16	CTGCCTTTCTTATCCCCATT	41	n/a	n/a	203

			Junction					
588584	2225	2244	Exon 15-16 Junction	AGCTGCCTTTCTTATCCCCA	43	n/a	n/a	528
588662	2226	2245	Exon 15-16 Junction	CAGCTGCCTTTCTTATCCCC	52	n/a	n/a	529
588585	2227	2246	Exon 15-16 Junction	ACAGCTGCCTTTCTTATCCC	39	n/a	n/a	530
588664	2238	2257	Exon 16	GCATCTCTCTCACAGCTGCC	69	7122	7141	531
588666	2276	2295	Exon 16	AGATGTCCTTGACTTTGTCA	46	7160	7179	532
588668	2330	2349	Exon 16	CAGCATAGGGACTCACTCCT	47	7214	7233	533
588670	2361	2380	Exon 16-17 Junction	CCGCCAGAATCACCTCTGCA	58	n/a	n/a	534
588672	2397	2416	Exon 17	TGAATGAAACGACTTCTCTT	48	7362	7381	535
588674	2430	2449	Exon 18	ACATCCACTACTCCCCAGCT	29	7665	7684	536
588676	2448	2467	Exon 18	CGCTTCTGGTTTTTGCAGAC	58	7683	7702	537
588678	2454	2473	Exon 18	TTTTGCCGCTTCTGGTTTTT	45	7689	7708	538
588680	2466	2485	Exon 18	GCAGGTACCTGCTTTTGCCG	36	7701	7720	539
588682	2532	2551	Exon 18	TCTTGGAGTTTCTCCTTCAG	47	7767	7786	540
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	96	7834	7853	239
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	96	7839	7858	317

Table 11

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
598973	2552	2568	Exon 18	GAAAACCCAAATCCTCA	40	7787	7803	3-10-4	619
599036	2552	2568	Exon 18	GAAAACCCAAATCCTCA	18	7787	7803	5-7-5	619
598974	2553	2569	Exon 18	AGAAAACCCAAATCCTC	28	7788	7804	3-10-4	620
599037	2553	2569	Exon 18	AGAAAACCCAAATCCTC	19	7788	7804	5-7-5	620
598975	2554	2570	Exon 18	TAGAAAACCCAAATCCT	15	7789	7805	3-10-4	621
599038	2554	2570	Exon 18	TAGAAAACCCAAATCCT	32	7789	7805	5-7-5	621
598976	2555	2571	Exon 18	ATAGAAAACCCAAATCC	12	7790	7806	3-10-4	622
599039	2555	2571	Exon 18	ATAGAAAACCCAAATCC	7	7790	7806	5-7-5	622
598977	2557	2573	Exon 18	TTATAGAAAACCCAAAT	13	7792	7808	3-10-4	623
599040	2557	2573	Exon 18	TTATAGAAAACCCAAAT	13	7792	7808	5-7-5	623
598978	2558	2574	Exon 18	CTTATAGAAAACCCAAA	0	7793	7809	3-10-4	624
599041	2558	2574	Exon 18	CTTATAGAAAACCCAAA	0	7793	7809	5-7-5	624
598979	2559	2575	Exon 18	CCTTATAGAAAACCCAA	8	7794	7810	3-10-4	625

599042	2559	2575	Exon 18	CCTTATAGAAAACCCAA	19	7794	7810	5-7-5	625
598980	2560	2576	Exon 18	CCCTTATAGAAAACCCA	42	7795	7811	3-10-4	626
599043	2560	2576	Exon 18	CCCTTATAGAAAACCCA	10	7795	7811	5-7-5	626
598981	2561	2577	Exon 18	CCCCTTATAGAAAACCC	20	7796	7812	3-10-4	627
599044	2561	2577	Exon 18	CCCCTTATAGAAAACCC	12	7796	7812	5-7-5	627
598982	2562	2578	Exon 18	ACCCCTTATAGAAAACC	10	7797	7813	3-10-4	628
599045	2562	2578	Exon 18	ACCCCTTATAGAAAACC	3	7797	7813	5-7-5	628
598983	2563	2579	Exon 18	AACCCCTTATAGAAAAC	0	7798	7814	3-10-4	629
599046	2563	2579	Exon 18	AACCCCTTATAGAAAAC	18	7798	7814	5-7-5	629
598984	2564	2580	Exon 18	AAACCCCTTATAGAAAA	0	7799	7815	3-10-4	630
599047	2564	2580	Exon 18	AAACCCCTTATAGAAAA	7	7799	7815	5-7-5	630
598985	2565	2581	Exon 18	GAAACCCCTTATAGAAA	0	7800	7816	3-10-4	631
599048	2565	2581	Exon 18	GAAACCCCTTATAGAAA	9	7800	7816	5-7-5	631
598986	2566	2582	Exon 18	GGAAACCCCTTATAGAA	0	7801	7817	3-10-4	632
599049	2566	2582	Exon 18	GGAAACCCCTTATAGAA	18	7801	7817	5-7-5	632
598988	2567	2583	Exon 18	AGGAAACCCCTTATAGA	0	7802	7818	3-10-4	633
599050	2567	2583	Exon 18	AGGAAACCCCTTATAGA	8	7802	7818	5-7-5	633
598989	2568	2584	Exon 18	CAGGAAACCCCTTATAG	0	7803	7819	3-10-4	634
598990	2569	2585	Exon 18	GCAGGAAACCCCTTATA	8	7804	7820	3-10-4	635
598991	2570	2586	Exon 18	AGCAGGAAACCCCTTAT	25	7805	7821	3-10-4	636
598992	2571	2587	Exon 18	CAGCAGGAAACCCCTTA	12	7806	7822	3-10-4	637
598993	2572	2588	Exon 18	CCAGCAGGAAACCCCTT	37	7807	7823	3-10-4	638
598994	2573	2589	Exon 18	TCCAGCAGGAAACCCCT	29	7808	7824	3-10-4	639
598995	2574	2590	Exon 18	GTCCAGCAGGAAACCCC	42	7809	7825	3-10-4	640
598996	2575	2591	Exon 18	TGTCCAGCAGGAAACCC	36	7810	7826	3-10-4	641
598997	2576	2592	Exon 18	CTGTCCAGCAGGAAACC	18	7811	7827	3-10-4	642
598998	2577	2593	Exon 18	CCTGTCCAGCAGGAAAC	27	7812	7828	3-10-4	643
598999	2578	2594	Exon 18	CCCTGTCCAGCAGGAAA	61	7813	7829	3-10-4	644
599000	2580	2596	Exon 18	GCCCCTGTCCAGCAGGA	71	7815	7831	3-10-4	645
599001	2581	2597	Exon 18	CGCCCCTGTCCAGCAGG	80	7816	7832	3-10-4	646
599002	2582	2598	Exon 18	ACGCCCCTGTCCAGCAG	68	7817	7833	3-10-4	647
599003	2583	2599	Exon 18	CACGCCCCTGTCCAGCA	71	7818	7834	3-10-4	648
599004	2584	2600	Exon 18	CCACGCCCCTGTCCAGC	76	7819	7835	3-10-4	649
599005	2585	2601	Exon 18	CCCACGCCCCTGTCCAG	70	7820	7836	3-10-4	650
599006	2586	2602	Exon 18	TCCCACGCCCCTGTCCA	65	7821	7837	3-10-4	651
599007	2587	2603	Exon 18	ATCCCACGCCCCTGTCC	60	7822	7838	3-10-4	652
599008	2588	2604	Exon 18	AATCCCACGCCCCTGTC	72	7823	7839	3-10-4	653
599009	2589	2605	Exon 18	CAATCCCACGCCCCTGT	79	7824	7840	3-10-4	654
599010	2590	2606	Exon 18	TCAATCCCACGCCCCTG	73	7825	7841	3-10-4	655
599011	2591	2607	Exon 18	TTCAATCCCACGCCCCT	79	7826	7842	3-10-4	656
599012	2592	2608	Exon 18	ATTCAATCCCACGCCCC	67	7827	7843	3-10-4	657
599013	2593	2609	Exon 18	AATTCAATCCCACGCCC	65	7828	7844	3-10-4	658
599014	2594	2610	Exon 18	TAATTCAATCCCACGCC	74	7829	7845	3-10-4	659

599015	2595	2611	Exon 18	TTAATTCAATCCCACGC	71	7830	7846	3-10-4	660
599016	2596	2612	Exon 18	TTTAATTCAATCCCACG	48	7831	7847	3-10-4	661
599017	2597	2613	Exon 18	TTTTAATTCAATCCCAC	34	7832	7848	3-10-4	662
599018	2598	2614	Exon 18	GTTTTAATTCAATCCCA	56	7833	7849	3-10-4	663
599019	2599	2615	Exon 18	TGTTTTAATTCAATCCC	60	7834	7850	3-10-4	664
599020	2600	2616	Exon 18	CTGTTTTAATTCAATCC	0	7835	7851	3-10-4	665
599021	2601	2617	Exon 18	GCTGTTTTAATTCAATC	33	7836	7852	3-10-4	666
599022	2602	2618	Exon 18	AGCTGTTTTAATTCAAT	17	7837	7853	3-10-4	667
599023	2603	2619	Exon 18	CAGCTGTTTTAATTCAA	52	7838	7854	3-10-4	668
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	86	7839	7858	5-10-5	317
599024	2604	2620	Exon 18	GCAGCTGTTTTAATTCA	88	7839	7855	3-10-4	669
599025	2605	2621	Exon 18	CGCAGCTGTTTTAATTC	85	7840	7856	3-10-4	670
599026	2606	2622	Exon 18	TCGCAGCTGTTTTAATT	69	7841	7857	3-10-4	671
599027	2607	2623	Exon 18	GTCGCAGCTGTTTTAAT	77	7842	7858	3-10-4	672
599028	2608	2624	Exon 18	TGTCGCAGCTGTTTTAA	73	7843	7859	3-10-4	673
599029	2609	2625	Exon 18	TTGTCGCAGCTGTTTTA	78	7844	7860	3-10-4	674
599030	2610	2626	Exon 18	GTTGTCGCAGCTGTTTT	75	7845	7861	3-10-4	675
599031	2611	2627	Exon 18	TGTTGTCGCAGCTGTTT	77	7846	7862	3-10-4	676
599032	2612	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTT	79	n/a	n/a	3-10-4	677
599033	2613	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGT	80	n/a	n/a	3-10-4	678
599034	2614	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTG	78	n/a	n/a	3-10-4	679
599035	2615	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCT	63	n/a	n/a	3-10-4	680

Table 12

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599098	2552	2568	Exon 18	GAAAACCCAAATCCTCA	57	7787	7803	4-8-5	619
599099	2553	2569	Exon 18	AGAAAACCCAAATCCTC	33	7788	7804	4-8-5	620
599100	2554	2570	Exon 18	TAGAAAACCCAAATCCT	32	7789	7805	4-8-5	621
599101	2555	2571	Exon 18	ATAGAAAACCCAAATCC	47	7790	7806	4-8-5	622
599102	2557	2573	Exon 18	TTATAGAAAACCCAAAT	59	7792	7808	4-8-5	623
599103	2558	2574	Exon 18	CTTATAGAAAACCCAAA	10	7793	7809	4-8-5	624
599104	2559	2575	Exon 18	CCTTATAGAAAACCCAA	3	7794	7810	4-8-5	625
599105	2560	2576	Exon 18	CCCTTATAGAAAACCCA	45	7795	7811	4-8-5	626
599106	2561	2577	Exon 18	CCCCTTATAGAAAACCC	49	7796	7812	4-8-5	627
599107	2562	2578	Exon 18	ACCCCTTATAGAAAACC	35	7797	7813	4-8-5	628

599108	2563	2579	Exon 18	AACCCCTTATAGAAAAC	17	7798	7814	4-8-5	629
599109	2564	2580	Exon 18	AAACCCCTTATAGAAAA	36	7799	7815	4-8-5	630
599110	2565	2581	Exon 18	GAAACCCCTTATAGAAA	20	7800	7816	4-8-5	631
599111	2566	2582	Exon 18	GGAAACCCCTTATAGAA	20	7801	7817	4-8-5	632
599112	2567	2583	Exon 18	AGGAAACCCCTTATAGA	15	7802	7818	4-8-5	633
599113	2568	2584	Exon 18	CAGGAAACCCCTTATAG	19	7803	7819	4-8-5	634
599051	2568	2584	Exon 18	CAGGAAACCCCTTATAG	26	7803	7819	5-7-5	634
599114	2569	2585	Exon 18	GCAGGAAACCCCTTATA	18	7804	7820	4-8-5	635
599052	2569	2585	Exon 18	GCAGGAAACCCCTTATA	21	7804	7820	5-7-5	635
599115	2570	2586	Exon 18	AGCAGGAAACCCCTTAT	31	7805	7821	4-8-5	636
599053	2570	2586	Exon 18	AGCAGGAAACCCCTTAT	25	7805	7821	5-7-5	636
599116	2571	2587	Exon 18	CAGCAGGAAACCCCTTA	39	7806	7822	4-8-5	637
599054	2571	2587	Exon 18	CAGCAGGAAACCCCTTA	36	7806	7822	5-7-5	637
599117	2572	2588	Exon 18	CCAGCAGGAAACCCCTT	46	7807	7823	4-8-5	638
599055	2572	2588	Exon 18	CCAGCAGGAAACCCCTT	22	7807	7823	5-7-5	638
599118	2573	2589	Exon 18	TCCAGCAGGAAACCCCT	40	7808	7824	4-8-5	639
599056	2573	2589	Exon 18	TCCAGCAGGAAACCCCT	32	7808	7824	5-7-5	639
599119	2574	2590	Exon 18	GTCCAGCAGGAAACCCC	50	7809	7825	4-8-5	640
599057	2574	2590	Exon 18	GTCCAGCAGGAAACCCC	46	7809	7825	5-7-5	640
599120	2575	2591	Exon 18	TGTCCAGCAGGAAACCC	30	7810	7826	4-8-5	641
599058	2575	2591	Exon 18	TGTCCAGCAGGAAACCC	52	7810	7826	5-7-5	641
599121	2576	2592	Exon 18	CTGTCCAGCAGGAAACC	31	7811	7827	4-8-5	642
599059	2576	2592	Exon 18	CTGTCCAGCAGGAAACC	24	7811	7827	5-7-5	642
599122	2577	2593	Exon 18	CCTGTCCAGCAGGAAAC	23	7812	7828	4-8-5	643
599060	2577	2593	Exon 18	CCTGTCCAGCAGGAAAC	37	7812	7828	5-7-5	643
599123	2578	2594	Exon 18	CCCTGTCCAGCAGGAAA	51	7813	7829	4-8-5	644
599061	2578	2594	Exon 18	CCCTGTCCAGCAGGAAA	34	7813	7829	5-7-5	644
599124	2580	2596	Exon 18	GCCCCTGTCCAGCAGGA	56	7815	7831	4-8-5	645
599062	2580	2596	Exon 18	GCCCCTGTCCAGCAGGA	51	7815	7831	5-7-5	645
599125	2581	2597	Exon 18	CGCCCCTGTCCAGCAGG	70	7816	7832	4-8-5	646
599063	2581	2597	Exon 18	CGCCCCTGTCCAGCAGG	56	7816	7832	5-7-5	646
599126	2582	2598	Exon 18	ACGCCCCTGTCCAGCAG	76	7817	7833	4-8-5	647
599064	2582	2598	Exon 18	ACGCCCCTGTCCAGCAG	61	7817	7833	5-7-5	647
599127	2583	2599	Exon 18	CACGCCCCTGTCCAGCA	67	7818	7834	4-8-5	648
599065	2583	2599	Exon 18	CACGCCCCTGTCCAGCA	64	7818	7834	5-7-5	648
599066	2584	2600	Exon 18	CCACGCCCCTGTCCAGC	40	7819	7835	5-7-5	649
599067	2585	2601	Exon 18	CCCACGCCCCTGTCCAG	37	7820	7836	5-7-5	650
599068	2586	2602	Exon 18	TCCCACGCCCCTGTCCA	31	7821	7837	5-7-5	651
599069	2587	2603	Exon 18	ATCCCACGCCCCTGTCC	39	7822	7838	5-7-5	652
599070	2588	2604	Exon 18	AATCCCACGCCCCTGTC	59	7823	7839	5-7-5	653
599071	2589	2605	Exon 18	CAATCCCACGCCCCTGT	63	7824	7840	5-7-5	657
599072	2590	2606	Exon 18	TCAATCCCACGCCCCTG	74	7825	7841	5-7-5	655
599073	2591	2607	Exon 18	TTCAATCCCACGCCCCT	53	7826	7842	5-7-5	656
599074	2592	2608	Exon 18	ATTCAATCCCACGCCCC	56	7827	7843	5-7-5	657
599075	2593	2609	Exon 18	AATTCAATCCCACGCCC	49	7828	7844	5-7-5	658

599076	2594	2610	Exon 18	TAATTCAATCCCACGCC	54	7829	7845	5-7-5	659
599077	2595	2611	Exon 18	TTAATTCAATCCCACGC	79	7830	7846	5-7-5	660
599078	2596	2612	Exon 18	TTTAATTCAATCCCACG	67	7831	7847	5-7-5	661
599079	2597	2613	Exon 18	TTTTAATTCAATCCCAC	69	7832	7848	5-7-5	662
599080	2598	2614	Exon 18	GTTTTAATTCAATCCCA	79	7833	7849	5-7-5	663
599081	2599	2615	Exon 18	TGTTTTAATTCAATCCC	57	7834	7850	5-7-5	664
599082	2600	2616	Exon 18	CTGTTTTAATTCAATCC	50	7835	7851	5-7-5	665
599083	2601	2617	Exon 18	GCTGTTTTAATTCAATC	67	7836	7852	5-7-5	666
599084	2602	2618	Exon 18	AGCTGTTTTAATTCAAT	60	7837	7853	5-7-5	667
599085	2603	2619	Exon 18	CAGCTGTTTTAATTCAA	71	7838	7854	5-7-5	668
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	82	7839	7858	5-10-5	317
599086	2604	2620	Exon 18	GCAGCTGTTTTAATTCA	81	7839	7855	5-7-5	669
599087	2605	2621	Exon 18	CGCAGCTGTTTTAATTC	88	7840	7856	5-7-5	670
599088	2606	2622	Exon 18	TCGCAGCTGTTTTAATT	84	7841	7857	5-7-5	671
599089	2607	2623	Exon 18	GTCGCAGCTGTTTTAAT	81	7842	7858	5-7-5	672
599090	2608	2624	Exon 18	TGTCGCAGCTGTTTTAA	77	7843	7859	5-7-5	673
599091	2609	2625	Exon 18	TTGTCGCAGCTGTTTTA	74	7844	7860	5-7-5	674
599092	2610	2626	Exon 18	GTTGTCGCAGCTGTTTT	66	7845	7861	5-7-5	675
599093	2611	2627	Exon 18	TGTTGTCGCAGCTGTTT	89	7846	7862	5-7-5	676
599094	2612	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTT	82	n/a	n/a	5-7-5	677
599095	2613	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGT	87	n/a	n/a	5-7-5	678
599096	2614	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTG	85	n/a	n/a	5-7-5	679
599097	2615	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCT	78	n/a	n/a	5-7-5	680

Table 13

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599510	2552	2570	Exon 18	TAGAAAACCCAAATCCTCA	45	7787	7805	5-9-5	681
599331	2553	2571	Exon 18	ATAGAAAACCCAAATCCTC	46	7788	7806	5-9-5	682
599332	2554	2572	Exon 18	TATAGAAAACCCAAATCCT	38	7789	7807	5-9-5	683
599333	2556	2574	Exon 18	CTTATAGAAAACCCAAATC	1	7791	7809	5-9-5	684
599334	2557	2575	Exon 18	CCTTATAGAAAACCCAAAT	5	7792	7810	5-9-5	685
599335	2558	2576	Exon 18	CCCTTATAGAAAACCCAAA	34	7793	7811	5-9-5	686
599336	2559	2577	Exon 18	CCCCTTATAGAAAACCCAA	40	7794	7812	5-9-5	687
599337	2560	2578	Exon 18	ACCCCTTATAGAAAACCCA	39	7795	7813	5-9-5	688
599338	2561	2579	Exon 18	AACCCCTTATAGAAAACCC	57	7796	7814	5-9-5	689
599339	2562	2580	Exon 18	AAACCCCTTATAGAAAACC	26	7797	7815	5-9-5	690
599281	2562	2580	Exon 18	AAACCCCTTATAGAAAACC	15	7797	7815	6-7-6	690

599340	2563	2581	Exon 18	GAAACCCCTTATAGAAAAC	17	7798	7816	5-9-5	691
599282	2563	2581	Exon 18	GAAACCCCTTATAGAAAAC	12	7798	7816	6-7-6	691
599341	2564	2582	Exon 18	GGAAACCCCTTATAGAAAA	23	7799	7817	5-9-5	692
599283	2564	2582	Exon 18	GGAAACCCCTTATAGAAAA	18	7799	7817	6-7-6	692
599342	2565	2583	Exon 18	AGGAAACCCCTTATAGAAA	10	7800	7818	5-9-5	693
599284	2565	2583	Exon 18	AGGAAACCCCTTATAGAAA	14	7800	7818	6-7-6	693
599343	2566	2584	Exon 18	CAGGAAACCCCTTATAGAA	10	7801	7819	5-9-5	694
599285	2566	2584	Exon 18	CAGGAAACCCCTTATAGAA	13	7801	7819	6-7-6	694
599344	2567	2585	Exon 18	GCAGGAAACCCCTTATAGA	22	7802	7820	5-9-5	695
599286	2567	2585	Exon 18	GCAGGAAACCCCTTATAGA	31	7802	7820	6-7-6	695
599345	2568	2586	Exon 18	AGCAGGAAACCCCTTATAG	19	7803	7821	5-9-5	696
599287	2568	2586	Exon 18	AGCAGGAAACCCCTTATAG	12	7803	7821	6-7-6	696
599346	2569	2587	Exon 18	CAGCAGGAAACCCCTTATA	30	7804	7822	5-9-5	697
599288	2569	2587	Exon 18	CAGCAGGAAACCCCTTATA	28	7804	7822	6-7-6	697
599347	2570	2588	Exon 18	CCAGCAGGAAACCCCTTAT	46	7805	7823	5-9-5	698
599289	2570	2588	Exon 18	CCAGCAGGAAACCCCTTAT	32	7805	7823	6-7-6	698
599348	2571	2589	Exon 18	TCCAGCAGGAAACCCCTTA	44	7806	7824	5-9-5	699
599290	2571	2589	Exon 18	TCCAGCAGGAAACCCCTTA	24	7806	7824	6-7-6	699
599349	2572	2590	Exon 18	GTCCAGCAGGAAACCCCTT	60	7807	7825	5-9-5	700
599291	2572	2590	Exon 18	GTCCAGCAGGAAACCCCTT	38	7807	7825	6-7-6	700
599350	2573	2591	Exon 18	TGTCCAGCAGGAAACCCCT	49	7808	7826	5-9-5	701
599292	2573	2591	Exon 18	TGTCCAGCAGGAAACCCCT	35	7808	7826	6-7-6	701
599351	2575	2593	Exon 18	CCTGTCCAGCAGGAAACCC	46	7810	7828	5-9-5	702
599293	2575	2593	Exon 18	CCTGTCCAGCAGGAAACCC	12	7810	7828	6-7-6	702
599352	2576	2594	Exon 18	CCCTGTCCAGCAGGAAACC	49	7811	7829	5-9-5	703
599294	2576	2594	Exon 18	CCCTGTCCAGCAGGAAACC	38	7811	7829	6-7-6	703
599353	2577	2595	Exon 18	CCCCTGTCCAGCAGGAAAC	64	7812	7830	5-9-5	704
599295	2577	2595	Exon 18	CCCCTGTCCAGCAGGAAAC	33	7812	7830	6-7-6	704
599354	2578	2596	Exon 18	GCCCCTGTCCAGCAGGAAA	56	7813	7831	5-9-5	705
599296	2578	2596	Exon 18	GCCCCTGTCCAGCAGGAAA	13	7813	7831	6-7-6	705
599355	2580	2598	Exon 18	ACGCCCCTGTCCAGCAGGA	81	7815	7833	5-9-5	706
599297	2580	2598	Exon 18	ACGCCCCTGTCCAGCAGGA	57	7815	7833	6-7-6	706
599356	2581	2599	Exon 18	CACGCCCCTGTCCAGCAGG	64	7816	7834	5-9-5	707
599298	2581	2599	Exon 18	CACGCCCCTGTCCAGCAGG	39	7816	7834	6-7-6	707
599299	2582	2600	Exon 18	CCACGCCCCTGTCCAGCAG	55	7817	7835	6-7-6	708
599300	2583	2601	Exon 18	CCCACGCCCCTGTCCAGCA	45	7818	7836	6-7-6	709
599301	2584	2602	Exon 18	TCCCACGCCCCTGTCCAGC	39	7819	7837	6-7-6	710
599302	2585	2603	Exon 18	ATCCCACGCCCCTGTCCAG	27	7820	7838	6-7-6	711
599303	2586	2604	Exon 18	AATCCCACGCCCCTGTCCA	35	7821	7839	6-7-6	712
599304	2587	2605	Exon 18	CAATCCCACGCCCCTGTCC	16	7822	7840	6-7-6	713
599305	2588	2606	Exon 18	TCAATCCCACGCCCCTGTC	41	7823	7841	6-7-6	714
599306	2589	2607	Exon 18	TTCAATCCCACGCCCCTGT	70	7824	7842	6-7-6	715
599307	2590	2608	Exon 18	ATTCAATCCCACGCCCCTG	66	7825	7843	6-7-6	716

599308	2591	2609	Exon 18	AATTCAATCCCACGCCCCT	68	7826	7844	6-7-6	717
599309	2592	2610	Exon 18	TAATTCAATCCCACGCCCC	52	7827	7845	6-7-6	718
599310	2593	2611	Exon 18	TTAATTCAATCCCACGCCC	39	7828	7846	6-7-6	719
599311	2594	2612	Exon 18	TTTAATTCAATCCCACGCC	83	7829	7847	6-7-6	720
599312	2595	2613	Exon 18	TTTTAATTCAATCCCACGC	72	7830	7848	6-7-6	721
599313	2596	2614	Exon 18	GTTTTAATTCAATCCCACG	86	7831	7849	6-7-6	722
599314	2597	2615	Exon 18	TGTTTTAATTCAATCCCAC	91	7832	7850	6-7-6	723
599315	2598	2616	Exon 18	CTGTTTTAATTCAATCCCA	71	7833	7851	6-7-6	724
599316	2599	2617	Exon 18	GCTGTTTTAATTCAATCCC	89	7834	7852	6-7-6	725
599317	2600	2618	Exon 18	AGCTGTTTTAATTCAATCC	87	7835	7853	6-7-6	726
599318	2601	2619	Exon 18	CAGCTGTTTTAATTCAATC	81	7836	7854	6-7-6	727
599319	2602	2620	Exon 18	GCAGCTGTTTTAATTCAAT	75	7837	7855	6-7-6	728
599320	2603	2621	Exon 18	CGCAGCTGTTTTAATTCAA	84	7838	7856	6-7-6	729
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	92	7839	7858	5-10-5	317
599321	2604	2622	Exon 18	TCGCAGCTGTTTTAATTCA	90	7839	7857	6-7-6	730
599322	2605	2623	Exon 18	GTCGCAGCTGTTTTAATTC	89	7840	7858	6-7-6	731
599323	2606	2624	Exon 18	TGTCGCAGCTGTTTTAATT	81	7841	7859	6-7-6	732
599324	2607	2625	Exon 18	TTGTCGCAGCTGTTTTAAT	68	7842	7860	6-7-6	733
599325	2608	2626	Exon 18	GTTGTCGCAGCTGTTTTAA	71	7843	7861	6-7-6	734
599326	2609	2627	Exon 18	TGTTGTCGCAGCTGTTTTA	52	7844	7862	6-7-6	735
599327	2610	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTTT	88	n/a	n/a	6-7-6	736
599328	2611	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTTT	87	n/a	n/a	6-7-6	737
599329	2612	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGTT	84	n/a	n/a	6-7-6	738
599330	2613	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTGT	87	n/a	n/a	6-7-6	739

Table 14

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599512	2552	2571	Exon 18	ATAGAAAACCCAAATCCTCA	74	7787	7806	3-10-7	410
599449	2553	2572	Exon 18	TATAGAAAACCCAAATCCTC	43	7788	7807	3-10-7	411
599450	2554	2573	Exon 18	TTATAGAAAACCCAAATCCT	51	7789	7808	3-10-7	412
599451	2555	2574	Exon 18	CTTATAGAAAACCCAAATCC	35	7790	7809	3-10-7	413
599452	2556	2575	Exon 18	CCTTATAGAAAACCCAAATC	34	7791	7810	3-10-7	414
599453	2557	2576	Exon 18	CCCTTATAGAAAACCCAAAT	44	7792	7811	3-10-7	415
599454	2558	2577	Exon 18	CCCCTTATAGAAAACCCAAA	54	7793	7812	3-10-7	416
599455	2559	2578	Exon 18	ACCCCTTATAGAAAACCCAA	53	7794	7813	3-10-7	417

599456	2560	2579	Exon 18	AACCCCTTATAGAAAACCCA	69	7795	7814	3-10-7	418
599457	2561	2580	Exon 18	AAACCCCTTATAGAAAACCC	46	7796	7815	3-10-7	419
599458	2562	2581	Exon 18	GAAACCCCTTATAGAAAACC	0	7797	7816	3-10-7	420
599459	2563	2582	Exon 18	GGAAACCCCTTATAGAAAAC	12	7798	7817	3-10-7	421
599460	2564	2583	Exon 18	AGGAAACCCCTTATAGAAAA	17	7799	7818	3-10-7	422
599461	2565	2584	Exon 18	CAGGAAACCCCTTATAGAAA	24	7800	7819	3-10-7	423
599462	2566	2585	Exon 18	GCAGGAAACCCCTTATAGAA	33	7801	7820	3-10-7	424
599463	2567	2586	Exon 18	AGCAGGAAACCCCTTATAGA	38	7802	7821	3-10-7	425
599464	2568	2587	Exon 18	CAGCAGGAAACCCCTTATAG	33	7803	7822	3-10-7	426
599465	2569	2588	Exon 18	CCAGCAGGAAACCCCTTATA	49	7804	7823	3-10-7	427
599466	2570	2589	Exon 18	TCCAGCAGGAAACCCCTTAT	45	7805	7824	3-10-7	428
599467	2571	2590	Exon 18	GTCCAGCAGGAAACCCCTTA	60	7806	7825	3-10-7	237
599468	2572	2591	Exon 18	TGTCCAGCAGGAAACCCCTT	61	7807	7826	3-10-7	429
599469	2573	2592	Exon 18	CTGTCCAGCAGGAAACCCCT	52	7808	7827	3-10-7	430
599470	2574	2593	Exon 18	CCTGTCCAGCAGGAAACCCC	45	7809	7828	3-10-7	431
599471	2575	2594	Exon 18	CCCTGTCCAGCAGGAAACCC	67	7810	7829	3-10-7	432
599472	2576	2595	Exon 18	CCCCTGTCCAGCAGGAAACC	79	7811	7830	3-10-7	433
599473	2577	2596	Exon 18	GCCCCTGTCCAGCAGGAAAC	72	7812	7831	3-10-7	238
599474	2578	2597	Exon 18	CGCCCCTGTCCAGCAGGAAA	87	7813	7832	3-10-7	434
599475	2579	2598	Exon 18	ACGCCCCTGTCCAGCAGGAA	76	7814	7833	3-10-7	435
599476	2580	2599	Exon 18	CACGCCCCTGTCCAGCAGGA	81	7815	7834	3-10-7	436
599477	2581	2600	Exon 18	CCACGCCCCTGTCCAGCAGG	83	7816	7835	3-10-7	437
599478	2582	2601	Exon 18	CCCACGCCCCTGTCCAGCAG	72	7817	7836	3-10-7	438
599479	2583	2602	Exon 18	TCCCACGCCCCTGTCCAGCA	81	7818	7837	3-10-7	439
599480	2584	2603	Exon 18	ATCCCACGCCCCTGTCCAGC	77	7819	7838	3-10-7	440
599481	2585	2604	Exon 18	AATCCCACGCCCCTGTCCAG	83	7820	7839	3-10-7	441
599482	2586	2605	Exon 18	CAATCCCACGCCCCTGTCCA	87	7821	7840	3-10-7	442
599483	2587	2606	Exon 18	TCAATCCCACGCCCCTGTCC	90	7822	7841	3-10-7	443
599484	2588	2607	Exon 18	TTCAATCCCACGCCCCTGTC	72	7823	7842	3-10-7	444
599485	2589	2608	Exon 18	ATTCAATCCCACGCCCCTGT	82	7824	7843	3-10-7	445
599486	2590	2609	Exon 18	AATTCAATCCCACGCCCCTG	84	7825	7844	3-10-7	446
599487	2591	2610	Exon 18	TAATTCAATCCCACGCCCCT	84	7826	7845	3-10-7	447
599488	2592	2611	Exon 18	TTAATTCAATCCCACGCCCC	87	7827	7846	3-10-7	448
599489	2593	2612	Exon 18	TTTAATTCAATCCCACGCCC	87	7828	7847	3-10-7	449
599490	2594	2613	Exon 18	TTTTAATTCAATCCCACGCC	86	7829	7848	3-10-7	450
599491	2595	2614	Exon 18	GTTTTAATTCAATCCCACGC	87	7830	7849	3-10-7	451
599492	2596	2615	Exon 18	TGTTTTAATTCAATCCCACG	88	7831	7850	3-10-7	452
599493	2597	2616	Exon 18	CTGTTTTAATTCAATCCCAC	75	7832	7851	3-10-7	453
599433	2597	2616	Exon 18	CTGTTTTAATTCAATCCCAC	89	7832	7851	6-8-6	453
599494	2598	2617	Exon 18	GCTGTTTTAATTCAATCCCA	90	7833	7852	3-10-7	454
599434	2598	2617	Exon 18	GCTGTTTTAATTCAATCCCA	89	7833	7852	6-8-6	454
599495	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	88	7834	7853	3-10-7	239
599435	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	91	7834	7853	6-8-6	239

599496	2600	2619	Exon 18	CAGCTGTTTTAATTCAATCC	89	7835	7854	3-10-7	455
599436	2600	2619	Exon 18	CAGCTGTTTTAATTCAATCC	89	7835	7854	6-8-6	455
599497	2601	2620	Exon 18	GCAGCTGTTTTAATTCAATC	89	7836	7855	3-10-7	456
599437	2601	2620	Exon 18	GCAGCTGTTTTAATTCAATC	91	7836	7855	6-8-6	456
599498	2602	2621	Exon 18	CGCAGCTGTTTTAATTCAAT	88	7837	7856	3-10-7	457
599438	2602	2621	Exon 18	CGCAGCTGTTTTAATTCAAT	90	7837	7856	6-8-6	457
599499	2603	2622	Exon 18	TCGCAGCTGTTTTAATTCAA	81	7838	7857	3-10-7	458
599439	2603	2622	Exon 18	TCGCAGCTGTTTTAATTCAA	88	7838	7857	6-8-6	458
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	90	7839	7858	5-10-5	317
599500	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	88	7839	7858	3-10-7	317
599440	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	88	7839	7858	6-8-6	317
599501	2605	2624	Exon 18	TGTCGCAGCTGTTTTAATTC	78	7840	7859	3-10-7	459
599441	2605	2624	Exon 18	TGTCGCAGCTGTTTTAATTC	90	7840	7859	6-8-6	459
599502	2606	2625	Exon 18	TTGTCGCAGCTGTTTTAATT	87	7841	7860	3-10-7	460
599442	2606	2625	Exon 18	TTGTCGCAGCTGTTTTAATT	76	7841	7860	6-8-6	460
599503	2607	2626	Exon 18	GTTGTCGCAGCTGTTTTAAT	83	7842	7861	3-10-7	461
599443	2607	2626	Exon 18	GTTGTCGCAGCTGTTTTAAT	77	7842	7861	6-8-6	461
599504	2608	2627	Exon 18	TGTTGTCGCAGCTGTTTTAA	89	7843	7862	3-10-7	395
599444	2608	2627	Exon 18	TGTTGTCGCAGCTGTTTTAA	69	7843	7862	6-8-6	395
599505	2609	2628	Exon 19 / Repeat	TTGTTGTCGCAGCTGTTTTA	83	n/a	n/a	3-10-7	462
599445	2609	2628	Exon 19 / Repeat	TTGTTGTCGCAGCTGTTTTA	85	n/a	n/a	6-8-6	462
599506	2610	2629	Exon 19 / Repeat	TTTGTTGTCGCAGCTGTTTT	89	n/a	n/a	3-10-7	463
599446	2610	2629	Exon 19 / Repeat	TTTGTTGTCGCAGCTGTTTT	85	n/a	n/a	6-8-6	463
599507	2611	2630	Exon 19 / Repeat	TTTTGTTGTCGCAGCTGTTT	82	n/a	n/a	3-10-7	464
599447	2611	2630	Exon 19 / Repeat	TTTTGTTGTCGCAGCTGTTT	83	n/a	n/a	6-8-6	464
599508	2612	2631	Exon 19 / Repeat	TTTTTGTTGTCGCAGCTGTT	90	n/a	n/a	3-10-7	465
599448	2612	2631	Exon 19 / Repeat	TTTTTGTTGTCGCAGCTGTT	87	n/a	n/a	6-8-6	465

Example 5: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells by MOE gapmers

Additional antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 2,000 nM antisense oligonucleotide. After a treatment period of

approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 4-8-5 MOE, 5-8-5 MOE, 5-9-5 MOE, 5-10-5 MOE, 6-7-6- MOE, 3-10-5 MOE, or 6-8-6 MOE gapmers.

The 4-8-5 MOE gapmers are 17 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising four and five nucleosides respectively. The 5-8-5 MOE gapmers are 18 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 5-9-5 MOE gapmers are 19 nucleosides in length, wherein the central gap segment comprises of nine 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 3-10-5 MOE gapmers are 18 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising three and five nucleosides respectively. The 6-7-6 MOE gapmers are 19 nucleosides in length, wherein the central gap segment comprises of seven 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising six nucleosides each. The 6-8-6 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising six nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity.

Table 15

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599160	2560	2577	Exon 18	CCCCTTATAGAAAACCCA	26	7795	7812	5-8-5	740
599161	2561	2578	Exon 18	ACCCCTTATAGAAAACCC	20	7796	7813	5-8-5	741
599162	2562	2579	Exon 18	AACCCCTTATAGAAAACC	12	7797	7814	5-8-5	742
599163	2563	2580	Exon 18	AAACCCCTTATAGAAAAC	11	7798	7815	5-8-5	743
599164	2564	2581	Exon 18	GAAACCCCTTATAGAAAA	11	7799	7816	5-8-5	744
599165	2566	2583	Exon 18	AGGAAACCCCTTATAGAA	0	7801	7818	5-8-5	745
599166	2567	2584	Exon 18	CAGGAAACCCCTTATAGA	12	7802	7819	5-8-5	746
599167	2568	2585	Exon 18	GCAGGAAACCCCTTATAG	14	7803	7820	5-8-5	747
599168	2569	2586	Exon 18	AGCAGGAAACCCCTTATA	16	7804	7821	5-8-5	748
599169	2570	2587	Exon 18	CAGCAGGAAACCCCTTAT	24	7805	7822	5-8-5	749
599170	2571	2588	Exon 18	CCAGCAGGAAACCCCTTA	37	7806	7823	5-8-5	750
599171	2572	2589	Exon 18	TCCAGCAGGAAACCCCTT	30	7807	7824	5-8-5	751
599172	2573	2590	Exon 18	GTCCAGCAGGAAACCCCT	43	7808	7825	5-8-5	752
599173	2574	2591	Exon 18	TGTCCAGCAGGAAACCCC	47	7809	7826	5-8-5	753
599174	2575	2592	Exon 18	CTGTCCAGCAGGAAACCC	27	7810	7827	5-8-5	754
599175	2576	2593	Exon 18	CCTGTCCAGCAGGAAACC	30	7811	7828	5-8-5	755
599176	2577	2594	Exon 18	CCCTGTCCAGCAGGAAAC	34	7812	7829	5-8-5	756
599177	2578	2595	Exon 18	CCCCTGTCCAGCAGGAAA	41	7813	7830	5-8-5	757
599178	2580	2597	Exon 18	CGCCCCTGTCCAGCAGGA	67	7815	7832	5-8-5	758
599179	2581	2598	Exon 18	ACGCCCCTGTCCAGCAGG	61	7816	7833	5-8-5	759
599180	2582	2599	Exon 18	CACGCCCCTGTCCAGCAG	62	7817	7834	5-8-5	760
599181	2583	2600	Exon 18	CCACGCCCCTGTCCAGCA	63	7818	7835	5-8-5	761
599128	2584	2600	Exon 18	CCACGCCCCTGTCCAGC	55	7819	7835	4-8-5	649
599182	2584	2601	Exon 18	CCCACGCCCCTGTCCAGC	58	7819	7836	5-8-5	762
599129	2585	2601	Exon 18	CCCACGCCCCTGTCCAG	41	7820	7836	4-8-5	650
599183	2585	2602	Exon 18	TCCCACGCCCCTGTCCAG	43	7820	7837	5-8-5	763
599130	2586	2602	Exon 18	TCCCACGCCCCTGTCCA	46	7821	7837	4-8-5	651
599184	2586	2603	Exon 18	ATCCCACGCCCCTGTCCA	32	7821	7838	5-8-5	764
599131	2587	2603	Exon 18	ATCCCACGCCCCTGTCC	30	7822	7838	4-8-5	652
599185	2587	2604	Exon 18	AATCCCACGCCCCTGTCC	35	7822	7839	5-8-5	765
599132	2588	2604	Exon 18	AATCCCACGCCCCTGTC	52	7823	7839	4-8-5	653
599186	2588	2605	Exon 18	CAATCCCACGCCCCTGTC	55	7823	7840	5-8-5	766
599133	2589	2605	Exon 18	CAATCCCACGCCCCTGT	66	7824	7840	4-8-5	654
599187	2589	2606	Exon 18	TCAATCCCACGCCCCTGT	72	7824	7841	5-8-5	767
599134	2590	2606	Exon 18	TCAATCCCACGCCCCTG	80	7825	7841	4-8-5	655
599188	2590	2607	Exon 18	TTCAATCCCACGCCCCTG	92	7825	7842	5-8-5	768

599135	2591	2607	Exon 18	TTCAATCCCACGCCCCT	61	7826	7842	4-8-5	656
599189	2591	2608	Exon 18	ATTCAATCCCACGCCCCT	52	7826	7843	5-8-5	769
599136	2592	2608	Exon 18	ATTCAATCCCACGCCCC	68	7827	7843	4-8-5	657
599190	2592	2609	Exon 18	AATTCAATCCCACGCCCC	62	7827	7844	5-8-5	770
599137	2593	2609	Exon 18	AATTCAATCCCACGCCC	51	7828	7844	4-8-5	658
599191	2593	2610	Exon 18	TAATTCAATCCCACGCCC	54	7828	7845	5-8-5	771
599138	2594	2610	Exon 18	TAATTCAATCCCACGCC	71	7829	7845	4-8-5	659
599192	2594	2611	Exon 18	TTAATTCAATCCCACGCC	66	7829	7846	5-8-5	772
599139	2595	2611	Exon 18	TTAATTCAATCCCACGC	80	7830	7846	4-8-5	660
599193	2595	2612	Exon 18	TTTAATTCAATCCCACGC	74	7830	7847	5-8-5	773
599140	2596	2612	Exon 18	TTTAATTCAATCCCACG	66	7831	7847	4-8-5	786
599194	2596	2613	Exon 18	TTTTAATTCAATCCCACG	66	7831	7848	5-8-5	774
599141	2597	2613	Exon 18	TTTTAATTCAATCCCAC	63	7832	7848	4-8-5	662
599195	2597	2614	Exon 18	GTTTTAATTCAATCCCAC	86	7832	7849	5-8-5	775
599142	2598	2614	Exon 18	GTTTTAATTCAATCCCA	69	7833	7849	4-8-5	663
599196	2598	2615	Exon 18	TGTTTTAATTCAATCCCA	82	7833	7850	5-8-5	776
599143	2599	2615	Exon 18	TGTTTTAATTCAATCCC	59	7834	7850	4-8-5	664
599197	2599	2616	Exon 18	CTGTTTTAATTCAATCCC	79	7834	7851	5-8-5	777
599144	2600	2616	Exon 18	CTGTTTTAATTCAATCC	52	7835	7851	4-8-5	665
599198	2600	2617	Exon 18	GCTGTTTTAATTCAATCC	86	7835	7852	5-8-5	778
599145	2601	2617	Exon 18	GCTGTTTTAATTCAATC	53	7836	7852	4-8-5	666
599199	2601	2618	Exon 18	AGCTGTTTTAATTCAATC	72	7836	7853	5-8-5	779
599146	2602	2618	Exon 18	AGCTGTTTTAATTCAAT	42	7837	7853	4-8-5	667
599200	2602	2619	Exon 18	CAGCTGTTTTAATTCAAT	76	7837	7854	5-8-5	780
599147	2603	2619	Exon 18	CAGCTGTTTTAATTCAA	55	7838	7854	4-8-5	668
599201	2603	2620	Exon 18	GCAGCTGTTTTAATTCAA	87	7838	7855	5-8-5	781
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	93	7839	7858	5-10-5	317
599148	2604	2620	Exon 18	GCAGCTGTTTTAATTCA	84	7839	7855	4-8-5	669
599202	2604	2621	Exon 18	CGCAGCTGTTTTAATTCA	89	7839	7856	5-8-5	782
599149	2605	2621	Exon 18	CGCAGCTGTTTTAATTC	92	7840	7856	4-8-5	670
599203	2605	2622	Exon 18	TCGCAGCTGTTTTAATTC	90	7840	7857	5-8-5	783
599150	2606	2622	Exon 18	TCGCAGCTGTTTTAATT	75	7841	7857	4-8-5	671
599151	2607	2623	Exon 18	GTCGCAGCTGTTTTAAT	80	7842	7858	4-8-5	672
599152	2608	2624	Exon 18	TGTCGCAGCTGTTTTAA	76	7843	7859	4-8-5	673
599153	2609	2625	Exon 18	TTGTCGCAGCTGTTTTA	56	7844	7860	4-8-5	674
599154	2610	2626	Exon 18	GTTGTCGCAGCTGTTTT	85	7845	7861	4-8-5	675
599155	2611	2627	Exon 18	TGTTGTCGCAGCTGTTT	89	7846	7862	4-8-5	676
599156	2612	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTT	83	n/a	n/a	4-8-5	813
599157	2613	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGT	78	n/a	n/a	4-8-5	678
599158	2614	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTG	83	n/a	n/a	4-8-5	679

599159	2615	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCT	65	n/a	n/a	4-8-5	680
599204	2606	2623	Exon 18	GTCGCAGCTGTTTTAATT	83	7841	7858	5-8-5	784

Table 16

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599509	2552	2570	Exon 18	TAGAAAACCCAAATCCTCA	45	7787	7805	6-7-6	681
599213	2553	2570	Exon 18	TAGAAAACCCAAATCCTC	89	7788	7805	3-10-5	785
599273	2553	2571	Exon 18	ATAGAAAACCCAAATCCTC	85	7788	7806	6-7-6	682
599214	2554	2571	Exon 18	ATAGAAAACCCAAATCCT	79	7789	7806	3-10-5	786
599274	2554	2572	Exon 18	TATAGAAAACCCAAATCCT	75	7789	7807	6-7-6	683
599215	2555	2572	Exon 18	TATAGAAAACCCAAATCC	81	7790	7807	3-10-5	787
599216	2556	2573	Exon 18	TTATAGAAAACCCAAATC	87	7791	7808	3-10-5	788
599275	2556	2574	Exon 18	CTTATAGAAAACCCAAATC	84	7791	7809	6-7-6	684
599217	2557	2574	Exon 18	CTTATAGAAAACCCAAAT	84	7792	7809	3-10-5	789
599276	2557	2575	Exon 18	CCTTATAGAAAACCCAAAT	68	7792	7810	6-7-6	685
599218	2558	2575	Exon 18	CCTTATAGAAAACCCAAA	82	7793	7810	3-10-5	790
599277	2558	2576	Exon 18	CCCTTATAGAAAACCCAAA	82	7793	7811	6-7-6	686
599219	2559	2576	Exon 18	CCCTTATAGAAAACCCAA	81	7794	7811	3-10-5	791
599278	2559	2577	Exon 18	CCCCTTATAGAAAACCCAA	84	7794	7812	6-7-6	687
599220	2560	2577	Exon 18	CCCCTTATAGAAAACCCA	92	7795	7812	3-10-5	740
599279	2560	2578	Exon 18	ACCCCTTATAGAAAACCCA	92	7795	7813	6-7-6	688
599221	2561	2578	Exon 18	ACCCCTTATAGAAAACCC	93	7796	7813	3-10-5	741
599280	2561	2579	Exon 18	AACCCCTTATAGAAAACCC	90	7796	7814	6-7-6	689
599222	2562	2579	Exon 18	AACCCCTTATAGAAAACC	95	7797	7814	3-10-5	742
599223	2563	2580	Exon 18	AAACCCCTTATAGAAAAC	93	7798	7815	3-10-5	743
599224	2564	2581	Exon 18	GAAACCCCTTATAGAAAA	90	7799	7816	3-10-5	744
599225	2566	2583	Exon 18	AGGAAACCCCTTATAGAA	93	7801	7818	3-10-5	745
599226	2567	2584	Exon 18	CAGGAAACCCCTTATAGA	95	7802	7819	3-10-5	746
599227	2568	2585	Exon 18	GCAGGAAACCCCTTATAG	94	7803	7820	3-10-5	747
599228	2569	2586	Exon 18	AGCAGGAAACCCCTTATA	96	7804	7821	3-10-5	748
599229	2570	2587	Exon 18	CAGCAGGAAACCCCTTAT	92	7805	7822	3-10-5	749
599230	2571	2588	Exon 18	CCAGCAGGAAACCCCTTA	88	7806	7823	3-10-5	750
599231	2572	2589	Exon 18	TCCAGCAGGAAACCCCTT	83	7807	7824	3-10-5	751
599232	2573	2590	Exon 18	GTCCAGCAGGAAACCCCT	89	7808	7825	3-10-5	752
599233	2574	2591	Exon 18	TGTCCAGCAGGAAACCCC	83	7809	7826	3-10-5	753
599234	2575	2592	Exon 18	CTGTCCAGCAGGAAACCC	88	7810	7827	3-10-5	754
599235	2576	2593	Exon 18	CCTGTCCAGCAGGAAACC	91	7811	7828	3-10-5	755
599236	2577	2594	Exon 18	CCCTGTCCAGCAGGAAAC	90	7812	7829	3-10-5	756

599237	2578	2595	Exon 18	CCCCTGTCCAGCAGGAAA	34	7813	7830	3-10-5	757
599238	2580	2597	Exon 18	CGCCCCTGTCCAGCAGGA	14	7815	7832	3-10-5	758
599239	2581	2598	Exon 18	ACGCCCCTGTCCAGCAGG	10	7816	7833	3-10-5	759
599240	2582	2599	Exon 18	CACGCCCCTGTCCAGCAG	26	7817	7834	3-10-5	760
599241	2583	2600	Exon 18	CCACGCCCCTGTCCAGCA	11	7818	7835	3-10-5	761
599242	2584	2601	Exon 18	CCCACGCCCCTGTCCAGC	24	7819	7836	3-10-5	762
599243	2585	2602	Exon 18	TCCCACGCCCCTGTCCAG	23	7820	7837	3-10-5	763
599244	2586	2603	Exon 18	ATCCCACGCCCCTGTCCA	29	7821	7838	3-10-5	764
599245	2587	2604	Exon 18	AATCCCACGCCCCTGTCC	11	7822	7839	3-10-5	765
599246	2588	2605	Exon 18	CAATCCCACGCCCCTGTC	0	7823	7840	3-10-5	766
599247	2589	2606	Exon 18	TCAATCCCACGCCCCTGT	21	7824	7841	3-10-5	767
599248	2590	2607	Exon 18	TTCAATCCCACGCCCCTG	0	7825	7842	3-10-5	768
599249	2591	2608	Exon 18	ATTCAATCCCACGCCCCT	9	7826	7843	3-10-5	769
599250	2592	2609	Exon 18	AATTCAATCCCACGCCCC	4	7827	7844	3-10-5	770
599251	2593	2610	Exon 18	TAATTCAATCCCACGCCC	12	7828	7845	3-10-5	771
599252	2594	2611	Exon 18	TTAATTCAATCCCACGCC	2	7829	7846	3-10-5	772
599253	2595	2612	Exon 18	TTTAATTCAATCCCACGC	28	7830	7847	3-10-5	773
599254	2596	2613	Exon 18	TTTTAATTCAATCCCACG	27	7831	7848	3-10-5	774
599255	2597	2614	Exon 18	GTTTTAATTCAATCCCAC	38	7832	7849	3-10-5	775
599256	2598	2615	Exon 18	TGTTTTAATTCAATCCCA	36	7833	7850	3-10-5	776
599257	2599	2616	Exon 18	CTGTTTTAATTCAATCCC	48	7834	7851	3-10-5	777
599258	2600	2617	Exon 18	GCTGTTTTAATTCAATCC	19	7835	7852	3-10-5	778
599259	2601	2618	Exon 18	AGCTGTTTTAATTCAATC	36	7836	7853	3-10-5	779
599260	2602	2619	Exon 18	CAGCTGTTTTAATTCAAT	58	7837	7854	3-10-5	780
599261	2603	2620	Exon 18	GCAGCTGTTTTAATTCAA	35	7838	7855	3-10-5	781
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTC A	96	7839	7858	5-10-5	317
599262	2604	2621	Exon 18	CGCAGCTGTTTTAATTCA	52	7839	7856	3-10-5	782
599263	2605	2622	Exon 18	TCGCAGCTGTTTTAATTC	66	7840	7857	3-10-5	783
599264	2606	2623	Exon 18	GTCGCAGCTGTTTTAATT	48	7841	7858	3-10-5	784
599265	2607	2624	Exon 18	TGTCGCAGCTGTTTTAAT	46	7842	7859	3-10-5	792
599205	2607	2624	Exon 18	TGTCGCAGCTGTTTTAAT	83	7842	7859	5-8-5	792
599266	2608	2625	Exon 18	TTGTCGCAGCTGTTTTAA	76	7843	7860	3-10-5	793
599206	2608	2625	Exon 18	TTGTCGCAGCTGTTTTAA	90	7843	7860	5-8-5	793
599267	2609	2626	Exon 18	GTTGTCGCAGCTGTTTTA	53	7844	7861	3-10-5	794
599207	2609	2626	Exon 18	GTTGTCGCAGCTGTTTTA	82	7844	7861	5-8-5	794
599268	2610	2627	Exon 18	TGTTGTCGCAGCTGTTTT	58	7845	7862	3-10-5	795
599208	2610	2627	Exon 18	TGTTGTCGCAGCTGTTTT	70	7845	7862	5-8-5	795
599269	2611	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTT	38	n/a	n/a	3-10-5	796
599209	2611	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTT	50	n/a	n/a	5-8-5	796
599270	2612	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTT	46	n/a	n/a	3-10-5	797

599210	2612	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTT	76	n/a	n/a	5-8-5	797
599271	2613	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGT	64	n/a	n/a	3-10-5	798
599211	2613	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGT	78	n/a	n/a	5-8-5	798
599272	2614	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTG	89	n/a	n/a	3-10-5	799
599212	2614	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTG	84	n/a	n/a	5-8-5	799

Table 17

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599511	2552	2571	Exon 18	ATAGAAAACCCAAATCCTCA	38	7787	7806	6-8-6	410
599389	2553	2572	Exon 18	TATAGAAAACCCAAATCCTC	80	7788	7807	6-8-6	411
599390	2554	2573	Exon 18	TTATAGAAAACCCAAATCCT	92	7789	7808	6-8-6	412
599391	2555	2574	Exon 18	CTTATAGAAAACCCAAATCC	90	7790	7809	6-8-6	413
599392	2556	2575	Exon 18	CCTTATAGAAAACCCAAATC	87	7791	7810	6-8-6	414
599393	2557	2576	Exon 18	CCCTTATAGAAAACCCAAAT	87	7792	7811	6-8-6	415
599394	2558	2577	Exon 18	CCCCTTATAGAAAACCCAAA	74	7793	7812	6-8-6	416
599395	2559	2578	Exon 18	ACCCCTTATAGAAAACCCAA	78	7794	7813	6-8-6	417
599396	2560	2579	Exon 18	AACCCCTTATAGAAAACCCA	77	7795	7814	6-8-6	418
599397	2561	2580	Exon 18	AAACCCCTTATAGAAAACCC	89	7796	7815	6-8-6	419
599398	2562	2581	Exon 18	GAAACCCCTTATAGAAAACC	90	7797	7816	6-8-6	420
599399	2563	2582	Exon 18	GGAAACCCCTTATAGAAAAC	91	7798	7817	6-8-6	421
599400	2564	2583	Exon 18	AGGAAACCCCTTATAGAAAA	88	7799	7818	6-8-6	422
599401	2565	2584	Exon 18	CAGGAAACCCCTTATAGAAA	85	7800	7819	6-8-6	423
599402	2566	2585	Exon 18	GCAGGAAACCCCTTATAGAA	77	7801	7820	6-8-6	424
599403	2567	2586	Exon 18	AGCAGGAAACCCCTTATAGA	85	7802	7821	6-8-6	425
599404	2568	2587	Exon 18	CAGCAGGAAACCCCTTATAG	90	7803	7822	6-8-6	426
599405	2569	2588	Exon 18	CCAGCAGGAAACCCCTTATA	89	7804	7823	6-8-6	427
599406	2570	2589	Exon 18	TCCAGCAGGAAACCCCTTAT	72	7805	7824	6-8-6	428
599407	2571	2590	Exon 18	GTCCAGCAGGAAACCCCTTA	87	7806	7825	6-8-6	237
599408	2572	2591	Exon 18	TGTCCAGCAGGAAACCCCTT	87	7807	7826	6-8-6	429
599409	2573	2592	Exon 18	CTGTCCAGCAGGAAACCCCT	83	7808	7827	6-8-6	430
599410	2574	2593	Exon 18	CCTGTCCAGCAGGAAACCCC	88	7809	7828	6-8-6	431
599411	2575	2594	Exon 18	CCCTGTCCAGCAGGAAACCC	45	7810	7829	6-8-6	432
599412	2576	2595	Exon 18	CCCCTGTCCAGCAGGAAACC	66	7811	7830	6-8-6	433
599413	2577	2596	Exon 18	GCCCCTGTCCAGCAGGAAAC	92	7812	7831	6-8-6	238
599414	2578	2597	Exon 18	CGCCCCTGTCCAGCAGGAAA	92	7813	7832	6-8-6	434
599415	2579	2598	Exon 18	ACGCCCCTGTCCAGCAGGAA	87	7814	7833	6-8-6	435

599416	2580	2599	Exon 18	CACGCCCCTGTCCAGCAGGA	91	7815	7834	6-8-6	436
599417	2581	2600	Exon 18	CCACGCCCCTGTCCAGCAGG	84	7816	7835	6-8-6	437
599357	2582	2600	Exon 18	CCACGCCCCTGTCCAGCAG	88	7817	7835	5-9-5	708
599418	2582	2601	Exon 18	CCCACGCCCCTGTCCAGCAG	85	7817	7836	6-8-6	438
599358	2583	2601	Exon 18	CCCACGCCCCTGTCCAGCA	86	7818	7836	5-9-5	709
599419	2583	2602	Exon 18	TCCCACGCCCCTGTCCAGCA	91	7818	7837	6-8-6	833
599359	2584	2602	Exon 18	TCCCACGCCCCTGTCCAGC	85	7819	7837	5-9-5	834
599420	2584	2603	Exon 18	ATCCCACGCCCCTGTCCAGC	91	7819	7838	6-8-6	440
599360	2585	2603	Exon 18	ATCCCACGCCCCTGTCCAG	89	7820	7838	5-9-5	711
599421	2585	2604	Exon 18	AATCCCACGCCCCTGTCCAG	87	7820	7839	6-8-6	441
599361	2586	2604	Exon 18	AATCCCACGCCCCTGTCCA	89	7821	7839	5-9-5	712
599422	2586	2605	Exon 18	CAATCCCACGCCCCTGTCCA	90	7821	7840	6-8-6	442
599362	2587	2605	Exon 18	CAATCCCACGCCCCTGTCC	94	7822	7840	5-9-5	713
599423	2587	2606	Exon 18	TCAATCCCACGCCCCTGTCC	85	7822	7841	6-8-6	841
599363	2588	2606	Exon 18	TCAATCCCACGCCCCTGTC	88	7823	7841	5-9-5	714
599424	2588	2607	Exon 18	TTCAATCCCACGCCCCTGTC	88	7823	7842	6-8-6	444
599364	2589	2607	Exon 18	TTCAATCCCACGCCCCTGT	88	7824	7842	5-9-5	715
599425	2589	2608	Exon 18	ATTCAATCCCACGCCCCTGT	68	7824	7843	6-8-6	445
599365	2590	2608	Exon 18	ATTCAATCCCACGCCCCTG	48	7825	7843	5-9-5	716
599426	2590	2609	Exon 18	AATTCAATCCCACGCCCCTG	55	7825	7844	6-8-6	446
599366	2591	2609	Exon 18	AATTCAATCCCACGCCCCT	28	7826	7844	5-9-5	717
599427	2591	2610	Exon 18	TAATTCAATCCCACGCCCCT	13	7826	7845	6-8-6	849
599367	2592	2610	Exon 18	TAATTCAATCCCACGCCCC	21	7827	7845	5-9-5	718
599428	2592	2611	Exon 18	TTAATTCAATCCCACGCCCC	39	7827	7846	6-8-6	448
599368	2593	2611	Exon 18	TTAATTCAATCCCACGCCC	20	7828	7846	5-9-5	719
599429	2593	2612	Exon 18	TTTAATTCAATCCCACGCCC	18	7828	7847	6-8-6	449
599369	2594	2612	Exon 18	TTTAATTCAATCCCACGCC	78	7829	7847	5-9-5	720
599430	2594	2613	Exon 18	TTTTAATTCAATCCCACGCC	24	7829	7848	6-8-6	450
599370	2595	2613	Exon 18	TTTTAATTCAATCCCACGC	25	7830	7848	5-9-5	721
599431	2595	2614	Exon 18	GTTTTAATTCAATCCCACGC	30	7830	7849	6-8-6	451
599371	2596	2614	Exon 18	GTTTTAATTCAATCCCACG	84	7831	7849	5-9-5	722
599432	2596	2615	Exon 18	TGTTTTAATTCAATCCCACG	29	7831	7850	6-8-6	452
599372	2597	2615	Exon 18	TGTTTTAATTCAATCCCAC	83	7832	7850	5-9-5	723
599373	2598	2616	Exon 18	CTGTTTTAATTCAATCCCA	81	7833	7851	5-9-5	724
599374	2599	2617	Exon 18	GCTGTTTTAATTCAATCCC	26	7834	7852	5-9-5	725
599375	2600	2618	Exon 18	AGCTGTTTTAATTCAATCC	26	7835	7853	5-9-5	726
599376	2601	2619	Exon 18	CAGCTGTTTTAATTCAATC	62	7836	7854	5-9-5	727
599377	2602	2620	Exon 18	GCAGCTGTTTTAATTCAAT	21	7837	7855	5-9-5	728
599378	2603	2621	Exon 18	CGCAGCTGTTTTAATTCAA	90	7838	7856	5-9-5	729
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	95	7839	7858	5-10-5	867
599379	2604	2622	Exon 18	TCGCAGCTGTTTTAATTCA	88	7839	7857	5-9-5	730
599380	2605	2623	Exon 18	GTCGCAGCTGTTTTAATTC	37	7840	7858	5-9-5	869

599381	2606	2624	Exon 18	TGTCGCAGCTGTTTTAATT	33	7841	7859	5-9-5	732
599382	2607	2625	Exon 18	TTGTCGCAGCTGTTTTAAT	81	7842	7860	5-9-5	733
599383	2608	2626	Exon 18	GTTGTCGCAGCTGTTTTAA	54	7843	7861	5-9-5	734
599384	2609	2627	Exon 18	TGTTGTCGCAGCTGTTTTA	85	7844	7862	5-9-5	873
599385	2610	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTTT	59	n/a	n/a	5-9-5	736
599386	2611	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTTT	81	n/a	n/a	5-9-5	737
599387	2612	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGTT	80	n/a	n/a	5-9-5	738
599388	2613	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTGT	84	n/a	n/a	5-9-5	739

Example 6: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells

Additional antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 1,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as deoxy, MOE and cEt oligonucleotides. The deoxy, MOE and cEt oligonucleotides are 16 nucleosides in length wherein the nucleoside have either a MOE sugar modification, an cEt sugar modification, or a deoxy modification. The 'Chemistry' column describes the sugar modifications of each oligonucleotide. 'k' indicates an cEt sugar modification; 'd' indicates deoxyribose; and 'e' indicates a MOE modification.

"Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity.

Table 18

Inhibition of CFB mRNA by deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599513	2551	2566	Exon 18	AAACCCAAATCCTCAT	11	7786	7801	ekkeekkddddddddkk	557
599514	2553	2568	Exon 18	GAAAACCCAAATCCTC	13	7788	7803	ekkeekkddddddddkk	801
599515	2555	2570	Exon 18	TAGAAAACCCAAATCC	54	7790	7805	ekkeekkddddddddkk	559
599516	2559	2574	Exon 18	CTTATAGAAAACCCAA	16	7794	7809	ekkeekkddddddddkk	561
599517	2560	2575	Exon 18	CCTTATAGAAAACCCA	29	7795	7810	ekkeekkddddddddkk	562
599518	2561	2576	Exon 18	CCCTTATAGAAAACCC	55	7796	7811	ekkeekkddddddddkk	563
599519	2562	2577	Exon 18	CCCCTTATAGAAAACC	31	7797	7812	ekkeekkddddddddkk	564
599520	2563	2578	Exon 18	ACCCCTTATAGAAAAC	14	7798	7813	ekkeekkddddddddkk	565
599521	2564	2579	Exon 18	AACCCCTTATAGAAAA	9	7799	7814	ekkeekkddddddddkk	566
599522	2565	2580	Exon 18	AAACCCCTTATAGAAA	8	7800	7815	ekkeekkddddddddkk	567
599523	2566	2581	Exon 18	GAAACCCCTTATAGAA	6	7801	7816	ekkeekkddddddddkk	568
599524	2567	2582	Exon 18	GGAAACCCCTTATAGA	14	7802	7817	ekkeekkddddddddkk	569
599525	2568	2583	Exon 18	AGGAAACCCCTTATAG	6	7803	7818	ekkeekkddddddddkk	570
599526	2569	2584	Exon 18	CAGGAAACCCCTTATA	16	7804	7819	ekkeekkddddddddkk	571
599527	2570	2585	Exon 18	GCAGGAAACCCCTTAT	0	7805	7820	ekkeekkddddddddkk	572
599528	2571	2586	Exon 18	AGCAGGAAACCCCTTA	6	7806	7821	ekkeekkddddddddkk	573
599529	2572	2587	Exon 18	CAGCAGGAAACCCCTT	6	7807	7822	ekkeekkddddddddkk	574
599530	2574	2589	Exon 18	TCCAGCAGGAAACCCC	29	7809	7824	ekkeekkddddddddkk	576
599531	2575	2590	Exon 18	GTCCAGCAGGAAACCC	64	7810	7825	ekkeekkddddddddkk	577
599532	2576	2591	Exon 18	TGTCCAGCAGGAAACC	43	7811	7826	ekkeekkddddddddkk	578
599533	2577	2592	Exon 18	CTGTCCAGCAGGAAAC	25	7812	7827	ekkeekkddddddddkk	820
599534	2578	2593	Exon 18	CCTGTCCAGCAGGAAA	12	7813	7828	ekkeekkddddddddkk	580
599535	2580	2595	Exon 18	CCCCTGTCCAGCAGGA	16	7815	7830	ekkeekkddddddddkk	582
599536	2582	2597	Exon 18	CGCCCCTGTCCAGCAG	27	7817	7832	ekkeekkddddddddkk	584
599537	2583	2598	Exon 18	ACGCCCCTGTCCAGCA	35	7818	7833	ekkeekkddddddddkk	585
599538	2584	2599	Exon 18	CACGCCCCTGTCCAGC	26	7819	7834	ekkeekkddddddddkk	586
599539	2585	2600	Exon 18	CCACGCCCCTGTCCAG	33	7820	7835	ekkeekkddddddddkk	587
599540	2586	2601	Exon 18	CCCACGCCCCTGTCCA	27	7821	7836	ekkeekkddddddddkk	588
599541	2587	2602	Exon 18	TCCCACGCCCCTGTCC	52	7822	7837	ekkeekkddddddddkk	589
599542	2588	2603	Exon 18	ATCCCACGCCCCTGTC	16	7823	7838	ekkeekkddddddddkk	590
599543	2589	2604	Exon 18	AATCCCACGCCCCTGT	19	7824	7839	ekkeekkddddddddkk	591
599544	2590	2605	Exon 18	CAATCCCACGCCCCTG	33	7825	7840	ekkeekkddddddddkk	831
599545	2591	2606	Exon 18	TCAATCCCACGCCCCT	24	7826	7841	ekkeekkddddddddkk	593
599546	2592	2607	Exon 18	TTCAATCCCACGCCCC	54	7827	7842	ekkeekkddddddddkk	594
599547	2593	2608	Exon 18	ATTCAATCCCACGCCC	87	7828	7843	ekkeekkddddddddkk	595
599548	2594	2609	Exon 18	AATTCAATCCCACGCC	79	7829	7844	ekkeekkddddddddkk	596

599549	2595	2610	Exon 18	TAATTCAATCCCACGC	62	7830	7845	ekkeekkddddddkk	597
599550	2596	2611	Exon 18	TTAATTCAATCCCACG	52	7831	7846	ekkeekkddddddkk	598
599551	2597	2612	Exon 18	TTTAATTCAATCCCAC	27	7832	7847	ekkeekkddddddkk	599
599577	2597	2613	Exon 18	TTTTAATTCAATCCCAC	90	7832	7848	eeekkddddddkkeee	662
599552	2598	2613	Exon 18	TTTTAATTCAATCCCA	92	7833	7848	ekkeekkddddddkk	600
599578	2598	2614	Exon 18	GTTTTAATTCAATCCCA	88	7833	7849	eeekkddddddkkeee	663
599553	2599	2614	Exon 18	GTTTTAATTCAATCCC	91	7834	7849	ekkeekkddddddkk	601
599579	2599	2615	Exon 18	TGTTTTAATTCAATCCC	79	7834	7850	eeekkddddddkkeee	664
599554	2600	2615	Exon 18	TGTTTTAATTCAATCC	90	7835	7850	ekkeekkddddddkk	602
599580	2600	2616	Exon 18	CTGTTTTAATTCAATCC	79	7835	7851	eeekkddddddkkeee	665
599555	2601	2616	Exon 18	CTGTTTTAATTCAATC	79	7836	7851	ekkeekkddddddkk	846
599581	2601	2617	Exon 18	GCTGTTTTAATTCAATC	90	7836	7852	eeekkddddddkkeee	666
599556	2602	2617	Exon 18	GCTGTTTTAATTCAAT	47	7837	7852	ekkeekkddddddkk	604
599582	2602	2618	Exon 18	AGCTGTTTTAATTCAAT	89	7837	7853	eeekkddddddkkeee	849
599557	2603	2618	Exon 18	AGCTGTTTTAATTCAA	67	7838	7853	ekkeekkddddddkk	850
599583	2603	2619	Exon 18	CAGCTGTTTTAATTCAA	49	7838	7854	eeekkddddddkkeee	668
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	78	7839	7858	eeeeeddddddddddeeeee	317
599558	2604	2619	Exon 18	CAGCTGTTTTAATTCA	80	7839	7854	ekkeekkddddddkk	606
599584	2604	2620	Exon 18	GCAGCTGTTTTAATTCA	66	7839	7855	eeekkddddddkkeee	669
599559	2605	2620	Exon 18	GCAGCTGTTTTAATTC	38	7840	7855	ekkeekkddddddkk	607
599585	2605	2621	Exon 18	CGCAGCTGTTTTAATTC	80	7840	7856	eeekkddddddkkeee	670
599560	2606	2621	Exon 18	CGCAGCTGTTTTAATT	16	7841	7856	ekkeekkddddddkk	608
599586	2606	2622	Exon 18	TCGCAGCTGTTTTAATT	78	7841	7857	eeekkddddddkkeee	671
599561	2607	2622	Exon 18	TCGCAGCTGTTTTAAT	58	7842	7857	ekkeekkddddddkk	609
599587	2607	2623	Exon 18	GTCGCAGCTGTTTTAAT	81	7842	7858	eeekkddddddkkeee	672
588860	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	92	7843	7858	eekddddddddddkke	610
599562	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	78	7843	7858	ekkeekkddddddkk	610
599588	2608	2624	Exon 18	TGTCGCAGCTGTTTTAA	81	7843	7859	eeekkddddddkkeee	673
599563	2609	2624	Exon 18	TGTCGCAGCTGTTTTA	86	7844	7859	ekkeekkddddddkk	611
599589	2609	2625	Exon 18	TTGTCGCAGCTGTTTTA	75	7844	7860	eeekkddddddkkeee	674
599564	2610	2625	Exon 18	TTGTCGCAGCTGTTTT	75	7845	7860	ekkeekkddddddkk	612
599590	2610	2626	Exon 18	GTTGTCGCAGCTGTTTT	88	7845	7861	eeekkddddddkkeee	675
599565	2611	2626	Exon 18	GTTGTCGCAGCTGTTT	65	7846	7861	ekkeekkddddddkk	613
599591	2611	2627	Exon 18	TGTTGTCGCAGCTGTTT	94	7846	7862	eeekkddddddkkeee	676
599566	2612	2627	Exon 18	TGTTGTCGCAGCTGTT	72	7847	7862	ekkeekkddddddkk	614
599592	2612	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTT	90	n/a	n/a	eeekkddddddkkeee	677
599567	2613	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGT	82	n/a	n/a	ekkeekkddddddkk	615
599593	2613	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGT	95	n/a	n/a	eeekkddddddkkeee	678
599568	2614	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTG	92	n/a	n/a	ekkeekkddddddkk	616
599594	2614	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTG	86	n/a	n/a	eeekkddddddkkeee	679

599569	2615	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCT	89	n/a	n/a	ekkeekkddddddkk	617
599595	2615	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCT	76	n/a	n/a	eeekkddddddkkeee	680
599570	2616	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGC	95	n/a	n/a	ekkeekkddddddkk	618

Example 7: Antisense inhibition of human Complement Factor B (CFB) in HepG2 cells

Additional antisense oligonucleotides were designed targeting human Complement Factor B (CFB) nucleic acid and were tested for their effects on CFB mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as deoxy, MOE and cEt oligonucleotides, or as 5-8-5 MOE, 5-9-5 MOE, 5-10-5 MOE, 6-7-6- MOE, 3-10-5 MOE, or 6-8-6 MOE gapmers.

The deoxy, MOE and cEt oligonucleotides are 16 nucleosides in length wherein the nucleoside have either a MOE sugar modification, an cEt sugar modification, or a deoxy modification. The 'Chemistry' column describes the sugar modifications of each oligonucleotide. 'k' indicates an cEt sugar modification; 'd' indicates deoxyribose; and 'e' indicates a MOE modification.

The 5-8-5 MOE gapmers are 18 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 5-9-5 MOE gapmers are 19 nucleosides in length, wherein the central gap segment comprises of nine 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 3-10-5 MOE gapmers are 18 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising three and five nucleosides respectively. The 6-7-6 MOE gapmers are 19 nucleosides in length, wherein the central gap segment comprises of seven 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising six nucleosides each. The 6-8-6 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of eight 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3'

direction comprising six nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human CFB mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001710.5) or the human CFB genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_007592.15 truncated from nucleotides 31852000 to 31861000), or both. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity.

Table 19

Inhibition of CFB mRNA by deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
601152	2551	2566	Exon 18	AAACCCAAATCCTCAT	22	7786	7801	eekkddddddddkkee	557
601218	2551	2566	Exon 18	AAACCCAAATCCTCAT	21	7786	7801	ekkkddddddddkeee	557
601153	2552	2567	Exon 18	AAAACCCAAATCCTCA	27	7787	7802	eekkddddddddkkee	800
601219	2552	2567	Exon 18	AAAACCCAAATCCTCA	19	7787	7802	ekkkddddddddkeee	800
601154	2553	2568	Exon 18	GAAAACCCAAATCCTC	23	7788	7803	eekkddddddddkkee	558
601220	2553	2568	Exon 18	GAAAACCCAAATCCTC	24	7788	7803	ekkkddddddddkeee	558
601155	2554	2569	Exon 18	AGAAAACCCAAATCCT	20	7789	7804	eekkddddddddkkee	801
601221	2554	2569	Exon 18	AGAAAACCCAAATCCT	0	7789	7804	ekkkddddddddkeee	801
601156	2555	2570	Exon 18	TAGAAAACCCAAATCC	11	7790	7805	eekkddddddddkkee	559
601222	2555	2570	Exon 18	TAGAAAACCCAAATCC	23	7790	7805	ekkkddddddddkeee	559
601157	2556	2571	Exon 18	ATAGAAAACCCAAATC	9	7791	7806	eekkddddddddkkee	560
601223	2556	2571	Exon 18	ATAGAAAACCCAAATC	0	7791	7806	ekkkddddddddkeee	560
601158	2557	2572	Exon 18	TATAGAAAACCCAAAT	0	7792	7807	eekkddddddddkkee	802
601224	2557	2572	Exon 18	TATAGAAAACCCAAAT	0	7792	7807	ekkkddddddddkeee	802
601159	2558	2573	Exon 18	TTATAGAAAACCCAAA	2	7793	7808	eekkddddddddkkee	803
601225	2558	2573	Exon 18	TTATAGAAAACCCAAA	0	7793	7808	ekkkddddddddkeee	803
601160	2559	2574	Exon 18	CTTATAGAAAACCCAA	0	7794	7809	eekkddddddddkkee	561
601226	2559	2574	Exon 18	CTTATAGAAAACCCAA	0	7794	7809	ekkkddddddddkeee	561
601161	2560	2575	Exon 18	CCTTATAGAAAACCCA	1	7795	7810	eekkddddddddkkee	562
601227	2560	2575	Exon 18	CCTTATAGAAAACCCA	14	7795	7810	ekkkddddddddkeee	562
601162	2561	2576	Exon 18	CCCTTATAGAAAACCC	9	7796	7811	eekkddddddddkkee	563
601228	2561	2576	Exon 18	CCCTTATAGAAAACCC	9	7796	7811	ekkkddddddddkeee	563

601163	2562	2577	Exon 18	CCCCTTATAGAAAACC	0	7797	7812	eekkddddddddkkee	564
601164	2563	2578	Exon 18	ACCCCTTATAGAAAAC	3	7798	7813	eekkddddddddkkee	565
601165	2564	2579	Exon 18	AACCCCTTATAGAAAA	0	7799	7814	eekkddddddddkkee	566
601166	2565	2580	Exon 18	AAACCCCTTATAGAAA	0	7800	7815	eekkddddddddkkee	567
601167	2566	2581	Exon 18	GAAACCCCTTATAGAA	0	7801	7816	eekkddddddddkkee	568
601168	2567	2582	Exon 18	GGAAACCCCTTATAGA	0	7802	7817	eekkddddddddkkee	569
601169	2568	2583	Exon 18	AGGAAACCCCTTATAG	0	7803	7818	eekkddddddddkkee	570
601170	2569	2584	Exon 18	CAGGAAACCCCTTATA	10	7804	7819	eekkddddddddkkee	571
601171	2570	2585	Exon 18	GCAGGAAACCCCTTAT	9	7805	7820	eekkddddddddkkee	572
601172	2571	2586	Exon 18	AGCAGGAAACCCCTTA	15	7806	7821	eekkddddddddkkee	573
601173	2572	2587	Exon 18	CAGCAGGAAACCCCTT	29	7807	7822	eekkddddddddkkee	574
601174	2573	2588	Exon 18	CCAGCAGGAAACCCCT	25	7808	7823	eekkddddddddkkee	575
601175	2574	2589	Exon 18	TCCAGCAGGAAACCCC	15	7809	7824	eekkddddddddkkee	576
601176	2575	2590	Exon 18	GTCCAGCAGGAAACCC	18	7810	7825	eekkddddddddkkee	577
601177	2576	2591	Exon 18	TGTCCAGCAGGAAACC	10	7811	7826	eekkddddddddkkee	578
601178	2577	2592	Exon 18	CTGTCCAGCAGGAAAC	11	7812	7827	eekkddddddddkkee	579
601179	2578	2593	Exon 18	CCTGTCCAGCAGGAAA	19	7813	7828	eekkddddddddkkee	580
601180	2579	2594	Exon 18	CCCTGTCCAGCAGGAA	7	7814	7829	eekkddddddddkkee	581
601181	2580	2595	Exon 18	CCCCTGTCCAGCAGGA	3	7815	7830	eekkddddddddkkee	582
601182	2581	2596	Exon 18	GCCCCTGTCCAGCAGG	0	7816	7831	eekkddddddddkkee	583
601183	2582	2597	Exon 18	CGCCCCTGTCCAGCAG	4	7817	7832	eekkddddddddkkee	584
601184	2583	2598	Exon 18	ACGCCCCTGTCCAGCA	14	7818	7833	eekkddddddddkkee	585
601185	2584	2599	Exon 18	CACGCCCCTGTCCAGC	26	7819	7834	eekkddddddddkkee	586
601186	2585	2600	Exon 18	CCACGCCCCTGTCCAG	8	7820	7835	eekkddddddddkkee	587
601187	2586	2601	Exon 18	CCCACGCCCCTGTCCA	18	7821	7836	eekkddddddddkkee	588
601188	2587	2602	Exon 18	TCCCACGCCCCTGTCC	20	7822	7837	eekkddddddddkkee	589
601189	2588	2603	Exon 18	ATCCCACGCCCCTGTC	12	7823	7838	eekkddddddddkkee	590
601190	2589	2604	Exon 18	AATCCCACGCCCCTGT	33	7824	7839	eekkddddddddkkee	591
601191	2590	2605	Exon 18	CAATCCCACGCCCCTG	52	7825	7840	eekkddddddddkkee	592
601192	2591	2606	Exon 18	TCAATCCCACGCCCCT	46	7826	7841	eekkddddddddkkee	593
601193	2592	2607	Exon 18	TTCAATCCCACGCCCC	30	7827	7842	eekkddddddddkkee	594
601194	2593	2608	Exon 18	ATTCAATCCCACGCCC	41	7828	7843	eekkddddddddkkee	595
601195	2594	2609	Exon 18	AATTCAATCCCACGCC	40	7829	7844	eekkddddddddkkee	596
601196	2595	2610	Exon 18	TAATTCAATCCCACGC	71	7830	7845	eekkddddddddkkee	597
601197	2596	2611	Exon 18	TTAATTCAATCCCACG	42	7831	7846	eekkddddddddkkee	598
601198	2597	2612	Exon 18	TTTAATTCAATCCCAC	63	7832	7847	eekkddddddddkkee	599
601199	2598	2613	Exon 18	TTTTAATTCAATCCCA	51	7833	7848	eekkddddddddkkee	600
601200	2599	2614	Exon 18	GTTTTAATTCAATCCC	65	7834	7849	eekkddddddddkkee	601
601201	2600	2615	Exon 18	TGTTTTAATTCAATCC	49	7835	7850	eekkddddddddkkee	602
601202	2601	2616	Exon 18	CTGTTTTAATTCAATC	33	7836	7851	eekkddddddddkkee	603
601203	2602	2617	Exon 18	GCTGTTTTAATTCAAT	63	7837	7852	eekkddddddddkkee	604
601204	2603	2618	Exon 18	AGCTGTTTTAATTCAA	69	7838	7853	eekkddddddddkkee	605

532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	73	7839	7858	eeeeeddddddddddeeeee	317
601205	2604	2619	Exon 18	CAGCTGTTTTAATTCA	51	7839	7854	eekkddddddddkkee	606
601206	2605	2620	Exon 18	GCAGCTGTTTTAATTC	43	7840	7855	eekkddddddddkkee	607
601207	2606	2621	Exon 18	CGCAGCTGTTTTAATT	52	7841	7856	eekkddddddddkkee	608
601208	2607	2622	Exon 18	TCGCAGCTGTTTTAAT	61	7842	7857	eekkddddddddkkee	609
588860	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	75	7843	7858	eekddddddddddkke	610
601209	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	73	7843	7858	eekkddddddddkkee	610
601210	2609	2624	Exon 18	TGTCGCAGCTGTTTTA	80	7844	7859	eekkddddddddkkee	611
601211	2610	2625	Exon 18	TTGTCGCAGCTGTTTT	64	7845	7860	eekkddddddddkkee	612
601212	2611	2626	Exon 18	GTTGTCGCAGCTGTTT	86	7846	7861	eekkddddddddkkee	613
601213	2612	2627	Exon 18	TGTTGTCGCAGCTGTT	87	7847	7862	eekkddddddddkkee	614
601214	2613	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGT	84	n/a	n/a	eekkddddddddkkee	615
601215	2614	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTG	78	n/a	n/a	eekkddddddddkkee	616
601216	2615	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCT	73	n/a	n/a	eekkddddddddkkee	617
601217	2616	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGC	66	n/a	n/a	eekkddddddddkkee	618

Table 20

Inhibition of CFB mRNA by deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
601284	2551	2566	Exon 18	AAACCCAAATCCTCAT	8	7786	7801	ekkddddddddkkeee	557
601285	2552	2567	Exon 18	AAAACCCAAATCCTCA	15	7787	7802	ekkddddddddkkeee	800
601286	2553	2568	Exon 18	GAAAACCCAAATCCTC	21	7788	7803	ekkddddddddkkeee	558
601287	2554	2569	Exon 18	AGAAAACCCAAATCCT	9	7789	7804	ekkddddddddkkeee	801
601288	2555	2570	Exon 18	TAGAAAACCCAAATCC	0	7790	7805	ekkddddddddkkeee	559
601289	2556	2571	Exon 18	ATAGAAAACCCAAATC	40	7791	7806	ekkddddddddkkeee	560
601290	2557	2572	Exon 18	TATAGAAAACCCAAAT	16	7792	7807	ekkddddddddkkeee	802
601291	2558	2573	Exon 18	TTATAGAAAACCCAAA	15	7793	7808	ekkddddddddkkeee	803
601292	2559	2574	Exon 18	CTTATAGAAAACCCAA	5	7794	7809	ekkddddddddkkeee	561
601293	2560	2575	Exon 18	CCTTATAGAAAACCCA	15	7795	7810	ekkddddddddkkeee	562
601294	2561	2576	Exon 18	CCCTTATAGAAAACCC	3	7796	7811	ekkddddddddkkeee	563
601229	2562	2577	Exon 18	CCCCTTATAGAAAACC	15	7797	7812	ekkddddddddkkeee	564
601295	2562	2577	Exon 18	CCCCTTATAGAAAACC	5	7797	7812	ekkddddddddkkeee	564
601230	2563	2578	Exon 18	ACCCCTTATAGAAAAC	14	7798	7813	ekkddddddddkkeee	565
601296	2563	2578	Exon 18	ACCCCTTATAGAAAAC	0	7798	7813	ekkddddddddkkeee	565
601231	2564	2579	Exon 18	AACCCCTTATAGAAAA	14	7799	7814	ekkddddddddkkeee	566
601297	2564	2579	Exon 18	AACCCCTTATAGAAAA	14	7799	7814	ekkddddddddkkeee	566

601232	2565	2580	Exon 18	AAACCCCTTATAGAAA	15	7800	7815	ekkkddddddddkeee	567
601298	2565	2580	Exon 18	AAACCCCTTATAGAAA	7	7800	7815	ekkkddddddddkkeee	567
601233	2566	2581	Exon 18	GAAACCCCTTATAGAA	0	7801	7816	ekkkddddddddkeee	568
601299	2566	2581	Exon 18	GAAACCCCTTATAGAA	0	7801	7816	ekkkddddddddkkeee	568
601234	2567	2582	Exon 18	GGAAACCCCTTATAGA	0	7802	7817	ekkkddddddddkeee	569
601300	2567	2582	Exon 18	GGAAACCCCTTATAGA	9	7802	7817	ekkkddddddddkkeee	569
601235	2568	2583	Exon 18	AGGAAACCCCTTATAG	3	7803	7818	ekkkddddddddkeee	570
601301	2568	2583	Exon 18	AGGAAACCCCTTATAG	14	7803	7818	ekkkddddddddkkeee	570
601236	2569	2584	Exon 18	CAGGAAACCCCTTATA	0	7804	7819	ekkkddddddddkeee	571
601302	2569	2584	Exon 18	CAGGAAACCCCTTATA	0	7804	7819	ekkkddddddddkkeee	571
601237	2570	2585	Exon 18	GCAGGAAACCCCTTAT	16	7805	7820	ekkkddddddddkeee	572
601303	2570	2585	Exon 18	GCAGGAAACCCCTTAT	16	7805	7820	ekkkddddddddkkeee	572
601238	2571	2586	Exon 18	AGCAGGAAACCCCTTA	11	7806	7821	ekkkddddddddkeee	573
601304	2571	2586	Exon 18	AGCAGGAAACCCCTTA	10	7806	7821	ekkkddddddddkkeee	573
601239	2572	2587	Exon 18	CAGCAGGAAACCCCTT	21	7807	7822	ekkkddddddddkeee	574
601305	2572	2587	Exon 18	CAGCAGGAAACCCCTT	7	7807	7822	ekkkddddddddkkeee	574
601240	2573	2588	Exon 18	CCAGCAGGAAACCCCT	6	7808	7823	ekkkddddddddkeee	575
601241	2574	2589	Exon 18	TCCAGCAGGAAACCCC	10	7809	7824	ekkkddddddddkeee	576
601242	2575	2590	Exon 18	GTCCAGCAGGAAACCC	19	7810	7825	ekkkddddddddkeee	577
601243	2576	2591	Exon 18	TGTCCAGCAGGAAACC	10	7811	7826	ekkkddddddddkeee	578
601244	2577	2592	Exon 18	CTGTCCAGCAGGAAAC	28	7812	7827	ekkkddddddddkeee	579
601245	2578	2593	Exon 18	CCTGTCCAGCAGGAAA	5	7813	7828	ekkkddddddddkeee	580
601246	2579	2594	Exon 18	CCCTGTCCAGCAGGAA	18	7814	7829	ekkkddddddddkeee	581
601247	2580	2595	Exon 18	CCCCTGTCCAGCAGGA	4	7815	7830	ekkkddddddddkeee	582
601248	2581	2596	Exon 18	GCCCCTGTCCAGCAGG	6	7816	7831	ekkkddddddddkeee	583
601249	2582	2597	Exon 18	CGCCCCTGTCCAGCAG	18	7817	7832	ekkkddddddddkeee	584
601250	2583	2598	Exon 18	ACGCCCCTGTCCAGCA	26	7818	7833	ekkkddddddddkeee	585
601251	2584	2599	Exon 18	CACGCCCCTGTCCAGC	27	7819	7834	ekkkddddddddkeee	586
601252	2585	2600	Exon 18	CCACGCCCCTGTCCAG	21	7820	7835	ekkkddddddddkeee	587
601253	2586	2601	Exon 18	CCCACGCCCCTGTCCA	0	7821	7836	ekkkddddddddkeee	588
601254	2587	2602	Exon 18	TCCCACGCCCCTGTCC	31	7822	7837	ekkkddddddddkeee	589
601255	2588	2603	Exon 18	ATCCCACGCCCCTGTC	3	7823	7838	ekkkddddddddkeee	590
601256	2589	2604	Exon 18	AATCCCACGCCCCTGT	21	7824	7839	ekkkddddddddkeee	591
601257	2590	2605	Exon 18	CAATCCCACGCCCCTG	47	7825	7840	ekkkddddddddkeee	592
601258	2591	2606	Exon 18	TCAATCCCACGCCCCT	48	7826	7841	ekkkddddddddkeee	593
601259	2592	2607	Exon 18	TTCAATCCCACGCCCC	38	7827	7842	ekkkddddddddkeee	594
601260	2593	2608	Exon 18	ATTCAATCCCACGCCC	33	7828	7843	ekkkddddddddkeee	595
601261	2594	2609	Exon 18	AATTCAATCCCACGCC	17	7829	7844	ekkkddddddddkeee	596
601262	2595	2610	Exon 18	TAATTCAATCCCACGC	40	7830	7845	ekkkddddddddkeee	597
601263	2596	2611	Exon 18	TTAATTCAATCCCACG	31	7831	7846	ekkkddddddddkeee	598
601264	2597	2612	Exon 18	TTTAATTCAATCCCAC	72	7832	7847	ekkkddddddddkeee	599
601265	2598	2613	Exon 18	TTTTAATTCAATCCCA	48	7833	7848	ekkkddddddddkeee	600
601266	2599	2614	Exon 18	GTTTTAATTCAATCCC	64	7834	7849	ekkkddddddddkeee	601

601267	2600	2615	Exon 18	TGTTTTAATTCAATCC	43	7835	7850	ekkkddddddddkeee	602
601268	2601	2616	Exon 18	CTGTTTTAATTCAATC	44	7836	7851	ekkkddddddddkeee	603
601269	2602	2617	Exon 18	GCTGTTTTAATTCAAT	66	7837	7852	ekkkddddddddkeee	604
601270	2603	2618	Exon 18	AGCTGTTTTAATTCAA	47	7838	7853	ekkkddddddddkeee	605
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	3	7839	7858	eeeeeddddddddddeeeee	317
601271	2604	2619	Exon 18	CAGCTGTTTTAATTCA	26	7839	7854	ekkkddddddddkeee	606
601272	2605	2620	Exon 18	GCAGCTGTTTTAATTC	33	7840	7855	ekkkddddddddkeee	607
601273	2606	2621	Exon 18	CGCAGCTGTTTTAATT	34	7841	7856	ekkkddddddddkeee	608
601274	2607	2622	Exon 18	TCGCAGCTGTTTTAAT	39	7842	7857	ekkkddddddddkeee	609
588860	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	72	7843	7858	eekddddddddddkke	610
601275	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	65	7843	7858	ekkkddddddddkeee	610
601276	2609	2624	Exon 18	TGTCGCAGCTGTTTTA	65	7844	7859	ekkkddddddddkeee	611
601277	2610	2625	Exon 18	TTGTCGCAGCTGTTTT	51	7845	7860	ekkkddddddddkeee	612
601278	2611	2626	Exon 18	GTTGTCGCAGCTGTTT	78	7846	7861	ekkkddddddddkeee	613
601279	2612	2627	Exon 18	TGTTGTCGCAGCTGTT	79	7847	7862	ekkkddddddddkeee	614
601280	2613	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGT	70	n/a	n/a	ekkkddddddddkeee	615
601281	2614	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTG	78	n/a	n/a	ekkkddddddddkeee	616
601282	2615	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCT	68	n/a	n/a	ekkkddddddddkeee	617
601283	2616	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGC	61	n/a	n/a	ekkkddddddddkeee	618

Table 21

Inhibition of CFB mRNA by deoxy, MOE and cEt oligonucleotides targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
601306	2573	2588	Exon 18	CCAGCAGGAAACCCCT	22	7808	7823	ekkddddddddkkeee	575
601307	2574	2589	Exon 18	TCCAGCAGGAAACCCC	22	7809	7824	ekkddddddddkkeee	576
601308	2575	2590	Exon 18	GTCCAGCAGGAAACCC	33	7810	7825	ekkddddddddkkeee	577
601309	2576	2591	Exon 18	TGTCCAGCAGGAAACC	33	7811	7826	ekkddddddddkkeee	578
601310	2577	2592	Exon 18	CTGTCCAGCAGGAAAC	28	7812	7827	ekkddddddddkkeee	579
601311	2578	2593	Exon 18	CCTGTCCAGCAGGAAA	33	7813	7828	ekkddddddddkkeee	580
601312	2579	2594	Exon 18	CCCTGTCCAGCAGGAA	13	7814	7829	ekkddddddddkkeee	581
601313	2580	2595	Exon 18	CCCCTGTCCAGCAGGA	32	7815	7830	ekkddddddddkkeee	582
601314	2581	2596	Exon 18	GCCCCTGTCCAGCAGG	0	7816	7831	ekkddddddddkkeee	583
601315	2582	2597	Exon 18	CGCCCCTGTCCAGCAG	36	7817	7832	ekkddddddddkkeee	584
601316	2583	2598	Exon 18	ACGCCCCTGTCCAGCA	39	7818	7833	ekkddddddddkkeee	585
601317	2584	2599	Exon 18	CACGCCCCTGTCCAGC	33	7819	7834	ekkddddddddkkeee	586
601356	2584	2599	Exon 18	CACGCCCCTGTCCAGC	27	7819	7834	kkkddddddddkeeee	586
601318	2585	2600	Exon 18	CCACGCCCCTGTCCAG	35	7820	7835	ekkddddddddkkeee	587

601357	2585	2600	Exon 18	CCACGCCCCTGTCCAG	26	7820	7835	kkkddddddddkeeee	587
601319	2586	2601	Exon 18	CCCACGCCCCTGTCCA	33	7821	7836	ekkddddddddkkeee	588
601358	2586	2601	Exon 18	CCCACGCCCCTGTCCA	26	7821	7836	kkkddddddddkeeee	588
601320	2587	2602	Exon 18	TCCCACGCCCCTGTCC	25	7822	7837	ekkddddddddkkeee	589
601359	2587	2602	Exon 18	TCCCACGCCCCTGTCC	23	7822	7837	kkkddddddddkeeee	589
601321	2588	2603	Exon 18	ATCCCACGCCCCTGTC	50	7823	7838	ekkddddddddkkeee	590
601360	2588	2603	Exon 18	ATCCCACGCCCCTGTC	33	7823	7838	kkkddddddddkeeee	590
601322	2589	2604	Exon 18	AATCCCACGCCCCTGT	52	7824	7839	ekkddddddddkkeee	591
601361	2589	2604	Exon 18	AATCCCACGCCCCTGT	48	7824	7839	kkkddddddddkeeee	591
601323	2590	2605	Exon 18	CAATCCCACGCCCCTG	67	7825	7840	ekkddddddddkkeee	592
601362	2590	2605	Exon 18	CAATCCCACGCCCCTG	51	7825	7840	kkkddddddddkeeee	592
601324	2591	2606	Exon 18	TCAATCCCACGCCCCT	42	7826	7841	ekkddddddddkkeee	593
601363	2591	2606	Exon 18	TCAATCCCACGCCCCT	42	7826	7841	kkkddddddddkeeee	593
601325	2592	2607	Exon 18	TTCAATCCCACGCCCC	52	7827	7842	ekkddddddddkkeee	594
601364	2592	2607	Exon 18	TTCAATCCCACGCCCC	48	7827	7842	kkkddddddddkeeee	594
601326	2593	2608	Exon 18	ATTCAATCCCACGCCC	27	7828	7843	ekkddddddddkkeee	595
601365	2593	2608	Exon 18	ATTCAATCCCACGCCC	36	7828	7843	kkkddddddddkeeee	595
601327	2594	2609	Exon 18	AATTCAATCCCACGCC	66	7829	7844	ekkddddddddkkeee	596
601366	2594	2609	Exon 18	AATTCAATCCCACGCC	49	7829	7844	kkkddddddddkeeee	596
601328	2595	2610	Exon 18	TAATTCAATCCCACGC	55	7830	7845	ekkddddddddkkeee	597
601367	2595	2610	Exon 18	TAATTCAATCCCACGC	57	7830	7845	kkkddddddddkeeee	597
601329	2596	2611	Exon 18	TTAATTCAATCCCACG	69	7831	7846	ekkddddddddkkeee	598
601368	2596	2611	Exon 18	TTAATTCAATCCCACG	68	7831	7846	kkkddddddddkeeee	598
601330	2597	2612	Exon 18	TTTAATTCAATCCCAC	58	7832	7847	ekkddddddddkkeee	599
601369	2597	2612	Exon 18	TTTAATTCAATCCCAC	65	7832	7847	kkkddddddddkeeee	599
601331	2598	2613	Exon 18	TTTTAATTCAATCCCA	45	7833	7848	ekkddddddddkkeee	600
601370	2598	2613	Exon 18	TTTTAATTCAATCCCA	42	7833	7848	kkkddddddddkeeee	600
601332	2599	2614	Exon 18	GTTTTAATTCAATCCC	84	7834	7849	ekkddddddddkkeee	601
601371	2599	2614	Exon 18	GTTTTAATTCAATCCC	79	7834	7849	kkkddddddddkeeee	601
601333	2600	2615	Exon 18	TGTTTTAATTCAATCC	61	7835	7850	ekkddddddddkkeee	602
601372	2600	2615	Exon 18	TGTTTTAATTCAATCC	71	7835	7850	kkkddddddddkeeee	602
601334	2601	2616	Exon 18	CTGTTTTAATTCAATC	61	7836	7851	ekkddddddddkkeee	603
601373	2601	2616	Exon 18	CTGTTTTAATTCAATC	57	7836	7851	kkkddddddddkeeee	603
601335	2602	2617	Exon 18	GCTGTTTTAATTCAAT	73	7837	7852	ekkddddddddkkeee	604
601374	2602	2617	Exon 18	GCTGTTTTAATTCAAT	66	7837	7852	kkkddddddddkeeee	604
601336	2603	2618	Exon 18	AGCTGTTTTAATTCAA	64	7838	7853	ekkddddddddkkeee	605
601375	2603	2618	Exon 18	AGCTGTTTTAATTCAA	61	7838	7853	kkkddddddddkeeee	605
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	66	7839	7858	eeeeeddddddddddeeee	317
601337	2604	2619	Exon 18	CAGCTGTTTTAATTCA	53	7839	7854	ekkddddddddkkeee	606
601376	2604	2619	Exon 18	CAGCTGTTTTAATTCA	39	7839	7854	kkkddddddddkeeee	606
601338	2605	2620	Exon 18	GCAGCTGTTTTAATTC	67	7840	7855	ekkddddddddkkeee	607
601377	2605	2620	Exon 18	GCAGCTGTTTTAATTC	67	7840	7855	kkkddddddddkeeee	607

601339	2606	2621	Exon 18	CGCAGCTGTTTTAATT	63	7841	7856	ekkddddddddkkeee	608
601378	2606	2621	Exon 18	CGCAGCTGTTTTAATT	60	7841	7856	kkkddddddddkeeee	608
601340	2607	2622	Exon 18	TCGCAGCTGTTTTAAT	40	7842	7857	ekkddddddddkkeee	609
601379	2607	2622	Exon 18	TCGCAGCTGTTTTAAT	36	7842	7857	kkkddddddddkeeee	609
588860	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	84	7843	7858	eekddddddddddkke	610
601341	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	74	7843	7858	ekkddddddddkkeee	610
601380	2608	2623	Exon 18	GTCGCAGCTGTTTTAA	78	7843	7858	kkkddddddddkeeee	610
601342	2609	2624	Exon 18	TGTCGCAGCTGTTTTA	68	7844	7859	ekkddddddddkkeee	611
601381	2609	2624	Exon 18	TGTCGCAGCTGTTTTA	66	7844	7859	kkkddddddddkeeee	611
601343	2610	2625	Exon 18	TTGTCGCAGCTGTTTT	71	7845	7860	ekkddddddddkkeee	612
601382	2610	2625	Exon 18	TTGTCGCAGCTGTTTT	84	7845	7860	kkkddddddddkeeee	612
601344	2611	2626	Exon 18	GTTGTCGCAGCTGTTT	87	7846	7861	ekkddddddddkkeee	613
601383	2611	2626	Exon 18	GTTGTCGCAGCTGTTT	85	7846	7861	kkkddddddddkeeee	613
601345	2612	2627	Exon 18	TGTTGTCGCAGCTGTT	82	7847	7862	ekkddddddddkkeee	614
601384	2612	2627	Exon 18	TGTTGTCGCAGCTGTT	79	7847	7862	kkkddddddddkeeee	614
601346	2613	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGT	73	n/a	n/a	ekkddddddddkkeee	615
601385	2613	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGT	84	n/a	n/a	kkkddddddddkeeee	615
601347	2614	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTG	70	n/a	n/a	ekkddddddddkkeee	616
601386	2614	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTG	71	n/a	n/a	kkkddddddddkeeee	616
601348	2615	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCT	71	n/a	n/a	ekkddddddddkkeee	617
601387	2615	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCT	76	n/a	n/a	kkkddddddddkeeee	617
601349	2616	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGC	71	n/a	n/a	ekkddddddddkkeee	618
601388	2616	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGC	67	n/a	n/a	kkkddddddddkeeee	618

Table 22

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599357	2582	2600	Exon 18	CCACGCCCCTGTCCAGCAG	26	7817	7835	5-9-5	708
599358	2583	2601	Exon 18	CCCACGCCCCTGTCCAGCA	22	7818	7836	5-9-5	709
599359	2584	2602	Exon 18	TCCCACGCCCCTGTCCAGC	13	7819	7837	5-9-5	710
599360	2585	2603	Exon 18	ATCCCACGCCCCTGTCCAG	7	7820	7838	5-9-5	711
599361	2586	2604	Exon 18	AATCCCACGCCCCTGTCCA	11	7821	7839	5-9-5	712
599362	2587	2605	Exon 18	CAATCCCACGCCCCTGTCC	14	7822	7840	5-9-5	713
599363	2588	2606	Exon 18	TCAATCCCACGCCCCTGTC	17	7823	7841	5-9-5	714
599364	2589	2607	Exon 18	TTCAATCCCACGCCCCTGT	20	7824	7842	5-9-5	715

599365	2590	2608	Exon 18	ATTCAATCCCACGCCCCTG	22	7825	7843	5-9-5	716
599366	2591	2609	Exon 18	AATTCAATCCCACGCCCCT	13	7826	7844	5-9-5	717
599367	2592	2610	Exon 18	TAATTCAATCCCACGCCCC	11	7827	7845	5-9-5	718
599368	2593	2611	Exon 18	TTAATTCAATCCCACGCCC	10	7828	7846	5-9-5	719
599369	2594	2612	Exon 18	TTTAATTCAATCCCACGCC	19	7829	7847	5-9-5	720
599370	2595	2613	Exon 18	TTTTAATTCAATCCCACGC	23	7830	7848	5-9-5	721
599371	2596	2614	Exon 18	GTTTTAATTCAATCCCACG	4	7831	7849	5-9-5	722
599372	2597	2615	Exon 18	TGTTTTAATTCAATCCCAC	16	7832	7850	5-9-5	723
599373	2598	2616	Exon 18	CTGTTTTAATTCAATCCCA	3	7833	7851	5-9-5	724
599374	2599	2617	Exon 18	GCTGTTTTAATTCAATCCC	10	7834	7852	5-9-5	725
599375	2600	2618	Exon 18	AGCTGTTTTAATTCAATCC	17	7835	7853	5-9-5	726
599376	2601	2619	Exon 18	CAGCTGTTTTAATTCAATC	18	7836	7854	5-9-5	727
599377	2602	2620	Exon 18	GCAGCTGTTTTAATTCAAT	22	7837	7855	5-9-5	728
599378	2603	2621	Exon 18	CGCAGCTGTTTTAATTCAA	11	7838	7856	5-9-5	729
599511	2552	2571	Exon 18	ATAGAAAACCCAAATCCTCA	7	7787	7806	6-8-6	410
599389	2553	2572	Exon 18	TATAGAAAACCCAAATCCTC	22	7788	7807	6-8-6	411
599390	2554	2573	Exon 18	TTATAGAAAACCCAAATCCT	21	7789	7808	6-8-6	412
599391	2555	2574	Exon 18	CTTATAGAAAACCCAAATCC	27	7790	7809	6-8-6	413
599392	2556	2575	Exon 18	CCTTATAGAAAACCCAAATC	30	7791	7810	6-8-6	414
599393	2557	2576	Exon 18	CCCTTATAGAAAACCCAAAT	30	7792	7811	6-8-6	415
599394	2558	2577	Exon 18	CCCCTTATAGAAAACCCAAA	28	7793	7812	6-8-6	416
599395	2559	2578	Exon 18	ACCCCTTATAGAAAACCCAA	23	7794	7813	6-8-6	417
599396	2560	2579	Exon 18	AACCCCTTATAGAAAACCCA	53	7795	7814	6-8-6	418
599397	2561	2580	Exon 18	AAACCCCTTATAGAAAACCC	33	7796	7815	6-8-6	419
599398	2562	2581	Exon 18	GAAACCCCTTATAGAAAACC	58	7797	7816	6-8-6	420
599399	2563	2582	Exon 18	GGAAACCCCTTATAGAAAAC	23	7798	7817	6-8-6	421
599400	2564	2583	Exon 18	AGGAAACCCCTTATAGAAAA	54	7799	7818	6-8-6	422
599401	2565	2584	Exon 18	CAGGAAACCCCTTATAGAAA	30	7800	7819	6-8-6	423
599402	2566	2585	Exon 18	GCAGGAAACCCCTTATAGAA	25	7801	7820	6-8-6	424
599403	2567	2586	Exon 18	AGCAGGAAACCCCTTATAGA	17	7802	7821	6-8-6	425
599404	2568	2587	Exon 18	CAGCAGGAAACCCCTTATAG	20	7803	7822	6-8-6	426
599405	2569	2588	Exon 18	CCAGCAGGAAACCCCTTATA	12	7804	7823	6-8-6	427
599406	2570	2589	Exon 18	TCCAGCAGGAAACCCCTTAT	51	7805	7824	6-8-6	428
599407	2571	2590	Exon 18	GTCCAGCAGGAAACCCCTTA	39	7806	7825	6-8-6	237
599408	2572	2591	Exon 18	TGTCCAGCAGGAAACCCCTT	53	7807	7826	6-8-6	429
599409	2573	2592	Exon 18	CTGTCCAGCAGGAAACCCCT	65	7808	7827	6-8-6	430
599410	2574	2593	Exon 18	CCTGTCCAGCAGGAAACCCC	56	7809	7828	6-8-6	431
599411	2575	2594	Exon 18	CCCTGTCCAGCAGGAAACCC	60	7810	7829	6-8-6	432
599412	2576	2595	Exon 18	CCCCTGTCCAGCAGGAAACC	61	7811	7830	6-8-6	433
599413	2577	2596	Exon 18	GCCCCTGTCCAGCAGGAAAC	40	7812	7831	6-8-6	238
599414	2578	2597	Exon 18	CGCCCCTGTCCAGCAGGAAA	41	7813	7832	6-8-6	434
599415	2579	2598	Exon 18	ACGCCCCTGTCCAGCAGGAA	37	7814	7833	6-8-6	435
599416	2580	2599	Exon 18	CACGCCCCTGTCCAGCAGGA	54	7815	7834	6-8-6	436

599417	2581	2600	Exon 18	CCACGCCCCTGTCCAGCAGG	36	7816	7835	6-8-6	437
599418	2582	2601	Exon 18	CCCACGCCCCTGTCCAGCAG	53	7817	7836	6-8-6	438
599419	2583	2602	Exon 18	TCCCACGCCCCTGTCCAGCA	54	7818	7837	6-8-6	439
599420	2584	2603	Exon 18	ATCCCACGCCCCTGTCCAGC	50	7819	7838	6-8-6	440
599421	2585	2604	Exon 18	AATCCCACGCCCCTGTCCAG	48	7820	7839	6-8-6	441
599422	2586	2605	Exon 18	CAATCCCACGCCCCTGTCCA	55	7821	7840	6-8-6	442
599423	2587	2606	Exon 18	TCAATCCCACGCCCCTGTCC	75	7822	7841	6-8-6	443
599424	2588	2607	Exon 18	TTCAATCCCACGCCCCTGTC	69	7823	7842	6-8-6	444
599425	2589	2608	Exon 18	ATTCAATCCCACGCCCCTGT	77	7824	7843	6-8-6	445
599426	2590	2609	Exon 18	AATTCAATCCCACGCCCCTG	60	7825	7844	6-8-6	446
599427	2591	2610	Exon 18	TAATTCAATCCCACGCCCCT	72	7826	7845	6-8-6	447
599428	2592	2611	Exon 18	TTAATTCAATCCCACGCCCC	81	7827	7846	6-8-6	448
599429	2593	2612	Exon 18	TTTAATTCAATCCCACGCCC	68	7828	7847	6-8-6	449
599430	2594	2613	Exon 18	TTTTAATTCAATCCCACGCC	58	7829	7848	6-8-6	450
599431	2595	2614	Exon 18	GTTTTAATTCAATCCCACGC	70	7830	7849	6-8-6	451
599432	2596	2615	Exon 18	TGTTTTAATTCAATCCCACG	85	7831	7850	6-8-6	452
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	85	7839	7858	5-10-5	317
599379	2604	2622	Exon 18	TCGCAGCTGTTTTAATTCA	73	7839	7857	5-9-5	730
599380	2605	2623	Exon 18	GTCGCAGCTGTTTTAATTC	77	7840	7858	5-9-5	731
599381	2606	2624	Exon 18	TGTCGCAGCTGTTTTAATT	69	7841	7859	5-9-5	732
599382	2607	2625	Exon 18	TTGTCGCAGCTGTTTTAAT	58	7842	7860	5-9-5	733
599383	2608	2626	Exon 18	GTTGTCGCAGCTGTTTTAA	52	7843	7861	5-9-5	734
599384	2609	2627	Exon 18	TGTTGTCGCAGCTGTTTTA	63	7844	7862	5-9-5	735
599385	2610	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTTT	53	n/a	n/a	5-9-5	736
599386	2611	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTTT	63	n/a	n/a	5-9-5	737
599387	2612	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGTT	64	n/a	n/a	5-9-5	438
599388	2613	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTGT	66	n/a	n/a	5-9-5	739

Table 23

Inhibition of CFB mRNA by MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	Motif	SEQ ID NO:
599213	2553	2570	Exon 18	TAGAAAACCCAAATCCTC	0	7788	7805	3-10-5	785
599214	2554	2571	Exon 18	ATAGAAAACCCAAATCCT	0	7789	7806	3-10-5	786
599215	2555	2572	Exon 18	TATAGAAAACCCAAATCC	36	7790	7807	3-10-5	787
599216	2556	2573	Exon 18	TTATAGAAAACCCAAATC	8	7791	7808	3-10-5	788
599217	2557	2574	Exon 18	CTTATAGAAAACCCAAAT	5	7792	7809	3-10-5	789
599218	2558	2575	Exon 18	CCTTATAGAAAACCCAAA	0	7793	7810	3-10-5	790

599219	2559	2576	Exon 18	CCCTTATAGAAAACCCAA	8	7794	7811	3-10-5	791
599220	2560	2577	Exon 18	CCCCTTATAGAAAACCCA	0	7795	7812	3-10-5	740
599221	2561	2578	Exon 18	ACCCCTTATAGAAAACCC	54	7796	7813	3-10-5	741
599222	2562	2579	Exon 18	AACCCCTTATAGAAAACC	3	7797	7814	3-10-5	742
599223	2563	2580	Exon 18	AAACCCCTTATAGAAAAC	0	7798	7815	3-10-5	743
599224	2564	2581	Exon 18	GAAACCCCTTATAGAAAA	0	7799	7816	3-10-5	744
599225	2566	2583	Exon 18	AGGAAACCCCTTATAGAA	60	7801	7818	3-10-5	745
599226	2567	2584	Exon 18	CAGGAAACCCCTTATAGA	0	7802	7819	3-10-5	746
599227	2568	2585	Exon 18	GCAGGAAACCCCTTATAG	37	7803	7820	3-10-5	747
599228	2569	2586	Exon 18	AGCAGGAAACCCCTTATA	0	7804	7821	3-10-5	748
599229	2570	2587	Exon 18	CAGCAGGAAACCCCTTAT	39	7805	7822	3-10-5	749
599230	2571	2588	Exon 18	CCAGCAGGAAACCCCTTA	10	7806	7823	3-10-5	750
599231	2572	2589	Exon 18	TCCAGCAGGAAACCCCTT	16	7807	7824	3-10-5	751
599232	2573	2590	Exon 18	GTCCAGCAGGAAACCCCT	9	7808	7825	3-10-5	752
599233	2574	2591	Exon 18	TGTCCAGCAGGAAACCCC	44	7809	7826	3-10-5	753
599234	2575	2592	Exon 18	CTGTCCAGCAGGAAACCC	14	7810	7827	3-10-5	754
599235	2576	2593	Exon 18	CCTGTCCAGCAGGAAACC	0	7811	7828	3-10-5	755
599236	2577	2594	Exon 18	CCCTGTCCAGCAGGAAAC	43	7812	7829	3-10-5	756
599237	2578	2595	Exon 18	CCCCTGTCCAGCAGGAAA	0	7813	7830	3-10-5	757
599238	2580	2597	Exon 18	CGCCCCTGTCCAGCAGGA	9	7815	7832	3-10-5	758
599239	2581	2598	Exon 18	ACGCCCCTGTCCAGCAGG	36	7816	7833	3-10-5	759
599240	2582	2599	Exon 18	CACGCCCCTGTCCAGCAG	11	7817	7834	3-10-5	760
599241	2583	2600	Exon 18	CCACGCCCCTGTCCAGCA	51	7818	7835	3-10-5	761
599242	2584	2601	Exon 18	CCCACGCCCCTGTCCAGC	7	7819	7836	3-10-5	762
599243	2585	2602	Exon 18	TCCCACGCCCCTGTCCAG	47	7820	7837	3-10-5	763
599244	2586	2603	Exon 18	ATCCCACGCCCCTGTCCA	37	7821	7838	3-10-5	764
599245	2587	2604	Exon 18	AATCCCACGCCCCTGTCC	35	7822	7839	3-10-5	765
599246	2588	2605	Exon 18	CAATCCCACGCCCCTGTC	21	7823	7840	3-10-5	766
599247	2589	2606	Exon 18	TCAATCCCACGCCCCTGT	61	7824	7841	3-10-5	767
599248	2590	2607	Exon 18	TTCAATCCCACGCCCCTG	51	7825	7842	3-10-5	768
599249	2591	2608	Exon 18	ATTCAATCCCACGCCCCT	58	7826	7843	3-10-5	769
599250	2592	2609	Exon 18	AATTCAATCCCACGCCCC	49	7827	7844	3-10-5	770
599251	2593	2610	Exon 18	TAATTCAATCCCACGCCC	46	7828	7845	3-10-5	771
599252	2594	2611	Exon 18	TTAATTCAATCCCACGCC	32	7829	7846	3-10-5	772
599253	2595	2612	Exon 18	TTTAATTCAATCCCACGC	23	7830	7847	3-10-5	773
599254	2596	2613	Exon 18	TTTTAATTCAATCCCACG	0	7831	7848	3-10-5	774
599255	2597	2614	Exon 18	GTTTTAATTCAATCCCAC	61	7832	7849	3-10-5	775
599256	2598	2615	Exon 18	TGTTTTAATTCAATCCCA	64	7833	7850	3-10-5	776
599257	2599	2616	Exon 18	CTGTTTTAATTCAATCCC	66	7834	7851	3-10-5	777
599258	2600	2617	Exon 18	GCTGTTTTAATTCAATCC	59	7835	7852	3-10-5	778
599259	2601	2618	Exon 18	AGCTGTTTTAATTCAATC	40	7836	7853	3-10-5	779
599260	2602	2619	Exon 18	CAGCTGTTTTAATTCAAT	38	7837	7854	3-10-5	780
599261	2603	2620	Exon 18	GCAGCTGTTTTAATTCAA	54	7838	7855	3-10-5	781

599509	2552	2570	Exon 18	TAGAAAACCCAAATCCTCA	54	7787	7805	6-7-6	681
599273	2553	2571	Exon 18	ATAGAAAACCCAAATCCTC	0	7788	7806	6-7-6	682
599274	2554	2572	Exon 18	TATAGAAAACCCAAATCCT	57	7789	7807	6-7-6	683
599275	2556	2574	Exon 18	CTTATAGAAAACCCAAATC	0	7791	7809	6-7-6	684
599276	2557	2575	Exon 18	CCTTATAGAAAACCCAAAT	44	7792	7810	6-7-6	685
599277	2558	2576	Exon 18	CCCTTATAGAAAACCCAAA	0	7793	7811	6-7-6	686
599278	2559	2577	Exon 18	CCCCTTATAGAAAACCCAA	0	7794	7812	6-7-6	687
599279	2560	2578	Exon 18	ACCCCTTATAGAAAACCCA	20	7795	7813	6-7-6	688
599280	2561	2579	Exon 18	AACCCCTTATAGAAAACCC	70	7796	7814	6-7-6	689
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	85	7839	7858	5-10-5	317
599262	2604	2621	Exon 18	CGCAGCTGTTTTAATTCA	49	7839	7856	3-10-5	782
599263	2605	2622	Exon 18	TCGCAGCTGTTTTAATTC	49	7840	7857	3-10-5	783
599264	2606	2623	Exon 18	GTCGCAGCTGTTTTAATT	62	7841	7858	3-10-5	784
599265	2607	2624	Exon 18	TGTCGCAGCTGTTTTAAT	63	7842	7859	3-10-5	792
599266	2608	2625	Exon 18	TTGTCGCAGCTGTTTTAA	41	7843	7860	3-10-5	793
599267	2609	2626	Exon 18	GTTGTCGCAGCTGTTTTA	52	7844	7861	3-10-5	794
599268	2610	2627	Exon 18	TGTTGTCGCAGCTGTTTT	51	7845	7862	3-10-5	795
599269	2611	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTT	58	n/a	n/a	3-10-5	796
599270	2612	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTT	69	n/a	n/a	3-10-5	797
599271	2613	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGT	69	n/a	n/a	3-10-5	798
599272	2614	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTG	72	n/a	n/a	3-10-5	799
599205	2607	2624	Exon 18	TGTCGCAGCTGTTTTAAT	54	7842	7859	5-8-5	792
599206	2608	2625	Exon 18	TTGTCGCAGCTGTTTTAA	62	7843	7860	5-8-5	793
599207	2609	2626	Exon 18	GTTGTCGCAGCTGTTTTA	62	7844	7861	5-8-5	794
599208	2610	2627	Exon 18	TGTTGTCGCAGCTGTTTT	66	7845	7862	5-8-5	795
599209	2611	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTT	60	n/a	n/a	5-8-5	796
599210	2612	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTT	62	n/a	n/a	5-8-5	797
599211	2613	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGT	65	n/a	n/a	5-8-5	798
599212	2614	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTG	67	n/a	n/a	5-8-5	799

Table 24

Inhibition of CFB mRNA by 5-10-5 MOE gapmers targeting SEQ ID NO: 1 or SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 start site	SEQ ID NO: 1 stop site	Target region	Sequence	% inhibition	SEQ ID NO: 2 start site	SEQ ID NO: 2 stop site	SEQ ID NO:
588570	150	169	Exon 1	TGGTCACATTCCCTTCCCCT	72	1871	1890	396

588571	152	171	Exon 1	CCTGGTCACATTCCCTTCCC	80	1873	1892	397
532614	154	173	Exon 1	GACCTGGTCACATTCCCTTC	65	1875	1894	12
588572	156	175	Exon 1	TAGACCTGGTCACATTCCCT	74	1877	1896	398
588573	158	177	Exon 1	CCTAGACCTGGTCACATTCC	72	1879	1898	399
588566	2189	2208	Exon 15	CCTTCCGAGTCAGCTTTTTC	66	6977	6996	400
588567	2191	2210	Exon 15	CTCCTTCCGAGTCAGCTTTT	66	6979	6998	401
532770	2193	2212	Exon 15	ACCTCCTTCCGAGTCAGCTT	64	6981	7000	198
588568	2195	2214	Exon 15	AGACCTCCTTCCGAGTCAGC	78	6983	7002	402
588569	2197	2216	Exon 15	GTAGACCTCCTTCCGAGTCA	74	6985	7004	403
588574	2453	2472	Exon 18	TTTGCCGCTTCTGGTTTTTG	71	7688	7707	404
588575	2455	2474	Exon 18	CTTTTGCCGCTTCTGGTTTT	72	7690	7709	405
532800	2457	2476	Exon 18	TGCTTTTGCCGCTTCTGGTT	71	7692	7711	228
588576	2459	2478	Exon 18	CCTGCTTTTGCCGCTTCTGG	59	7694	7713	406
588577	2461	2480	Exon 18	TACCTGCTTTTGCCGCTTCT	76	7696	7715	407
516350	2550	2569	Exon 18	AGAAAACCCAAATCCTCATC	58	7785	7804	408
588509	2551	2570	Exon 18	TAGAAAACCCAAATCCTCAT	6	7786	7805	409
588510	2552	2571	Exon 18	ATAGAAAACCCAAATCCTCA	10	7787	7806	410
588511	2553	2572	Exon 18	TATAGAAAACCCAAATCCTC	9	7788	7807	411
588512	2554	2573	Exon 18	TTATAGAAAACCCAAATCCT	80	7789	7808	412
588513	2555	2574	Exon 18	CTTATAGAAAACCCAAATCC	70	7790	7809	413
588514	2556	2575	Exon 18	CCTTATAGAAAACCCAAATC	71	7791	7810	414
588515	2557	2576	Exon 18	CCCTTATAGAAAACCCAAAT	78	7792	7811	415
588516	2558	2577	Exon 18	CCCCTTATAGAAAACCCAAA	72	7793	7812	416
588517	2559	2578	Exon 18	ACCCCTTATAGAAAACCCAA	80	7794	7813	417
588518	2560	2579	Exon 18	AACCCCTTATAGAAAACCCA	80	7795	7814	418
588519	2561	2580	Exon 18	AAACCCCTTATAGAAAACCC	62	7796	7815	419
588520	2562	2581	Exon 18	GAAACCCCTTATAGAAAACC	59	7797	7816	420
588521	2563	2582	Exon 18	GGAAACCCCTTATAGAAAAC	40	7798	7817	421
588522	2564	2583	Exon 18	AGGAAACCCCTTATAGAAAA	66	7799	7818	422
588523	2565	2584	Exon 18	CAGGAAACCCCTTATAGAAA	63	7800	7819	423
588524	2566	2585	Exon 18	GCAGGAAACCCCTTATAGAA	70	7801	7820	424
588525	2567	2586	Exon 18	AGCAGGAAACCCCTTATAGA	67	7802	7821	425
588526	2568	2587	Exon 18	CAGCAGGAAACCCCTTATAG	0	7803	7822	426
588527	2569	2588	Exon 18	CCAGCAGGAAACCCCTTATA	11	7804	7823	427
588528	2570	2589	Exon 18	TCCAGCAGGAAACCCCTTAT	15	7805	7824	428
532809	2571	2590	Exon 18	GTCCAGCAGGAAACCCCTTA	75	7806	7825	237
588529	2572	2591	Exon 18	TGTCCAGCAGGAAACCCCTT	16	7807	7826	429
588530	2573	2592	Exon 18	CTGTCCAGCAGGAAACCCCT	16	7808	7827	430
588531	2574	2593	Exon 18	CCTGTCCAGCAGGAAACCCC	19	7809	7828	431
588532	2575	2594	Exon 18	CCCTGTCCAGCAGGAAACCC	15	7810	7829	432
588533	2576	2595	Exon 18	CCCCTGTCCAGCAGGAAACC	29	7811	7830	433
532810	2577	2596	Exon 18	GCCCCTGTCCAGCAGGAAAC	74	7812	7831	238
588534	2578	2597	Exon 18	CGCCCCTGTCCAGCAGGAAA	21	7813	7832	434

588535	2579	2598	Exon 18	ACGCCCCTGTCCAGCAGGAA	16	7814	7833	435
588536	2580	2599	Exon 18	CACGCCCCTGTCCAGCAGGA	0	7815	7834	436
588537	2581	2600	Exon 18	CCACGCCCCTGTCCAGCAGG	8	7816	7835	437
588538	2582	2601	Exon 18	CCCACGCCCCTGTCCAGCAG	10	7817	7836	438
588539	2583	2602	Exon 18	TCCCACGCCCCTGTCCAGCA	23	7818	7837	439
588540	2584	2603	Exon 18	ATCCCACGCCCCTGTCCAGC	16	7819	7838	440
588541	2585	2604	Exon 18	AATCCCACGCCCCTGTCCAG	16	7820	7839	441
588542	2586	2605	Exon 18	CAATCCCACGCCCCTGTCCA	12	7821	7840	442
588543	2587	2606	Exon 18	TCAATCCCACGCCCCTGTCC	26	7822	7841	443
588544	2588	2607	Exon 18	TTCAATCCCACGCCCCTGTC	26	7823	7842	444
588545	2589	2608	Exon 18	ATTCAATCCCACGCCCCTGT	31	7824	7843	445
588546	2590	2609	Exon 18	AATTCAATCCCACGCCCCTG	22	7825	7844	446
588547	2591	2610	Exon 18	TAATTCAATCCCACGCCCCT	12	7826	7845	447
588548	2592	2611	Exon 18	TTAATTCAATCCCACGCCCC	20	7827	7846	448
588549	2593	2612	Exon 18	TTTAATTCAATCCCACGCCC	26	7828	7847	449
588550	2594	2613	Exon 18	TTTTAATTCAATCCCACGCC	32	7829	7848	450
588551	2595	2614	Exon 18	GTTTTAATTCAATCCCACGC	48	7830	7849	451
588552	2596	2615	Exon 18	TGTTTTAATTCAATCCCACG	57	7831	7850	452
588553	2597	2616	Exon 18	CTGTTTTAATTCAATCCCAC	49	7832	7851	453
588554	2598	2617	Exon 18	GCTGTTTTAATTCAATCCCA	64	7833	7852	454
532811	2599	2618	Exon 18	AGCTGTTTTAATTCAATCCC	78	7834	7853	239
588555	2600	2619	Exon 18	CAGCTGTTTTAATTCAATCC	48	7835	7854	455
588556	2601	2620	Exon 18	GCAGCTGTTTTAATTCAATC	55	7836	7855	456
588557	2602	2621	Exon 18	CGCAGCTGTTTTAATTCAAT	51	7837	7856	457
588558	2603	2622	Exon 18	TCGCAGCTGTTTTAATTCAA	51	7838	7857	458
532917	2604	2623	Exon 18	GTCGCAGCTGTTTTAATTCA	82	7839	7858	317
588559	2605	2624	Exon 18	TGTCGCAGCTGTTTTAATTC	58	7840	7859	459
588560	2606	2625	Exon 18	TTGTCGCAGCTGTTTTAATT	72	7841	7860	460
588561	2607	2626	Exon 18	GTTGTCGCAGCTGTTTTAAT	75	7842	7861	461
532952	2608	2627	Exon 18	TGTTGTCGCAGCTGTTTTAA	39	7843	7862	395
588562	2609	2628	Exon 18 / Repeat	TTGTTGTCGCAGCTGTTTTA	53	n/a	n/a	462
588563	2610	2629	Exon 18 / Repeat	TTTGTTGTCGCAGCTGTTTT	62	n/a	n/a	463
588564	2611	2630	Exon 18 / Repeat	TTTTGTTGTCGCAGCTGTTT	63	n/a	n/a	464
588565	2612	2631	Exon 18 / Repeat	TTTTTGTTGTCGCAGCTGTT	64	n/a	n/a	465

Example 8: Dose-dependent antisense inhibition of human CFB in HepG2 cells by 5-10-5 MOE gapmers

Gapmers from studies described above exhibiting *in vitro* inhibition of CFB mRNA were selected and tested at various doses in HepG2 cells. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.313 μM, 0.625 μM, 1.25 μM, 2.50 μM, 5.00 μM, or 10.00 μM concentrations of antisense oligonucleotide, as specified in the Table below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. CFB mRNA levels were reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 25

ISIS No	0.313 μM	0.625 μM	1.25 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532614	7	13	43	72	65	71	2.2
532635	12	0	3	28	0	0	>10
532692	26	0	12	52	55	74	3.7
532770	21	18	32	73	64	88	1.8
532775	8	0	26	35	47	59	6.2
532800	0	5	30	65	50	75	3.1
532809	12	30	28	40	46	66	4.6
532810	28	44	32	69	84	95	1.2
532811	66	83	90	94	97	99	<0.3
532917	64	85	88	96	97	99	<0.3
532952	50	53	68	80	91	94	0.4

Example 9: Dose-dependent antisense inhibition of human CFB in HepG2 cells

Gapmers from studies described above exhibiting *in vitro* inhibition of CFB mRNA were selected and tested at various doses in HepG2 cells. The antisense oligonucleotides were tested in a number of experiments with similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.08 μM, 0.25 μM, 0.74 μM, 2.22 μM, 6.67 μM, and 20.00 μM concentrations of antisense oligonucleotide, as specified in the Table below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according

to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. CFB mRNA levels were reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 26

ISIS No	0.08 μM	0.25 μM	0.74 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
532811	19	53	81	87	96	97	0.2
588834	7	42	64	92	98	98	0.5
588835	11	30	66	89	97	97	0.5
588836	14	40	61	91	97	97	0.5
588837	6	39	67	89	96	97	0.5
588838	0	27	41	81	87	97	1.0
588842	17	51	68	86	93	95	0.3
588843	21	38	72	90	95	96	0.4
588870	9	31	56	88	95	97	0.6
588871	14	25	47	79	93	97	0.7
588872	18	28	59	84	92	97	0.6

Table 27

ISIS No	0.08 μM	0.25 μM	0.74 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
532811	31	70	89	94	97	97	0.1
588844	31	60	77	91	95	96	0.1
588846	32	52	78	89	95	97	0.2
588847	22	52	77	91	95	97	0.2
588848	20	40	73	91	96	98	0.3
588851	40	52	82	94	97	97	0.1
588854	17	55	59	84	94	96	0.4
588855	10	32	56	82	93	96	0.6
588856	13	46	75	90	96	97	0.3
588857	11	52	73	94	96	97	0.3
588858	19	48	75	94	97	98	0.3

Table 28

ISIS No	0.08 μM	0.25 μM	0.74 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
532811	42	66	88	96	97	98	0.1
588859	18	46	66	90	96	97	0.4
588860	55	80	94	97	97	97	<0.1
588861	24	61	86	93	96	97	0.2

588862	25	64	85	94	96	98	0.1
588863	50	73	89	96	96	98	<0.1
588864	52	80	92	96	98	98	<0.1
588865	46	72	91	96	96	99	<0.1
588866	47	76	88	96	97	98	<0.1
588867	43	69	83	92	96	99	0.1
588868	43	56	65	84	93	97	0.1

Table 29

ISIS No	0.08 μM	0.25 μM	0.74 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
532810	0	14	38	72	89	96	1.2
532811	18	54	79	93	96	97	0.3
532952	19	34	73	87	94	96	0.4
588534	17	13	44	77	93	97	0.9
588544	12	43	69	86	89	93	0.4
588545	17	55	67	86	91	93	0.3
588546	10	32	67	85	91	93	0.6
588552	27	54	76	90	94	97	0.2
588553	32	68	87	93	95	97	0.1
588560	16	54	76	90	94	96	0.3
588561	18	45	68	85	93	96	0.4

Table 30

ISIS No	0.08 μM	0.25 μM	0.74 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
532811	22	60	82	94	97	98	0.2
588536	2	38	65	90	96	97	0.6
588537	12	38	63	87	94	97	0.5
588547	19	35	61	86	93	97	0.5
588548	19	36	75	88	95	96	0.4
588554	0	76	92	95	97	97	<0.1
588555	31	61	89	96	97	98	0.1
588556	33	56	82	95	94	97	0.1
588562	12	39	71	87	94	97	0.4
588563	25	48	72	86	94	96	0.3
588564	15	33	63	89	91	97	0.5

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Table 31

ISIS No	0.08 μM	0.25 μM	0.74 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
532811	39	68	86	96	98	98	0.1
588538	0	40	82	94	97	98	0.3

588539	34	65	88	95	98	98	0.1
588540	30	51	81	91	97	98	0.2
588549	31	57	82	95	96	98	0.1
588550	34	65	88	96	98	98	0.1
588551	47	66	87	96	98	99	<0.1
588557	40	84	95	98	98	98	<0.1
588558	45	73	93	97	98	99	<0.1
588559	51	69	83	96	98	99	<0.1
588565	19	56	81	92	96	98	0.2

Example 10: Dose-dependent antisense inhibition of human CFB in HepG2 cells

Gapmers from studies described above exhibiting *in vitro* inhibition of CFB mRNA were selected and tested at various doses in HepG2 cells. The antisense oligonucleotides were tested in a number of experiments with similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.06 μM, 0.25 μM, 1.00 μM, and 4.00 μM concentrations of antisense oligonucleotide, as specified in the Table below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. CFB mRNA levels were reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 32

ISIS No	0.06 μM	0.25 μM	1.00 μM	4.00 μM	IC_{50} (μM)
532917	31	58	87	92	0.2
588860	18	50	79	93	0.3
599001	16	28	69	90	0.5
599024	14	32	74	90	0.4
599025	0	31	56	92	0.7
599032	28	44	62	88	0.3
599033	28	46	80	92	0.2
599077	8	20	59	80	0.8
599080	9	33	48	76	0.9
599086	7	22	53	83	0.8
599087	21	31	74	87	0.4

599088	13	37	69	82	0.5
599089	3	36	55	79	0.7
599093	25	59	79	88	0.2
599094	19	29	75	89	0.4
599095	29	43	67	87	0.3
599096	23	51	70	88	0.3
599149	20	53	82	92	0.3
599188	0	21	62	85	0.8

Table 33

ISIS No	0.06 μM	0.25 μM	1.00 μM	4.00 μM	IC_{50} (μM)
532917	0	42	81	91	0.4
588860	17	49	74	92	0.3
599155	29	52	67	87	0.3
599198	3	25	64	89	0.6
599201	13	26	67	91	0.5
599202	0	44	72	87	0.5
599203	22	41	75	88	0.3
599314	12	34	71	84	0.5
599316	7	37	66	88	0.5
599317	8	1	54	83	1.0
599321	8	33	70	85	0.5
599322	24	38	66	87	0.4
599327	22	32	66	89	0.4
599328	0	31	59	88	0.7
599330	5	43	67	84	0.5
599374	23	42	80	91	0.3
599378	21	57	80	93	0.2
599380	23	56	82	93	0.2
599432	17	37	73	93	0.4

Table 34

ISIS No	0.06 μM	0.25 μM	1.00 μM	4.00 μM	IC_{50} (μM)
532917	23	65	76	93	0.2
588860	17	60	76	90	0.3
601282	48	68	81	88	0.1
601269	18	59	80	94	0.2
601276	34	64	81	91	0.1
601275	14	39	78	90	0.4
601344	52	84	92	94	<0.06

601383	53	81	86	94	<0.06
601382	41	76	88	94	0.1
601385	52	74	89	91	<0.06
601332	41	69	86	94	0.1
601345	36	75	86	95	0.1
601371	34	72	91	93	0.1
601384	50	78	91	95	<0.06
601380	28	57	83	92	0.2
601387	48	61	82	88	0.1
601341	28	65	83	91	0.2
601346	31	69	82	93	0.1
601335	24	56	85	92	0.2

Table 35

ISIS No	0.06 μM	0.25 μM	1.00 μM	4.00 μM	IC_{50} (μM)
532917	31	66	86	93	0.1
588860	28	62	85	94	0.2
599208	24	50	71	89	0.3
599261	31	49	81	94	0.2
599267	41	48	80	88	0.2
599268	28	56	75	92	0.2
599313	14	24	71	92	0.5
599441	24	57	80	87	0.2
599494	13	55	86	94	0.3
599552	30	69	93	95	0.1
599553	34	71	93	96	0.1
599554	30	74	93	96	0.1
599568	40	77	90	97	0.1
599570	61	82	93	96	<0.06
599577	18	62	81	93	0.2
599581	27	60	80	94	0.2
599591	49	74	93	96	<0.06
599592	46	76	90	94	0.1
599593	44	72	91	95	0.1

Table 36

ISIS No	0.06 μM	0.25 μM	1.00 μM	4.00 μM	IC_{50} (μM)
532917	25	56	84	92	0.2
588860	11	51	80	92	0.3
599547	23	60	82	90	0.2

599569	42	73	85	88	0.1
599578	29	49	82	89	0.2
599582	21	56	78	91	0.2
599590	24	62	80	90	0.2
601209	21	49	85	88	0.3
601210	34	64	86	92	0.1
601212	46	68	88	90	0.1
601213	54	80	90	92	<0.06
601214	38	77	88	95	0.1
601215	42	64	85	92	0.1
601216	45	57	76	89	0.1
601264	29	58	86	95	0.2
601278	51	82	83	93	<0.06
601279	44	80	92	96	0.1
601280	44	73	87	94	0.1
601281	51	80	91	94	<0.06

Example 11: Dose-dependent antisense inhibition of human CFB in HepG2 cells

Gapmers from studies described above exhibiting *in vitro* inhibition of CFB mRNA were selected and tested at various doses in HepG2 cells. Additionally, a deoxy, MOE and cEt oligonucleotide, ISIS 594430, was designed with the same sequence (CTCCTTCCGAGTCAGC, SEQ ID NO: 549) and target region (target start site 2195 of SEQ ID NO: 1 and target start site 6983 of SED ID NO: 2) as ISIS 588870, another deoxy, MOE, and cEt oligonucleotide. ISIS 594430 is a 3-10-3 cEt gapmer.

Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.01 μM, 0.04 μM,0.12 μM, 0.37 μM, 1.11 μM, 3.33 μM, and 10.00 μM concentrations of antisense oligonucleotide, as specified in the Table below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and CFB mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3459 was used to measure mRNA levels. CFB mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of CFB, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. CFB mRNA levels were reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 37

ISIS No	0.01 μM	0.04 μM	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
588536	0	0	0	5	45	73	94	1.4
588548	0	0	0	19	52	78	90	1.2

588553	0	0	9	42	76	85	94	0.6
588555	0	52	23	58	78	83	95	0.3
588847	4	1	18	45	67	84	96	0.5
588848	0	3	13	38	67	83	95	0.6
594430	0	0	10	34	50	55	84	1.4

Example 12: Tolerability of MOE gapmers targeting human CFB in CD1 mice

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

Study 1 (with 5-10-5 MOE gapmers)

Groups of seven-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 100 mg/kg of ISIS oligonucleotide. A group of male CD1 mice was injected subcutaneously once a week for 6 weeks with PBS. One group of mice was injected with subcutaneously once a week for 6 weeks with 100 mg/kg of control oligonucleotide ISIS 141923 (CCTTCCCTGAAGGTTCCTCC, designated herein as SEQ ID NO: 809, 5-10-5 MOE gapmer with no known murine target). Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

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

Table 38

Plasma chemistry markers in CD1 mice plasma on day 40

	ALT (IU/L)	AST (IU/L)	BUN (mg/dL)
PBS	25	46	20
ISIS 532614	513	407	22
ISIS 532692	131	130	24
ISIS 532770	36	53	25
ISIS 532775	193	158	23
ISIS 532800	127	110	25
ISIS 532809	36	42	22
ISIS 532810	229	286	26
ISIS 532811	197	183	21

ISIS 532917	207	204	27
ISIS 532952	246	207	25
ISIS 141923	39	67	23

Weights

Body weights of the mice were measured on day 40 before sacrificing the mice. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed. The results are presented in the Table below. ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 39

Weights (g) of CD1 mice on day 40

	Body	Kidney	Liver	Spleen
PBS	44	0.8	2.0	0.1
ISIS 532614	43	0.7	4.3	0.2
ISIS 532692	42	0.7	2.6	0.2
ISIS 532770	42	0.6	2.3	0.2
ISIS 532775	42	0.7	2.5	0.2
ISIS 532800	43	0.6	2.8	0.3
ISIS 532809	42	0.6	2.2	0.1
ISIS 532810	43	0.6	2.3	0.2
ISIS 532811	41	0.7	2.4	0.2
ISIS 532917	42	0.7	3.0	0.2
ISIS 532952	44	0.8	2.5	0.3
ISIS 141923	41	0.6	2.0	0.1

Study 2 (with 5-10-5 MOE gapmers)

Groups of six- to eight-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 100 mg/kg of ISIS oligonucleotide. Two groups of male CD1 mice were injected subcutaneously once a week for 6 weeks with PBS. One group of mice was injected with subcutaneously once a week for 6 weeks with 100 mg/kg of control oligonucleotide ISIS 141923. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

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

Table 40
Plasma chemistry markers in CD1 mice plasma on day 45

	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	BUN (mg/dL)
PBS	39	53	2.9	29
PBS	50	97	2.9	30
ISIS 141923	163	174	4.1	25
ISIS 532810	321	297	2.5	26
ISIS 532952	182	199	2.7	27
ISIS 588534	276	248	2.6	29
ISIS 588536	48	60	2.9	31
ISIS 588537	72	79	4.0	25
ISIS 588538	63	67	4.5	29
ISIS 588539	238	177	3.9	28
ISIS 588545	496	256	4.4	24
ISIS 588547	323	210	4.4	25
ISIS 588548	61	63	4.2	27
ISIS 588549	127	132	4.1	23
ISIS 588551	302	282	4.2	22
ISIS 588552	76	98	4.0	30
ISIS 588558	1066	521	3.9	27
ISIS 588559	76	94	4.1	26
ISIS 588561	502	500	4.4	26
ISIS 588563	50	99	4.4	28

Weights

Body weights of the mice were measured on day 42. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 45. The results are presented in the Table below. ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 41
Weights (g) of CD1 mice on day 40

	Body	Kidney	Liver	Spleen
PBS	44	0.7	2.4	0.1
PBS	43	0.7	2.4	0.2
ISIS 141923	43	0.6	2.4	0.2
ISIS 532810	41	0.6	1.9	0.1
ISIS 532952	43	0.6	2.4	0.2
ISIS 588534	44	0.7	2.8	0.2
ISIS 588536	43	0.7	2.7	0.2
ISIS 588537	43	0.7	2.4	0.2
ISIS 588538	44	0.7	2.8	0.2
ISIS 588539	44	0.6	2.7	0.2

ISIS 588545	44	0.8	3.3	0.3
ISIS 588547	42	0.6	3.3	0.3
ISIS 588548	43	0.6	2.8	0.2
ISIS 588549	42	0.6	2.8	0.3
ISIS 588551	39	0.6	2.2	0.2
ISIS 588552	41	0.6	2.2	0.2
ISIS 588558	44	0.7	3.3	0.3
ISIS 588559	43	0.6	2.7	0.3
ISIS 588561	40	0.7	2.4	0.3
ISIS 588563	41	0.7	2.4	0.2

Study 3 (with 5-10-5 MOE gapmers)

Groups of six- to eight-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 100 mg/kg of ISIS oligonucleotide. Two groups of male CD1 mice were injected subcutaneously once a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

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

Table 42

Plasma chemistry markers in CD1 mice plasma on day 42

	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	BUN (mg/dL)
PBS	37	108	3.1	30
PBS	45	51	3.0	27
ISIS 588544	209	168	2.9	26
ISIS 588546	526	279	3.0	22
ISIS 588550	82	136	2.7	25
ISIS 588553	79	105	3.0	24
ISIS 588554	112	220	3.2	19
ISIS 588555	95	162	2.8	25
ISIS 588556	345	236	3.0	26
ISIS 588557	393	420	2.8	24
ISIS 588560	109	148	2.7	27
ISIS 588562	279	284	2.8	22
ISIS 588564	152	188	3.0	23
ISIS 588565	247	271	2.8	28

Weights

Body weights of the mice were measured on day 42. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 42. The results are presented in the Table below. ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 43

Weights (g) of CD1 mice on day 40

	Body	Kidney	Liver	Spleen
PBS	42	0.7	2.4	0.1
PBS	41	0.7	2.4	0.2
ISIS 588544	44	0.6	1.9	0.1
ISIS 588546	43	0.6	2.4	0.2
ISIS 588550	41	0.7	2.8	0.2
ISIS 588553	44	0.7	2.7	0.2
ISIS 588554	40	0.7	2.4	0.2
ISIS 588555	44	0.7	2.8	0.2
ISIS 588556	39	0.6	2.7	0.2
ISIS 588557	41	0.8	3.3	0.3
ISIS 588560	38	0.6	3.2	0.3
ISIS 588562	41	0.6	2.8	0.2
ISIS 588564	40	0.6	2.8	0.3
ISIS 588565	39	0.6	2.2	0.2

Study 4 (with (S) cEt gapmers and deoxy, MOE and cEt oligonucleotides)

Groups of ten-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 50 mg/kg of ISIS oligonucleotide from the studies described above. In addition, two oligonucleotides, ISIS 594431 and ISIS 594432, were designed as 3-10-3 cEt gapmers and were also tested in this study. ISIS 594431(ACCTCCTTCCGAGTCA, SEQ ID NO: 550) targets the same region as ISIS 588871, a deoxy, MOE and cEt gapmer (target start site 2197 of SEQ ID NO: 1 and target start site 6985 of SEQ ID NO: 2). ISIS 594432 (TGGTCACATTCCCTTC, SEQ ID NO: 542) targets the same region as ISIS 588872 a deoxy, MOE and cEt gapmer (target start site 154 of SEQ ID NO: 1 and target start site 1875 of SEQ ID NO: 2).

Two groups of male CD1 mice were injected subcutaneously once a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, albumin, creatinine, and BUN were measured using an automated clinical chemistry analyzer

(Hitachi Olympus AU400e, Melville, NY). The results are presented in the Table below. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 44

Plasma chemistry markers in CD1 mice plasma on day 42

	Chemistry	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	-	71	77	2.7	0.2	29
PBS	-	30	36	2.7	0.2	26
ISIS 588834	Deoxy, MOE and cEt	436	510	2.8	0.2	25
ISIS 588835	Deoxy, MOE and cEt	70	98	3.0	0.2	27
ISIS 588836	Deoxy, MOE and cEt	442	312	2.7	0.2	27
ISIS 588846	Deoxy, MOE and cEt	50	75	2.5	0.1	28
ISIS 588847	Deoxy, MOE and cEt	44	71	2.6	0.1	24
ISIS 588848	Deoxy, MOE and cEt	47	70	2.4	0.1	27
ISIS 588857	Deoxy, MOE and cEt	1287	655	2.7	0.2	26
ISIS 588858	Deoxy, MOE and cEt	1169	676	2.5	0.2	26
ISIS 588859	Deoxy, MOE and cEt	1036	1300	3.2	0.2	25
ISIS 588861	Deoxy, MOE and cEt	749	466	3.1	0.1	24
ISIS 588862	Deoxy, MOE and cEt	1564	1283	2.9	0.2	22
ISIS 588863	Deoxy, MOE and cEt	477	362	2.8	0.1	23
ISIS 588864	Deoxy, MOE and cEt	118	165	2.9	0.2	27
ISIS 588866	Deoxy, MOE and cEt	843	784	3.2	0.2	25
ISIS 594430	3-10-3 cEt	89	99	2.4	0.1	28
ISIS 594431	3-10-3 cEt	590	433	3.0	0.2	24
ISIS 594432	3-10-3 cEt	2595	2865	2.4	0.1	25

Weights

Body weights of the mice were measured on day 39. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 42. The results are presented in the Table below. ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 45

Weights (g) of CD1 mice

	Chemistry	Body	Kidney	Liver	Spleen
PBS	-	37	0.6	2.1	0.1
PBS	-	45	0.7	2.5	0.2
ISIS 588834	Deoxy, MOE and cEt	40	0.6	3.2	0.2
ISIS 588835	Deoxy, MOE and cEt	38	0.7	2.8	0.3
ISIS 588836	Deoxy, MOE and cEt	41	0.7	2.3	0.2
ISIS 588837	Deoxy, MOE and cEt	38	0.6	2.4	0.3
ISIS 588846	Deoxy, MOE and cEt	39	0.6	2.3	0.2

ISIS 588847	Deoxy, MOE and cEt	40	0.7	2.5	0.2
ISIS 588848	Deoxy, MOE and cEt	43	0.7	2.6	0.3
ISIS 588857	Deoxy, MOE and cEt	39	0.6	3.3	0.2
ISIS 588858	Deoxy, MOE and cEt	37	0.6	3.4	0.2
ISIS 588859	Deoxy, MOE and cEt	41	0.7	2.5	0.3
ISIS 588861	Deoxy, MOE and cEt	39	0.6	2.6	0.4
ISIS 588862	Deoxy, MOE and cEt	34	0.6	2.5	0.4
ISIS 588863	Deoxy, MOE and cEt	40	0.6	2.7	0.3
ISIS 588864	Deoxy, MOE and cEt	40	0.7	2.3	0.2
ISIS 588866	Deoxy, MOE and cEt	45	0.7	3.0	0.2
ISIS 594430	3-10-3 cEt	39	0.6	2.2	0.2
ISIS 594431	3-10-3 cEt	36	0.6	3.2	0.2
ISIS 594432	3-10-3 cEt	31	0.4	1.9	0.1

Study 5 (with MOE gapmers, (S) cEt gapmers and deoxy, MOE and cEt oligonucleotides)

Groups of eight- to nine-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 50 mg/kg of ISIS oligonucleotide. Two groups of male CD1 mice were injected subcutaneously once a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

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

Table 46

Plasma chemistry markers in CD1 mice plasma on day 42

	Chemistry	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	-	33	84	2.9	0.2	28
PBS	-	32	65	2.5	0.1	27
ISIS 532692	5-10-5 MOE	363	281	3.0	0.2	30
ISIS 532770	5-10-5 MOE	69	100	2.9	0.1	28
ISIS 532775	5-10-5 MOE	371	333	2.6	0.1	29
ISIS 532800	5-10-5 MOE	104	106	2.7	0.1	31
ISIS 532809	5-10-5 MOE	69	127	2.8	0.1	26
ISIS 588540	5-10-5 MOE	66	110	2.8	0.1	26
ISIS 588838	3-10-3 cEt	391	330	2.9	0.1	25
ISIS 588842	Deoxy, MOE and cEt	224	264	2.6	0.1	26

ISIS 588843	3-10-3 cEt	185	160	2.8	0.1	24
ISIS 588844	Deoxy, MOE and cEt	304	204	2.7	0.1	25
ISIS 588851	Deoxy, MOE and cEt	186	123	2.7	0.1	31
ISIS 588854	Deoxy, MOE and cEt	1232	925	2.7	0.1	25
ISIS 588855	Deoxy, MOE and cEt	425	321	2.7	0.1	28
ISIS 588856	Deoxy, MOE and cEt	78	101	2.4	0.1	31
ISIS 588865	Deoxy, MOE and cEt	126	145	2.5	0.1	23
ISIS 588867	Deoxy, MOE and cEt	108	112	2.5	0.1	32
ISIS 588868	Deoxy, MOE and cEt	61	124	2.5	0.1	28
ISIS 588870	Deoxy, MOE and cEt	48	69	2.4	0.1	31
ISIS 588871	Deoxy, MOE and cEt	723	881	2.5	0.1	24
ISIS 588872	Deoxy, MOE and cEt	649	654	2.7	0.1	26

Weights

Body weights of the mice were measured on day 40. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 42. The results are presented in the Table below. ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 47

Weights (g) of CD1 mice

	Chemistry	Body	Kidney	Liver	Spleen
PBS	-	46	0.7	2.3	0.2
PBS	-	44	0.7	2.3	0.2
ISIS 532692	5-10-5 MOE	44	0.6	2.8	0.2
ISIS 532770	5-10-5 MOE	43	0.6	2.2	0.2
ISIS 532775	5-10-5 MOE	43	0.6	2.8	0.2
ISIS 532800	5-10-5 MOE	47	0.7	2.9	0.2
ISIS 532809	5-10-5 MOE	44	0.7	2.6	0.2
ISIS 588540	5-10-5 MOE	44	0.7	2.5	0.2
ISIS 588838	3-10-3 cEt	45	0.7	3.1	0.2
ISIS 588842	Deoxy, MOE and cEt	41	0.6	2.6	0.2
ISIS 588843	3-10-3 cEt	43	0.7	2.9	0.2
ISIS 588844	Deoxy, MOE and cEt	43	0.7	2.8	0.2
ISIS 588851	Deoxy, MOE and cEt	46	0.6	2.6	0.2
ISIS 588854	Deoxy, MOE and cEt	45	0.7	4.1	0.2
ISIS 588855	Deoxy, MOE and cEt	44	0.7	2.9	0.3
ISIS 588856	Deoxy, MOE and cEt	44	0.7	3.2	0.2
ISIS 588865	Deoxy, MOE and cEt	45	0.7	2.6	0.3
ISIS 588867	Deoxy, MOE and cEt	46	0.7	3.2	0.3
ISIS 588868	Deoxy, MOE and cEt	42	0.7	2.9	0.3
ISIS 588870	Deoxy, MOE and cEt	43	0.6	2.2	0.2
ISIS 588871	Deoxy, MOE and cEt	41	0.7	3.1	0.2

ISIS 588872	Deoxy, MOE and cEt	39	0.6	3.2	0.3

Study 6 (with deoxy, MOE and cEt oligonucleotides)

Groups of eight- to nine-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 50 mg/kg of deoxy, MOE, and cEt oligonucleotides. Two groups of male CD1 mice were injected subcutaneously once a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

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

Table 48

Plasma chemistry markers in CD1 mice plasma on day 45

	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	Creatinine (mg/dL)	Bilirubin (mg/dL)	BUN (mg/dL)
PBS	39	78	3.4	0.2	0.2	31
PBS	37	59	2.9	0.1	0.2	27
ISIS 599552	167	208	3.0	0.1	0.2	32
ISIS 599553	43	86	2.9	0.1	0.2	28
ISIS 599554	57	101	2.2	0.2	0.2	31
ISIS 599569	469	530	3.5	0.2	0.3	27
ISIS 599577	37	84	2.9	0.1	0.1	31
ISIS 599578	45	104	2.8	0.1	0.2	30
ISIS 599581	54	88	3.1	0.1	0.2	31
ISIS 599590	1741	1466	3.1	0.1	0.3	25
ISIS 599591	2230	1183	3.2	0.1	0.3	27
ISIS 601209	68	104	2.9	0.1	0.2	30
ISIS 601212	1795	968	3.2	0.1	0.3	22
ISIS 601215	424	385	3.1	0.1	0.4	25
ISIS 601216	90	125	2.9	0.1	0.2	29
ISIS 601276	946	366	2.9	0.1	0.5	31
ISIS 601282	831	540	3.3	0.2	0.2	32

Weights

Body weights of the mice were measured on day 40. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 45. The results are presented in the Table below.

ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 49

Weights (g) of CD1 mice

	Body	Kidney	Liver	Spleen
PBS	40	0.7	2.1	0.2
PBS	42	0.8	2.3	0.2
ISIS 599552	38	0.6	2.3	0.2
ISIS 599553	39	0.7	2.2	0.2
ISIS 599554	39	0.7	2.4	0.2
ISIS 599569	39	0.7	2.2	0.2
ISIS 599577	41	0.7	2.5	0.2
ISIS 599578	37	0.6	2.0	0.2
ISIS 599581	40	0.6	2.5	0.2
ISIS 599590	34	0.6	3.5	0.2
ISIS 599591	38	0.8	2.7	0.2
ISIS 601209	42	0.7	2.6	0.3
ISIS 601212	38	0.6	2.9	0.2
ISIS 601215	36	0.7	2.6	0.2
ISIS 601216	42	0.6	2.7	0.2
ISIS 601276	42	0.7	3.2	0.2
ISIS 601282	38	0.7	3.2	0.2

Study 7 (with MOE gapmers and deoxy, MOE and cEt oligonucleotides)

Groups of eight- to nine-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 100 mg/kg of ISIS oligonucleotides. One group of male CD1 mice was injected subcutaneously once a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

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

Table 50

Plasma chemistry markers in CD1 mice plasma on day 45

	Chemistry	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	-	120	102	2.7	0.2	26
ISIS 588842	Deoxy, MOE and cEt	177	164	2.7	0.1	23

ISIS 588843	Deoxy, MOE and cEt	98	194	2.7	0.1	24
ISIS 588851	Deoxy, MOE and cEt	91	142	2.6	0.1	23
ISIS 588856	Deoxy, MOE and cEt	78	110	2.7	0.1	23
ISIS 599024	3-10-4 MOE	91	108	2.7	0.1	23
ISIS 599087	5-7-5 MOE	198	183	2.6	0.2	28
ISIS 599093	5-7-5 MOE	3285	2518	2.6	0.2	24
ISIS 599149	4-8-5 MOE	30	64	2.9	0.2	25
ISIS 599155	4-8-5 MOE	145	189	2.6	0.2	25
ISIS 599202	5-8-5 MOE	150	128	2.8	0.2	23
ISIS 599203	5-8-5 MOE	111	127	2.8	0.2	24
ISIS 599208	5-8-5 MOE	146	178	2.9	0.2	22
ISIS 599261	3-10-5 MOE	144	165	2.8	0.2	26
ISIS 599267	3-10-5 MOE	96	132	2.6	0.2	27
ISIS 599268	3-10-5 MOE	87	115	2.6	0.1	23
ISIS 599322	6-7-6 MOE	115	138	2.7	0.1	22
ISIS 599374	5-9-5 MOE	375	271	2.6	0.1	21
ISIS 599378	5-9-5 MOE	77	99	2.7	0.1	23
ISIS 599441	6-8-6 MOE	150	250	2.9	0.1	23

Weights

Body weights of the mice were measured on day 44. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 49. The results are presented in the Table below. ISIS oligonucleotides that caused changes in the weights outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 51

Weights (g) of CD1 mice

	Chemistry	Body	Kidney	Liver	Spleen
PBS	-	39	0.6	1.9	0.1
ISIS 588842	Deoxy, MOE and cEt	38	0.5	2.1	0.1
ISIS 588843	Deoxy, MOE and cEt	41	0.6	2.4	0.2
ISIS 588851	Deoxy, MOE and cEt	42	0.6	2.2	0.2
ISIS 588856	Deoxy, MOE and cEt	42	0.7	2.6	0.2
ISIS 599024	3-10-4 MOE	41	0.6	4.0	0.2
ISIS 599087	5-7-5 MOE	44	0.8	2.6	0.3
ISIS 599093	5-7-5 MOE	39	0.6	2.3	0.2
ISIS 599149	4-8-5 MOE	42	0.7	2.8	0.2
ISIS 599155	4-8-5 MOE	41	0.7	2.1	0.2
ISIS 599202	5-8-5 MOE	43	0.6	2.6	0.2
ISIS 599203	5-8-5 MOE	42	0.6	2.6	0.2
ISIS 599208	5-8-5 MOE	40	0.6	2.1	0.2
ISIS 599261	3-10-5 MOE	39	0.7	3.4	0.3
ISIS 599267	3-10-5 MOE	42	0.8	2.5	0.3

ISIS 599268	3-10-5 MOE	41	0.7	2.1	0.2
ISIS 599322	6-7-6 MOE	43	0.6	2.2	0.2
ISIS 599374	5-9-5 MOE	37	0.6	2.2	0.2
ISIS 599378	5-9-5 MOE	43	0.7	2.7	0.2
ISIS 599441	6-8-6 MOE	42	0.6	2.5	0.3

Study 8 (with MOE gapmers, deoxy, MOE and cEt oligonucleotides, and cEt gapmers)

Groups of eight- to nine-week old male CD1 mice were injected subcutaneously once a week for 6 weeks with 100 mg/kg of MOE gapmers, or 50 mg/kg of deoxy, MOE and cEt oligonucleotides or cEt gapmers. One group of male CD1 mice was injected subcutaneously once a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, albumin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in the Table below.

Table 52

Plasma chemistry markers in CD1 mice plasma on day 43

	Chemistry	Dose (mg/kg/wk)	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	-	-	37	57	2.5	0.08	26
ISIS 532770	5-10-5 MOE	100	57	73	2.5	0.07	24
ISIS 532800	5-10-5 MOE	100	74	126	2.8	0.10	26
ISIS 532809	5-10-5 MOE	100	83	73	2.5	0.07	23
ISIS 588540	5-10-5 MOE	100	106	102	2.7	0.09	27
ISIS 588544	5-10-5 MOE	100	66	62	2.6	0.10	24
ISIS 588548	5-10-5 MOE	100	48	67	2.6	0.08	23
ISIS 588550	5-10-5 MOE	100	65	106	2.5	0.10	25
ISIS 588553	5-10-5 MOE	100	78	90	2.6	0.09	25
ISIS 588555	5-10-5 MOE	100	94	89	2.5	0.08	23
ISIS 588848	Deoxy, MOE and cEt	50	38	54	2.3	0.07	25
ISIS 594430	3-10-3 cEt	50	63	72	2.5	0.10	27

Weights

Body weights of the mice were measured on day 36. Weights of organs, liver, kidney, and spleen were also measured after the mice were sacrificed on day 43. The results for the organ weights were expressed as a ratio to the body weights and normalized to the PBS control ratio.

Table 53
Organ Weights/Body weight (BW) of CD1 mice

	Chemistry	Dose (mg/kg/wk)	Kidney/BW	Liver/BW	Spleen/BW
PBS	-	-	1.0	1.0	1.0
ISIS 532770	5-10-5 MOE	100	1.4	1.1	1.0
ISIS 532800	5-10-5 MOE	100	1.5	1.1	0.9
ISIS 532809	5-10-5 MOE	100	1.3	1.2	0.9
ISIS 588540	5-10-5 MOE	100	1.3	1.2	1.0
ISIS 588544	5-10-5 MOE	100	1.6	1.1	1.0
ISIS 588548	5-10-5 MOE	100	1.7	1.2	1.0
ISIS 588550	5-10-5 MOE	100	1.5	1.2	1.0
ISIS 588553	5-10-5 MOE	100	1.5	1.0	0.8
ISIS 588555	5-10-5 MOE	100	1.8	1.2	1.0
ISIS 588848	Deoxy, MOE and cEt	50	1.3	1.0	0.9
ISIS 594430	3-10-3 cEt	50	1.4	1.1	0.9

Cytokine assays

Blood obtained from all mice groups were sent to Antech Diagnostics for measurements of the various cytokine levels, such as IL-6, MDC, MIP1β, IP-10, MCP1, MIP-1α, and RANTES. The results are presented in Table 54.

Table 54
Cytokine levels (pg/mL) in CD1 mice plasma

	Chemistry	IL-6	MDC	MIP1β	IP-10	MCP1	MIP-1α	RANTES
PBS	-	70	16	23	20	17	6	2
ISIS 532770	5-10-5 MOE	101	18	146	116	101	24	6
ISIS 532800	5-10-5 MOE	78	17	83	53	105	1	3
ISIS 532809	5-10-5 MOE	66	19	60	32	55	20	4
ISIS 588540	5-10-5 MOE	51	18	126	70	75	4	3
ISIS 588544	5-10-5 MOE	157	14	94	34	102	1	3
ISIS 588548	5-10-5 MOE	164	12	90	66	84	10	4
ISIS 588550	5-10-5 MOE	58	21	222	124	157	3	5
ISIS 588553	5-10-5 MOE	62	14	183	60	103	9	4
ISIS 588555	5-10-5 MOE	70	19	172	171	178	16	9
ISIS 588848	Deoxy, MOE and cEt	59	13	61	27	63	12	4
ISIS 594430	3-10-3 cEt	48	14	56	38	85	10	3

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for measurements of hematocrit (HCT), as well as of the various blood cells, such as WBC, RBC, and platelets, and total hemoglobin (Hb) content. The results are presented in Table 55.

Table 55
Hematology markers in CD1 mice plasma

	Chemistry	HCT (%)	Hb (g/dL)	WBC (10^3/μL)	RBC (10^6/μL)	Platelets (10^3/μL)
PBS	-	46	15	7	9	960
ISIS 532770	5-10-5 MOE	45	14	5	9	879
ISIS 532800	5-10-5 MOE	45	14	5	9	690
ISIS 532809	5-10-5 MOE	46	14	6	9	1005
ISIS 588540	5-10-5 MOE	49	15	6	10	790
ISIS 588544	5-10-5 MOE	36	11	7	7	899
ISIS 588548	5-10-5 MOE	46	14	6	9	883
ISIS 588550	5-10-5 MOE	42	13	8	8	721
ISIS 588553	5-10-5 MOE	45	14	6	9	719
ISIS 588555	5-10-5 MOE	43	13	8	9	838
ISIS 588848	Deoxy, MOE and cEt	40	15	8	10	840
ISIS 594430	3-10-3 cEt	45	14	8	9	993

Example 13: Tolerability of antisense oligonucleotides targeting human CFB in Sprague-Dawley rats

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

Study 1 (with 5-10-5 MOE gapmers)

Male Sprague-Dawley rats, seven- to eight-week old, were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously once a week for 6 weeks with 100 mg/kg of 5-10-5 MOE gapmers. One control group of 6 rats was injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase) were measured and the results are presented in the Table below expressed in IU/L. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 56
Liver function markers in Sprague-Dawley rats

	ALT (IU/L)	AST (IU/L)
PBS	66	134
ISIS 588544	101	329
ISIS 588550	69	157
ISIS 588553	88	304
ISIS 588554	202	243
ISIS 588555	94	113
ISIS 588556	102	117
ISIS 588560	206	317
ISIS 588564	292	594

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in the Table below, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 57
Kidney function markers (mg/dL) in Sprague-Dawley rats

	BUN	Creatinine
PBS	18	3.5
ISIS 588544	21	3.1
ISIS 588550	21	3.0
ISIS 588553	22	2.8
ISIS 588554	23	3.0
ISIS 588555	22	3.5
ISIS 588556	21	3.2
ISIS 588560	26	2.4
ISIS 588564	24	2.7

Weights

Body weight measurements were taken on day 39. Liver, heart, spleen and kidney weights were measured at the end of the study on day 42, and are presented in the Table below. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 58
Weights (g)

	Body	Liver	Spleen	Kidney
PBS	422	16	1.2	3.9
ISIS 588544	353	15	1.7	2.9
ISIS 588550	321	14	2.1	3.2
ISIS 588553	313	15	2.3	3.2
ISIS 588554	265	11	1.6	2.7
ISIS 588555	345	14	1.4	3.3
ISIS 588556	328	13	1.7	3.1
ISIS 588560	270	13	2.4	3.0
ISIS 588564	253	12	2.9	3.0

Study 2 (with deoxy, MOE and cEt oligonucleotides)

Male Sprague-Dawley rats, nine- to ten-week old, were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously once a week for 6 weeks with 100 mg/kg of deoxy, MOE, and cEt oligonucleotides. Two control groups of 3 rats each were injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured on day 42 using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase), and albumin were measured and the results are presented in the Table below. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 59
Liver function markers in Sprague-Dawley rats

	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)
PBS	55	150	3.4
PBS	64	91	3.5
ISIS 588554	52	92	3.2
ISIS 588835	971	844	4.1
ISIS 588842	317	359	3.8
ISIS 588843	327	753	2.9
ISIS 588846	70	111	3.2
ISIS 588847	65	100	3.0
ISIS 588864	91	109	3.0

ISIS 594430	85	106	3.7

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in the Table below, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 60

Kidney function markers (mg/dL) in Sprague-Dawley rats

	BUN	Creatinine
PBS	17	0.4
PBS	21	0.4
ISIS 588554	20	0.4
ISIS 588835	23	0.5
ISIS 588842	22	0.4
ISIS 588843	51	0.4
ISIS 588846	25	0.5
ISIS 588847	23	0.5
ISIS 588864	23	0.4
ISIS 594430	22	0.5

Weights

Body weight measurements were taken on day 39. Liver, heart, spleen and kidney weights were measured at the end of the study on day 42, and are presented in the Table below. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 61

Weights (g)

	Body	Liver	Spleen	Kidney
PBS	466	16	0.9	3.8
PBS	485	16	0.9	3.6
ISIS 588554	393	15	2.3	2.6
ISIS 588835	387	16	1.0	3.3
ISIS 588842	414	22	1.5	3.7
ISIS 588843	427	20	2.5	4.2
ISIS 588846	366	16	2.1	3.3
ISIS 588847	402	15	1.6	3.1
ISIS 588864	364	15	2.1	3.8
ISIS 594430	420	16	1.2	3.6

Study 3 (with MOE gapmers)

Male Sprague-Dawley rats, nine- to ten-week old, were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously once a week for 6 weeks with 100 mg/kg of MOE gapmers. One control group of 6 rats was injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured on day 43 using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase) were measured and the results are presented in the Table below expressed in IU/L. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 62

Liver function markers in Sprague-Dawley rats

	Chemistry	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)
PBS	-	52	110	3.7
ISIS 588563	5-10-5 MOE	175	291	2.9
ISIS 599024	3-10-4 MOE	139	173	1.4
ISIS 599093	5-7-5 MOE	116	238	2.6
ISIS 599149	4-8-5 MOE	232	190	3.4
ISIS 599155	4-8-5 MOE	108	215	2.5
ISIS 599202	5-8-5 MOE	65	86	3.5
ISIS 599203	5-8-5 MOE	71	97	3.1
ISIS 599208	5-8-5 MOE	257	467	1.9
ISIS 599261	3-10-5 MOE	387	475	1.5
ISIS 599267	3-10-5 MOE	201	337	2.7

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in the Table below, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 63

Kidney function markers (mg/dL) in Sprague-Dawley rats

	Chemistry	BUN	Creatinine
PBS	-	16	0.3

ISIS 588563	5-10-5 MOE	26	0.4
ISIS 599024	3-10-4 MOE	135	1.2
ISIS 599093	5-7-5 MOE	29	0.4
ISIS 599149	4-8-5 MOE	23	0.4
ISIS 599155	4-8-5 MOE	29	0.4
ISIS 599202	5-8-5 MOE	19	0.4
ISIS 599203	5-8-5 MOE	22	0.4
ISIS 599208	5-8-5 MOE	26	0.3
ISIS 599261	3-10-5 MOE	228	1.6
ISIS 599267	3-10-5 MOE	24	0.4

Weights

Body weight measurements were taken on day 39. Liver, heart, spleen and kidney weights were measured at the end of the study on day 42, and are presented in the Table below. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 64
Weights (g)

	Chemistry	Body	Liver	Spleen	Kidney
PBS	-	471	16	1.0	4.1
ISIS 588563	5-10-5 MOE	311	16	3.4	4.1
ISIS 599024	3-10-4 MOE	297	11	1.0	3.5
ISIS 599093	5-7-5 MOE	332	18	4.1	5.0
ISIS 599149	4-8-5 MOE	388	16	2.3	3.7
ISIS 599155	4-8-5 MOE	290	15	2.9	4.5
ISIS 599202	5-8-5 MOE	359	13	1.3	3.2
ISIS 599203	5-8-5 MOE	334	14	1.8	3.3
ISIS 599208	5-8-5 MOE	353	29	4.7	4.6
ISIS 599261	3-10-5 MOE	277	10	0.9	3.2
ISIS 599267	3-10-5 MOE	344	21	3.9	4.7

Study 4 (with MOE gapmers)

Male Sprague-Dawley rats, nine- to ten-week old, were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously once a week for 6 weeks with 100 mg/kg of MOE gapmers. One control group of 6 rats was injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured on day 42 using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase) were measured and the results are presented in the Table below expressed in IU/L. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 65

Liver function markers in Sprague-Dawley rats

	Chemistry	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)
PBS	-	48	77	3.9
ISIS 532800	5-10-5 MOE	72	111	3.4
ISIS 532809	5-10-5 MOE	59	89	3.8
ISIS 588540	5-10-5 MOE	146	259	3.8
ISIS 599268	3-10-5 MOE	175	206	2.7
ISIS 599322	6-7-6 MOE	523	567	3.3
ISIS 599374	5-9-5 MOE	114	176	3.0
ISIS 599378	5-9-5 MOE	124	116	3.2
ISIS 599380	5-9-5 MOE	148	210	3.4
ISIS 599441	6-8-6 MOE	51	91	2.6

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in the Table below, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 66

Kidney function markers (mg/dL) in Sprague-Dawley rats

	Chemistry	BUN	Creatinine
PBS	-	15	0.4
ISIS 532800	5-10-5 MOE	26	0.5
ISIS 532809	5-10-5 MOE	18	0.5
ISIS 588540	5-10-5 MOE	22	0.5
ISIS 599268	3-10-5 MOE	28	0.5
ISIS 599322	6-7-6 MOE	24	0.5
ISIS 599374	5-9-5 MOE	29	0.5
ISIS 599378	5-9-5 MOE	22	0.4
ISIS 599380	5-9-5 MOE	26	0.5
ISIS 599441	6-8-6 MOE	24	0.4

Weights

Body weight measurements were taken on day 39. Liver, heart, spleen and kidney weights were measured at the end of the study on day 42, and are presented in the Table below. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 67
Weights (g)

	Chemistry	Body	Liver	Spleen	Kidney
PBS	-	502	16	0.9	3.7
ISIS 532800	5-10-5 MOE	376	16	2.0	3.4
ISIS 532809	5-10-5 MOE	430	16	1.4	3.4
ISIS 588540	5-10-5 MOE	391	16	1.8	3.5
ISIS 599268	3-10-5 MOE	332	16	3.6	3.6
ISIS 599322	6-7-6 MOE	348	13	2.1	3.4
ISIS 599374	5-9-5 MOE	302	12	2.0	3.3
ISIS 599378	5-9-5 MOE	332	11	1.1	2.8
ISIS 599380	5-9-5 MOE	350	11	1.5	3.3
ISIS 599441	6-8-6 MOE	368	16	2.5	3.3

Study 5 (with MOE gapmers and deoxy, MOE and cEt oligonucleotides)

Male Sprague-Dawley rats, nine- to ten-week old, were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously once a week for 6 weeks with 100 mg/kg of MOE gapmer or with 50 mg/kg of deoxy, MOE and cEt oligonucleotides. One control group of 4 rats was injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured on day 42 using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase) were measured and the results are presented in the Table below expressed in IU/L. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 68
Liver function markers in Sprague-Dawley rats

	Chemistry	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)
PBS	-	49	74	3.3
ISIS 532770	5-10-5 MOE	95	132	3.3
ISIS 588851	Deoxy, MOE, and cEt	47	72	3.1
ISIS 588856	Deoxy, MOE, and cEt	56	75	3.0
ISIS 588865	Deoxy, MOE, and cEt	62	84	2.9
ISIS 588867	Deoxy, MOE, and cEt	73	214	2.9
ISIS 588868	Deoxy, MOE, and cEt	59	83	3.1
ISIS 588870	Deoxy, MOE, and cEt	144	144	3.4

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma and urine levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in the Tables below, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 69
Kidney function markers (mg/dL) in the plasma of Sprague-Dawley rats

	Chemistry	BUN	Creatinine
PBS	-	18	0.3
ISIS 532770	5-10-5 MOE	20	0.4
ISIS 588851	Deoxy, MOE, and cEt	20	0.4
ISIS 588856	Deoxy, MOE, and cEt	22	0.4
ISIS 588865	Deoxy, MOE, and cEt	24	0.5
ISIS 588867	Deoxy, MOE, and cEt	22	0.4
ISIS 588868	Deoxy, MOE, and cEt	19	0.4
ISIS 588870	Deoxy, MOE, and cEt	20	0.5

Table 70
Kidney function markers (mg/dL) in the urine of Sprague-Dawley rats

	Chemistry	Total protein	Creatinine
PBS	-	80	92
ISIS 532770	5-10-5 MOE	466	69
ISIS 588851	Deoxy, MOE, and cEt	273	64
ISIS 588856	Deoxy, MOE, and cEt	259	68
ISIS 588865	Deoxy, MOE, and cEt	277	67
ISIS 588867	Deoxy, MOE, and cEt	337	68
ISIS 588868	Deoxy, MOE, and cEt	326	75
ISIS 588870	Deoxy, MOE, and cEt	388	82

Weights

Body weight measurements were taken on day 39. Liver, heart, spleen and kidney weights were measured at the end of the study on day 42, and are presented in the Table below. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 71
Weights (g)

	Chemistry	Body	Liver	Spleen	Kidney
PBS	-	489	16	0.9	3.5
ISIS 532770	5-10-5 MOE	372	15	1.7	3.1
ISIS 588851	Deoxy, MOE, and cEt	285	14	1.4	3.2
ISIS 588856	Deoxy, MOE, and cEt	415	15	1.1	3.3
ISIS 588865	Deoxy, MOE, and cEt	362	14	2.0	3.3
ISIS 588867	Deoxy, MOE, and cEt	406	15	2.4	3.4
ISIS 588868	Deoxy, MOE, and cEt	399	15	1.5	3.4
ISIS 588870	Deoxy, MOE, and cEt	446	14	1.4	3.3

Study 6 (with MOE gapmers, deoxy, MOE and cEt oligonucleotides, and cEt gapmers)

Male rats were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 rats each were injected subcutaneously once a week for 6 weeks with 100 mg/kg of MOE gapmers or with 50 mg/kg of deoxy, MOE and cEt oligonucleotide or cEt gapmer. One control group of 4 rats was injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured on day 42 using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase) were measured and the results are presented in the Table below expressed in IU/L.

Table 72
Liver function markers

	Chemistry	Dose (mg/kg/wk)	ALT (IU/L)	AST (IU/L)	Albumin (g/dL)
PBS	-	-	54	73	4.3
ISIS 532770	5-10-5 MOE	100	57	114	4.4
ISIS 532800	5-10-5 MOE	100	176	180	4.3
ISIS 532809	5-10-5 MOE	100	71	132	4.1
ISIS 588540	5-10-5 MOE	100	89	202	4.4
ISIS 588544	5-10-5 MOE	100	75	152	3.9

ISIS 588548	5-10-5 MOE	100	50	71	4.1
ISIS 588550	5-10-5 MOE	100	80	133	3.6
ISIS 588553	5-10-5 MOE	100	59	112	3.9
ISIS 588555	5-10-5 MOE	100	97	142	3.8
ISIS 588848	Deoxy, MOE and cEt	50	53	82	3.9
ISIS 594430	3-10-3 cEt	50	198	172	4.4

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, urine levels of total protein and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in the Table below. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 73

Total protein/creatinine ratio in the urine of rats

	Chemistry	Dose (mg/kg/wk)	P/C ratio
PBS	-	-	1.1
ISIS 532770	5-10-5 MOE	100	8.3
ISIS 532800	5-10-5 MOE	100	6.5
ISIS 532809	5-10-5 MOE	100	6.1
ISIS 588540	5-10-5 MOE	100	10.1
ISIS 588544	5-10-5 MOE	100	7.9
ISIS 588548	5-10-5 MOE	100	6.6
ISIS 588550	5-10-5 MOE	100	7.6
ISIS 588553	5-10-5 MOE	100	7.0
ISIS 588555	5-10-5 MOE	100	6.2
ISIS 588848	Deoxy, MOE and cEt	50	5.2
ISIS 594430	3-10-3 cEt	50	5.3

Weights

Body weight measurements were taken on day 39. Liver, heart, spleen and kidney weights were measured at the end of the study on day 42, and are presented in the Table below. The results for the organ weights were expressed as a ratio to the body weights and normalized to the PBS control ratio.

Table 74

Organ weights/Body weight (BW) ratios

	Chemistry	Dose (mg/kg/wk)	Spleen/BW	Liver/BW	Kidney/BW
PBS	-	-	1.0	1.0	1.0
ISIS 532770	5-10-5 MOE	100	2.0	1.2	1.0
ISIS 532800	5-10-5 MOE	100	2.8	1.3	1.0

ISIS 532809	5-10-5 MOE	100	2.2	1.1	1.0
ISIS 588540	5-10-5 MOE	100	2.2	1.4	1.0
ISIS 588544	5-10-5 MOE	100	2.5	1.3	1.1
ISIS 588548	5-10-5 MOE	100	2.1	1.3	1.1
ISIS 588550	5-10-5 MOE	100	3.9	1.4	1.1
ISIS 588553	5-10-5 MOE	100	4.1	1.4	1.4
ISIS 588555	5-10-5 MOE	100	1.8	1.3	1.0
ISIS 588848	Deoxy, MOE and cEt	50	3.1	1.3	1.1
ISIS 594430	3-10-3 cEt	50	1.7	1.0	1.1

Example 14: Efficacy of antisense oligonucleotides against CFB mRNA in hCFB transgenic mice

Selected compounds were tested for efficacy in human CFB transgenic mice, founder line #6. The human CFB gene is located on chromosome 6: position 31913721- 31919861. A Fosmid (ABC14-50933200C23) containing the CFB sequence was selected to make transgenic mice expressing the human CFB gene. Cla I (31926612) and Age I (31926815) restriction enzymes were used to generate a 22,127 bp fragment containing the CFB gene for pronuclear injection. DNA was confirmed by restriction enzyme analysis using Pvu I. The 22,127 bp DNA fragment was injected into C57BL/6NTac embryos. 6 positive founders were bred. Founder #6 expressed the liver human CFB mRNA and was crossbreed to the 3rd generation. Progeny from 3rd generation mice were used to evaluate human CFB ASOs for human CFB mRNA reduction.

Treatment

Groups of 3 mice each were injected subcutaneously twice a week for the first week with 50 mg/kg of ISIS oligonucleotides, followed by once a week dosing with 50 mg/kg of ISIS oligonucleotides for an additional three weeks. One control group of 4 mice was injected subcutaneously twice a week for 2 weeks for the first week with PBS for the first week for an additional three weeks. Forty eight hours after the last dose, mice were euthanized and organs and plasma were harvested for further analysis.

RNA Analysis

At the end of the dosing period, RNA was extracted from the liver and kidney for real-time PCR analysis of CFB mRNA levels. Human CFB mRNA levels were measured using the human primer probe set RTS3459. CFB mRNA levels were normalized to RIBOGREEN®, and also to the housekeeping gene, Cyclophilin. Results were calculated as percent inhibition of CFB mRNA expression compared to the control. All the antisense oligonucleotides effected inhibition of human CFB mRNA levels in the liver.

Table 75

Percent reduction of CFB mRNA levels in hCFB mice

ISIS No	Normalized to RIBOGREEN	Normalized to Cyclophilin
532770	86	87
532800	88	87
532809	69	69
588540	95	94
588544	91	91
588548	78	77
588550	89	88
588553	94	94
588555	94	94
588848	83	82
594430	78	76

Example 15: *In vivo* antisense inhibition of murine CFB

Several antisense oligonucleotides were designed that were targeted to murine CFB mRNA (GENBANK Accession No. NM_008198.2, incorporated herein as SEQ ID NO: 5). The target start sites and sequences of each oligonucleotide are described in the table below. The chimeric antisense oligonucleotides in the table below were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment is comprised of 10 2'-deoxynucleosides and is flanked on both sides (in the 5' and 3' directions) by wings comprising 5 nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines.

Table 76

Gapmers targeting murine CFB

ISIS No	Sequence	Target Start Site on SEQ ID NO: 5	SEQ ID NO
516269	GCATAAGAGGGTACCAGCTG	2593	804
516272	GTCCTTTAGCCAGGGCAGCA	2642	805
516323	TCCACCCATGTTGTGCAAGC	1568	806
516330	CCACACCATGCCACAGAGAC	1826	807
516341	TTCCGAGTCAGGCTCTTCCC	2308	808

Treatment

Groups of four C57BL/6 mice each were injected with 50 mg/kg of ISIS 516269, ISIS 516272, ISIS 516323, ISIS 516330, or ISIS 516341 administered weekly for 3 weeks. A control group of mice was injected with phosphate buffered saline (PBS) administered weekly for 3 weeks.

CFB RNA Analysis

At the end of the study, RNA was extracted from liver tissue for real-time PCR analysis of CFB, using primer probe set RTS3430 (forward sequence GGGCAAACAGCAATTTGTGA, designated herein as SEQ ID NO: 816; reverse sequence TGGCTACCCACCTTCCTTGT, designated herein as SEQ ID NO: 817; probe sequence CTGGATACTGTCCCAATCCCGGTATTCCX, designated herein as SEQ ID NO: 818). The mRNA levels were normalized using RIBOGREEN®. As shown in the Table below, some of the antisense oligonucleotides achieved reduction of murine CFB over the PBS control. Results are presented as percent inhibition of CFB, relative to control.

Table 77
Percent inhibition of murine CFB mRNA in C57BL/6 mice

ISIS No	%
516269	29
516272	72
516323	77
516330	62
516341	72

Protein Analysis

CFB protein levels were measured in the kidney, liver, plasma, and in the eye by western Blot using goat anti-CFB antibody (Sigma Aldrich). Results are presented as percent inhibition of CFB, relative to PBS control. 'n/a' indicates that measurements were not taken for that sample. As shown in the Table below, antisense inhibition of CFB by ISIS oligonucleotides resulted in a reduction of CFB protein in various tissues. As shown in the Table below, systemic administration of ISIS oligonucleotides was effective in reducing CFB levels in the eye.

Table 78
Percent inhibition of murine CFB protein in C57BL/6 mice

ISIS No	Kidney	Liver	Plasma	Eye
516269	20	58	n/a	70
516272	48	74	n/a	99
516323	73	85	90	93
516330	77	80	n/a	n/a
516341	80	88	68	n/a

Example 16: Dose-dependent antisense inhibition of murine CFB

Groups of four C57BL/6 mice each were injected with 25 mg/kg, 50 mg/kg, or 100 mg/kg of ISIS 516272, and ISIS 516323 administered weekly for 6 weeks. Another two groups of mice were injected with 100 mg/kg of ISIS 516330 or ISIS 516341 administered weekly for 6 weeks. Two control groups of mice were injected with phosphate buffered saline (PBS) administered weekly for 6 weeks.

CFB RNA Analysis

RNA was extracted from liver and kidney tissues for real-time PCR analysis of CFB, using primer probe set RTS3430. The mRNA levels were normalized using RIBOGREEN®. As shown in the Table below, the antisense oligonucleotides achieved dose-dependent reduction of murine CFB over the PBS control. Results are presented as percent inhibition of CFB, relative to control.

Table 79
Percent inhibition of murine CFB mRNA in C57BL/6 mice

ISIS No	Dose (mg/kg/wk)	Liver	Kidney
516272	25	39	32
	50	73	36
	100	87	42
516323	25	36	41
	50	65	47
	100	79	71
516330	100	85	45
516341	200	89	65

Protein Analysis

CFB protein levels were measured in the plasma by western Blot using goat anti-CFB antibody (Sigma Aldrich). As shown in the table below, antisense inhibition of CFB by the ISIS oligonucleotides resulted in a reduction of CFB protein. Results are presented as percent inhibition of CFB, relative to PBS control. 'n/a' indicates that measurements were not taken for that sample.

CFB protein levels were also measured in the eye by Western Blot. All treatment groups demonstrated an inhibition of CFB by 95%, with some sample measurements being below detection levels of the assay.

Table 80
Percent inhibition of murine CFB protein in C57BL/6 mice

ISIS No	Dose (mg/kg/wk)	Liver
516272	25	32
	50	70
	100	83

516323	25	43
	50	80
	100	90
516330	100	n/a
516341	200	n/a

Example 17: Effect of antisense inhibition of CFB in the NZB/W F1 mouse model

The NZB/W F1 is the oldest classical model of lupus, where the mice develop severe lupus-like phenotypes comparable to that of lupus patients (Theofilopoulos, A.N. and Dixon, F.J. Advances in Immunology, vol. 37, pp. 269–390, 1985). These lupus-like phenotypes include lymphadenopathy, splenomegaly, elevated serum antinuclear autoantibodies (ANA) including anti-dsDNA IgG, a majority of which are IgG2a and IgG3, and immune complex-mediated glomerulonephritis (GN) that becomes apparent at 5-6 months of age, leading to kidney failure and death at 10–12 months of age.

Study 1

A study was conducted to demonstrate that treatment with antisense oligonucleotides targeting CFB would improve renal pathology in the mouse model. Female NZB/W F1 mice, 17 weeks old, were purchased from Jackson Laboratories. Groups of 16 mice each received doses of 100 μg/kg/week of ISIS 516272 or ISIS 516323 for 20 weeks. Another group of 16 mice received doses of 100 μg/kg/week of control oligonucleotide ISIS 141923 for 20 weeks. Another group of 10 mice received doses of PBS for 20 weeks and served as the control group to which all the other groups were compared. Terminal endpoints were collected 48 hours after the last dose was injected.

CFB RNA Analysis

RNA was extracted from liver and kidney tissue for real-time PCR analysis of CFB, using primer probe set RTS3430. The mRNA levels were normalized using RIBOGREEN®. As shown in the Table below, some of the antisense oligonucleotides achieved reduction of murine CFB over the PBS control. Results are presented as percent inhibition of CFB, relative to control.

Table 81
Percent inhibition of murine CFB mRNA in NZB/W F1 mice

ISIS No	Liver	Kidney
516272	55	25
516323	63	43
141923	0	0

Proteinuria

Proteinuria is expected in 60% of animals in this mouse model. The cumulative incidence of severe proteinuria was measured by calculating the total protein to creatinine ratio using a clinical analyzer. The results are presented in the table below and demonstrate that treatment with antisense oligonucleotides targeting CFB achieved reduction of proteinuria in the mice compared to the PBS control and the control oligonucleotide treated mice.

Table 82
Percent cumulative incidence of severe proteinuria in NZB/W F1 mice

	%
PBS	40
ISIS 516272	6
ISIS 516323	0
ISIS 141923	25

Survival

Survival of the mice was monitored by keeping count of the mice at the start of treatment and then again at week 20. The results are presented in the table below and demonstrate that treatment with antisense oligonucleotides targeting CFB increased survival in the mice compared to the PBS control and the control oligonucleotide treated mice.

Table 83
Number of surviving mice and % survival

	Week 1	Week 20	% survival at week 20
PBS	10	6	60
ISIS 516272	16	15	94
ISIS 516323	16	16	100
ISIS 141923	16	12	75

Glomerular deposition

The amount of C3 deposition, as well as IgG deposition, in the glomeruli of the kidneys was measured by immunohistochemistry with an anti-C3 antibody. The results are presented in the table below and demonstrate that treatment with antisense oligonucleotides targeting CFB achieved reduction of both C3 and IgG depositions in the kidney glomeruli compared to the PBS control and the control oligonucleotide treated mice.

Table 84
Percent inhibition of glomerula deposition in NZB/W F1 mice

ISIS No	C3	IgG
516272	45	20

516323	48	2
141923	0	0

Study 2

Female NZB/W F1 mice, 16 weeks old, were purchased from Jackson Laboratories. A group of 10 mice received doses of 100 μg/kg/week of ISIS 516323 for 12 weeks. Another group of 10 mice received doses of 100 μg/kg/week of control oligonucleotide ISIS 141923 for 12 weeks. Another group of 10 mice received doses of PBS for 12 weeks and served as the control group to which all the other groups were compared. Terminal endpoints were collected 48 hours after the last dose was injected.

CFB RNA Analysis

RNA was extracted from liver and kidney tissue for real-time PCR analysis of CFB, using primer probe set RTS3430. As shown in the table below, treatment with ISIS 516323 achieved reduction of murine CFB over the PBS control. Results are presented as percent inhibition of CFB, relative to control.

Table 85
Percent inhibition of murine CFB mRNA in NZB/W F1 mice

ISIS No	Liver	Kidney
516323	75	46
141923	0	6

Proteinuria

The cumulative incidence of severe proteinuria was assessed by measuring urine total protein to creatinine ratio, as well as by measuring total microalbumin levels. The results are presented in the tables below and demonstrate that treatment with antisense oligonucleotides targeting CFB reduced proteinuria in the mice compared to the PBS control and the control oligonucleotide treated mice.

Table 86
Proteinuria in NZB/W F1 mice measured as urine microalbumin levels (mg/dl)

ISIS No	Week 0	Week 6	Week 8	Week 10
516323	0	0	5.4	0.4
141923	0	8.28	8.6	5.6

Table 87
Proteinuria in NZB/W F1 mice measured as total protein to creatinine ratio

ISIS No	Week 0	Week 6	Week 8	Week 10
516323	5.5	7.8	8.6	7.2
141923	6.9	10.0	13.5	7.2

Survival

Survival of the mice was monitored by keeping count of the mice at the start of treatment and then again at week 12. The results are presented in the table below and demonstrate that treatment with antisense oligonucleotides targeting CFB increased survival in the mice compared to the PBS control and the control oligonucleotide treated mice.

Table 88
Number of surviving mice

	Week 1	Week 12
PBS	10	9
ISIS 516323	10	10
ISIS 141923	10	9

Example 18: Effect of antisense inhibition of CFB in the MRL mouse model

The MRL/lpr lupus nephritis mouse model develops an SLE-like phenotype characterized by lymphadenopathy due to an accumulation of double negative ($CD4^-$ $CD8^-$) and $B220^+$ T-cells. These mice display an accelerated mortality rate. In addition, the mice have high concentrations of circulating immunoglobulins, which included elevated levels of autoantibodies such as ANA, anti-ssDNA, anti-dsDNA, anti-Sm, and rheumatoid factors, resulting in large amounts of immune complexes (Andrews, B. et al., J. Exp. Med. 148: 1198-1215, 1978).

Treatment

A study was conducted to investigate whether treatment with antisense oligonucleotides targeting CFB would reverse renal pathology in the mouse model. Female MRL/lpr mice, 14 weeks old, were purchased from Jackson Laboratories. A group of 10 mice received doses of 50 μg/kg/week of ISIS 516323 for 7 weeks. Another group of 10 mice received doses of 50 μg/kg/week of control oligonucleotide ISIS 141923 for 7 weeks. Another group of 10 mice received doses of PBS for 7 weeks and served as the control group to which all the other groups were compared. Terminal endpoints were collected 48 hours after the last dose was injected.

CFB RNA Analysis

RNA was extracted from liver tissue for real-time PCR analysis of CFB, using primer probe set RTS3430. As shown in the Table below, ISIS 516323 reduced CFB over the PBS control. Results are presented as percent inhibition of CFB, relative to control.

Table 89
Percent inhibition of murine CFB mRNA in MRL/lpr mice

ISIS No	%

516323	68
141923	4

Renal pathology

Renal pathology was evaluated by two methods. Histological sections of the kidney were stained with Haematoxylin & Eosin. The PBS control demonstrated presence of multiglomerular crescents tubular casts, which is a symptom of glomerulosclerosis. In contrast, the sections from mice treated with ISIS 516323 showed absent crescents tubular casts with minimal bowman capsule fibrotic changes, moderate to severe segmental mesangial cell expansion and glomerular basement membrane thickening.

Accumulation of C3 in the kidney was also assessed by immunohistochemistry with anti-C3 antibodies. The whole kidney C3 immunohistochemistry intensity score was calculated by intensity scoring system, which was computed by capturing 10 glomeruli per kidney and calculation the intensity of positive C3 staining. The results are presented in the table below and demonstrate that treatment with ISIS 516323 reduced renal C3 accumulation compared to the control groups.

Table 90

Renal C3 accumulation in MRL/lpr mice

	Whole kidney C3 intensity score	C3 quantification (area/total area) % of average PBS
PBS	2.5	100
ISIS 516323	1.6	68
ISIS 141923	2.2	99

Plasma C3 levels

Reduction of CFB inhibits activation of the alternative complement pathway, preventing C3 consumption and leading to an apparent elevation of plasma C3 levels. Plasma C3 levels from terminal bleed were measured by clinical analyzer. The results are presented in the table below and demonstrate that treatment with ISIS 516323 increased C3 levels ($p < 0.001$) in the plasma compared to the control groups.

Table 91

Plasma C3 levels (mg/dL) in MRL/lpr mice

ISIS No	C3
516323	28
141923	16

The results indicate that treatment with antisense oligonucleotides targeting CFB reverses renal pathology in the lupus mouse model.

Example 19: Effect of antisense inhibition of CFB in the CFH Het mouse model

CFH heterozygous (CFH Het, $CFH^{+/-}$) mouse model expresses a mutant Factor H protein in combination with the full-length mouse protein (Pickering, M.C. et al., J. Exp. Med. 2007. 204: 1249-56). Renal histology remains normal in these mice up to six months old.

Study 1

Groups of 8 $CFH^{+/-}$ mice, 6 weeks old, each received doses of 75 mg/kg/week of ISIS 516323 or ISIS 516341 for 6 weeks. Another group of 8 mice received doses of 75 mg/kg/week of control oligonucleotide ISIS 141923 for 6 weeks. Another group of 8 mice received doses of PBS for 6 weeks and served as the control group to which all the other groups were compared. Terminal endpoints were collected 48 hours after the last dose was injected.

CFB RNA Analysis

RNA was extracted from liver and kidney tissue for real-time PCR analysis of CFB, using primer probe set RTS3430. As shown in the Table below, the antisense oligonucleotides reduced CFB over the PBS control. Results are presented as percent inhibition of CFB, relative to control.

Table 92
Percent inhibition of murine CFB mRNA in $CFH^{+/-}$ mice

ISIS No	Liver	Kidney
516323	80	38
516341	90	44
141923	0	17

Plasma C3 levels

Reduction of CFB inhibits activation of the alternative complement pathway, preventing C3 consumption and leading to an apparent elevation of plasma C3 levels. Plasma C3 levels from terminal plasma collection were measured by clinical analyzer. The results are presented in the table below and demonstrate that treatment with ISIS 516323 increased C3 to normal levels in the plasma.

Table 93
Plasma C3 levels (mg/dL) in $CFH^{+/-}$ mice

ISIS No	C3
516323	15
516341	17
141923	8

Study 2

Groups of 5 $CFH^{+/-}$ mice each received doses of 12.5 mg/kg/week, 25 mg/kg/week, 50 mg/kg/week, 75 mg/kg/week, or 100 mg/kg/week of ISIS 516323 or ISIS 516341 for 6 weeks. Another group of 5 mice received doses of 75 μg/kg/week of control oligonucleotide ISIS 141923 for 6 weeks. Another group of 5

mice received doses of PBS for 6 weeks and served as the control group to which all the other groups were compared. Terminal endpoints were collected 48 hours after the last dose was injected.

CFB RNA Analysis

RNA was extracted from liver and kidney tissue for real-time PCR analysis of CFB, using primer probe set RTS3430. As shown in the Table below, the antisense oligonucleotides reduced CFB over the PBS control in a dose dependent manner. Results are presented as percent inhibition of CFB, relative to control.

Table 94

Percent inhibition of murine CFB mRNA in the liver of $CFH^{+/-}$ mice

ISIS No	Dose (mg/kg/week)	%
516323	12.5	34
	25	51
	50	72
	75	79
	100	92
516341	12.5	38
	25	57
	50	89
	75	92
	100	90
141923	75	13

Plasma C3 levels

Reduction of CFB inhibits activation of the alternative complement pathway, preventing C3 consumption and leading to an apparent elevation of plasma C3 levels. Plasma C3 levels from terminal plasma collection were measured by clinical analyzer. The results are presented in the table below and demonstrate that treatment with ISIS oligonucleotides targeting CFB increased C3 levels in the plasma.

Table 95

Plasma C3 levels (mg/dL) in $CFH^{+/-}$ mice

	Dose (mg/kg/week)	C3
PBS	-	10.1
516323	12.5	11.4
	25	15.5
	50	17.0
	75	18.3
	100	18.8
516341	12.5	12.1
	25	16.3
	50	18.6

	75	22.1
	100	19.1
141923	75	8.9

Example 20: Effect of ISIS antisense oligonucleotides targeting human CFB in cynomolgus monkeys

Cynomolgus monkeys were treated with ISIS antisense oligonucleotides selected from studies described in the Examples above. Antisense oligonucleotide efficacy and tolerability, as well as their pharmacokinetic profile in the liver and kidney, were evaluated.

At the time this study was undertaken, the cynomolgus monkey genomic sequence was not available in the National Center for Biotechnology Information (NCBI) database; therefore cross-reactivity with the cynomolgus monkey gene sequence could not be confirmed. Instead, the sequences of the ISIS antisense oligonucleotides used in the cynomolgus monkeys was compared to a rhesus monkey sequence for homology. The human antisense oligonucleotides tested below are cross-reactive (with 0 or 1 mismatches) with the rhesus genomic sequence (GENBANK Accession No. NW_001116486.1 truncated from nucleotides 536000 to 545000, designated herein as SEQ ID NO: 3). The start and stop sites of each oligonucleotide targeted to SEQ ID NO: 3 is presented in the Table below. "Start site" indicates the 5'-most nucleotide to which the gapmer is targeted in the rhesus monkey gene sequence. 'Mismatches' indicates the number of nucleobases in the human oligonucleotide that are mismatched with the rhesus genomic sequence.

Table 96

Antisense oligonucleotides complementary to the rhesus CFB genomic sequence (SEQ ID NO: 3)

ISIS No	Target Start Site	Mismatches	Chemistry	SEQ ID NO
532770	6788	0	5-10-5 MOE	198
532800	7500	0	5-10-5 MOE	228
532809	7614	0	5-10-5 MOE	237
588540	7627	1	5-10-5 MOE	440
588544	7631	1	5-10-5 MOE	444
588548	7635	1	5-10-5 MOE	448
588550	7637	1	5-10-5 MOE	450
588553	7640	1	5-10-5 MOE	453
588555	7643	0	5-10-5 MOE	455
588848	7639	1	Deoxy, MOE and cEt	598
594430	6790	0	3-10-3 cEt	549

Treatment

Prior to the study, the monkeys were kept in quarantine for at least a 30 day period, during which the animals were observed daily for general health. The monkeys were 2-4 years old and weighed between 2 and 4 kg. Eleven groups of 4-6 randomly assigned male cynomolgus monkeys each were injected subcutaneously with ISIS oligonucleotide or PBS at four sites on the back in a clockwise rotation (i.e. left, top, right, and bottom), one site per dose. The monkeys were given four loading doses of PBS or 40 mg/kg of ISIS 532800, ISIS 532809, ISIS 588540, ISIS 588544, ISIS 588548, ISIS 588550, ISIS 588553, ISIS 588555, ISIS 588848, or ISIS 594430 for the first week (days 1, 3, 5, and 7), and were subsequently dosed once a week for 12 weeks (days 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84) with PBS or 40 mg/kg of ISIS oligonucleotide. ISIS 532770 was tested in a separate study with similar conditions with two male and two female cynomolgus monkeys in the group.

Hepatic Target Reduction

RNA analysis

On day 86, liver and kidney samples were collected in duplicate (approximately 250 mg each) for CFB mRNA analysis. The samples were flash frozen in liquid nitrogen at necropsy within approximately 10 minutes of sacrifice.

RNA was extracted from liver and kidney for real-time PCR analysis of measurement of mRNA expression of CFB. Results are presented as percent change of mRNA, relative to PBS control, normalized with RIBOGREEN®. RNA levels were also normalized with the house-keeping gene, Cyclophilin A. RNA levels were measured with the primer probe sets RTS3459, described above, or RTS4445_MGB (forward sequence CGAAGAAGCTCAGTGAAATCAA, designated herein as SEQ ID NO: 819; reverse sequence TGCCTGGAGGGCCCTCTT, designated herein as SEQ ID NO: 820; probe sequence AGACCACAAGTTGAAGTC, designated herein as SEQ ID NO: 815).

As shown in the Tables below, treatment with ISIS antisense oligonucleotides resulted in reduction of CFB mRNA in comparison to the PBS control. Analysis of CFB mRNA levels revealed that several of the ISIS oligonucleotides reduced CFB levels in liver and/or kidney. Here '0' indicates that the expression levels were not inhibited. '*' indicates that the oligonucleotide was tested in a separate study with similar conditions.

Table 97

Percent inhibition of CFB mRNA in the cynomolgus monkey liver relative to the PBS control

ISIS No	RTS3459/ Cyclophilin A	RTS3459/ RIBOGREEN	RTS445_MGB/ Cyclophilin A	RTS445_MGB / RIBOGREEN
532770*	12	37	24	45

532800	54	45	56	46
588540	31	27	28	24
588548	68	67	68	67
588550	53	39	51	37
588553	74	59	74	59
588555	73	71	71	69
588848	9	0	6	0
594430	24	26	23	25

Table 98

Percent inhibition of CFB mRNA in the cynomolgus monkey kidney relative to the PBS control

ISIS No	RTS3459/ Cyclophilin A	RTS3459/ RIBOGREEN	RTS445_MGB/ Cyclophilin A	RTS445_MGB / RIBOGREEN
532770*	34	56	2	31
532800	36	30	43	37
588540	70	71	67	69
588548	83	84	82	83
588550	81	77	78	74
588553	86	84	86	85
588555	32	34	48	50
588848	89	91	87	90
594430	33	37	19	23

Protein analysis

Approximately 1 mL of blood was collected from all available animals at day 85 and placed in tubes containing the potassium salt of EDTA. The blood samples were placed in wet-ice or Kryorack immediately, and centrifuged (3000 rpm for 10 min at 4°C) to obtain plasma (approximately 0.4 mL) within 60 minutes of collection. Plasma levels of CFB were measured in the plasma by radial immunodiffusion (RID), using a polyclonal anti-Factor B antibody. The results are presented in the Table below. ISIS 532770 was tested in a separate study and plasma protein levels were measured on day 91 or 92 in that group.

Analysis of plasma CFB revealed that several ISIS oligonucleotides reduced protein levels in a sustained manner. ISIS 532770, which was tested in a separate study, reduced CFB protein levels on day 91/92 by 50% compared to baseline values. The reduction in plasma CFB protein levels correlates well with liver CFB mRNA level reduction in the corresponding groups of animals.

Table 99

Plasma protein levels (% baseline values) in the cynomolgus monkey

	Day 1	Day 30	Day 58	Day 72	Day 86
PBS	113	115	95	83	86
ISIS 532800	117	68	52	39	34
ISIS 532809	104	121	100	80	71

ISIS 588540	108	72	61	40	38
ISIS 588544	118	74	53	33	29
ISIS 588548	110	41	28	20	16
ISIS 588550	104	64	54	38	37
ISIS 588553	97	42	35	18	16
ISIS 588555	107	35	37	18	18
ISIS 588848	116	95	92	69	71
ISIS 594430	104	64	59	45	46

Tolerability studies

Body weight measurements

To evaluate the effect of ISIS oligonucleotides on the overall health of the animals, body and organ weights were measured and are presented in the Table below. '*' indicates that the oligonucleotide was tested in a separate study with similar conditions and is the average of the measurements from male and female monkeys. The results indicate that effect of treatment with antisense oligonucleotides on body and organ weights was within the expected range for antisense oligonucleotides.

Table 100

Final body weights (g) in cynomolgus monkey

	Day 1	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84
PBS	2887	2953	3028	3094	3125	3143	3193
ISIS 532770*	2963	2947	2966	3050	3097	3138	3160
ISIS 532800	2886	2976	3072	3149	3220	3269	3265
ISIS 532809	2755	2836	2927	2983	3019	3071	3098
ISIS 588540	2779	2834	2907	2934	2981	3034	3057
ISIS 588544	2837	2896	3009	3064	3132	3163	3199
ISIS 588548	2694	2816	2882	2990	3073	3149	3161
ISIS 588550	2855	2988	3062	3188	3219	3282	3323
ISIS 588553	3033	3156	3256	3335	3379	3372	3442
ISIS 588555	2757	2863	2965	3022	3075	3088	3158
ISIS 588848	2850	3018	3032	3187	3230	3212	3291
ISIS 594430	2884	2963	2953	3149	3187	3204	3256

Table 101

Final organ weights (g) in cynomolgus monkey

	Spleen	Heart	Kidney	Liver
PBS	2.8	11.6	11.9	55.8
ISIS 532770*	5.0	11.3	20.6	77.9
ISIS 532800	6.2	11.9	18.6	94.4
ISIS 588540	4.0	11.4	13.5	67.1
ISIS 588548	4.1	11.7	17.3	72.0

ISIS 588550	5.8	10.9	18.5	81.8
ISIS 588553	5.0	12.7	17.2	85.9
ISIS 588555	4.7	11.8	15.9	88.3
ISIS 588848	5.0	12.7	14.4	75.7
ISIS 594430	3.9	11.9	14.8	69.9

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, blood samples were collected from all the study groups. The blood samples were collected from the cephalic, saphenous, or femoral veins, 48 hours post-dosing. The monkeys were fasted overnight prior to blood collection. Blood (1.5 mL) was collected in tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 minutes and then centrifuged (approximately 3,000 rpm for 10 min) to obtain serum. Levels of various liver function markers were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan).

Plasma levels of ALT and AST were measured and the results are presented in the Table below, expressed in IU/L. Bilirubin, a liver function marker, was similarly measured and is presented in the Table below expressed in mg/dL. '*' indicates that the oligonucleotide was tested in a separate study with similar conditions and is the average of the measurements from male and female monkeys. The results indicate that most of the antisense oligonucleotides had no effect on liver function outside the expected range for antisense oligonucleotides.

Table 102

Liver chemistry marker levels in cynomolgus monkey plasma on day 86

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)
PBS	71	57	0.3
ISIS 532770*	59	58	0.1
ISIS 532800	65	86	0.1
ISIS 532809	35	58	0.1
ISIS 588540	70	88	0.2
ISIS 588544	55	97	0.2
ISIS 588548	61	85	0.2
ISIS 588550	94	84	0.2
ISIS 588553	44	65	0.2
ISIS 588555	63	84	0.2
ISIS 588848	69	65	0.2
ISIS 594430	86	53	0.2

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, blood samples were collected from all the study groups. The blood samples were collected from the cephalic, saphenous, or femoral veins, 48 hours post-dosing. The monkeys were fasted overnight prior to blood collection. Blood was collected in tubes without anticoagulant for serum separation. The tubes were kept at room temperature for a minimum of 90 minutes and then centrifuged (approximately 3,000 rpm for 10 min) to obtain serum. Levels of BUN and creatinine were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan). Results are presented in the Table below, expressed in mg/dL. '*' indicates that the oligonucleotide was tested in a separate study with similar conditions and is the average of the measurements from male and female monkeys.

For urinalysis, fresh urine from all the animals was collected in the morning using a clean cage pan on wet ice. Food was removed overnight the day before urine collection but water was supplied. Urine samples (approximately 1 mL) were analyzed for protein to creatinine (P/C) ratio using a Toshiba 200FR NEO automated chemistry analyzer (Toshiba Co., Japan). 'n.d.' indicates that the urine protein level was under the detection limit of the analyzer.

The plasma and urine chemistry data indicate that most of the ISIS oligonucleotides did not have any effect on the kidney function outside the expected range for antisense oligonucleotides.

Table 103

Renal chemistry marker levels (mg/dL) in cynomolgus monkey plasma on day 86

	BUN	Creatinine	Total protein
PBS	28	0.9	8.0
ISIS 532770*	20	0.9	6.9
ISIS 532800	25	0.9	7.5
ISIS 532809	23	0.8	7.4
ISIS 588540	30	0.8	7.5
ISIS 588544	26	0.9	7.4
ISIS 588548	25	0.9	7.6
ISIS 588550	24	0.9	7.2
ISIS 588553	25	0.8	7.2
ISIS 588555	25	0.8	7.6
ISIS 588848	24	0.9	7.5
ISIS 594430	25	0.8	7.2

Table 104

Total Protein/Creatinine ratio in cynomolgus monkey urine

	Day 44	Day 86
PBS	0.03	n.d.
ISIS 532800	0.01	n.d.
ISIS 532809	0.01	n.d.

ISIS 588540	0.03	n.d.
ISIS 588544	0.01	0.09
ISIS 588548	0.01	0.01
ISIS 588550	0.04	0.01
ISIS 588553	0.05	n.d.
ISIS 588555	0.03	0.03
ISIS 588848	0.09	n.d.
ISIS 594430	0.03	n.d.

Hematology

To evaluate any effect of ISIS oligonucleotides in cynomolgus monkeys on hematologic parameters, blood samples of approximately 0.5 mL of blood was collected from each of the available study animals in tubes containing K_2-EDTA. Samples were analyzed for red blood cell (RBC) count, white blood cells (WBC) count, individual white blood cell counts, such as that of monocytes, neutrophils, lymphocytes, as well as for platelet count, hemoglobin content and hematocrit, using an ADVIA120 hematology analyzer (Bayer, USA). The data is presented in the Tables below. '*' indicates that the oligonucleotide was tested in a separate study with similar conditions and is the average of the measurements from male and female monkeys.

The data indicate the oligonucleotides did not cause any changes in hematologic parameters outside the expected range for antisense oligonucleotides at this dose.

Table 105

Blood cell counts in cynomolgus monkeys

	RBC (x 10^6/μL)	Platelets (x 10^3/μL)	WBC (x 10^3/μL)	Neutrophils (% WBC)	Lymphocytes (% total)	Monocytes (% total)
PBS	5.8	347	9.4	42.7	53.1	3.0
ISIS 532770*	5.4	386	10.8	22.3	71.7	3.3
ISIS 532800	5.6	360	13.1	29.5	61.1	6.5
ISIS 532809	5.2	400	11.5	56.6	38.2	2.5
ISIS 588540	5.5	367	11.7	50.9	42.7	2.1
ISIS 588544	5.2	373	14.3	56.6	37.6	4.3
ISIS 588548	5.1	373	9.7	40.4	54.3	3.9
ISIS 588550	6.1	343	9.9	32.1	61.7	4.6
ISIS 588553	5.2	424	9.3	41.7	53.2	3.6
ISIS 588555	5.1	411	9.6	45.1	49.7	3.5
ISIS 588848	5.7	370	10.0	39.8	55.8	3.1
ISIS 594430	5.7	477	10.6	47.3	47.8	3.6

Table 106

Hematologic parameters in cynomolgus monkeys

	Hemoglobin (g/dL)	HCT (%)
PBS	14.1	46.6

ISIS 532770*	12.4	40.9
ISIS 532800	12.3	40.5
ISIS 532809	12.2	40.4
ISIS 588540	12.5	41.5
ISIS 588544	11.9	38.1
ISIS 588548	12.3	39.6
ISIS 588550	13.4	45.0
ISIS 588553	12.6	39.8
ISIS 588555	11.6	38.1
ISIS 588848	13.2	42.7
ISIS 594430	13.4	43.1

Measurement of oligonucleotide concentration

The concentration of the full-length oligonucleotide was measured in the kidney and liver tissues. The method used is a modification of previously published methods (Leeds et al., 1996; Geary et al., 1999) which consist of a phenol-chloroform (liquid-liquid) extraction followed by a solid phase extraction. Tissue sample concentrations were calculated using calibration curves, with a lower limit of quantitation (LLOQ) of approximately 1.14 μg/g. The results are presented in the Table below, expressed as μg/g liver or kidney tissue.

Table 107

Antisense oligonucleotide distribution

	Kidney (μg/g)	Liver (μg/g)	Kidney/Liver ratio
ISIS 532800	3881	1633	2.4
ISIS 588540	3074	1410	2.2
ISIS 588548	3703	1233	3.0
ISIS 588550	4242	860	4.9
ISIS 588553	3096	736	4.2
ISIS 588555	4147	1860	2.2
ISIS 588848	2235	738	3.0
ISIS 594430	1548	752	2.1

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CLAIMS

1. A compound comprising a modified oligonucleotide consisting of 16 to 30 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 440, 198, 228, 237, 444, 448, 450, 453, 455, 549, and 598, wherein the modified oligonucleotide has:

    a gap segment consisting of linked deoxynucleosides;

    a 5' wing segment consisting of linked nucleosides; and

    a 3' wing segment consisting of 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 modified sugar, wherein the modified sugar is a 2'-O-methoxyethyl sugar or a cEt sugar; wherein each internucleoside linkage of the modified oligonucleotide is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

2. The compound of claim 1, wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence consisting of the nucleobase sequence recited in SEQ ID NO: 440, 198, 228, 237, 444, 448, 450, 453, or 455, wherein the modified oligonucleotide has:

    a gap segment consisting of ten linked deoxynucleosides;

    a 5' wing segment consisting of five linked nucleosides; and

    a 3' wing segment consisting of five linked nucleosides;

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

3. A compound comprising a modified oligonucleotide consisting of 20 linked nucleosides and having a nucleobase sequence consisting of the nucleobase sequence recited in SEQ ID NO: 440, wherein the modified oligonucleotide has:

    a gap segment consisting of ten linked deoxynucleosides;

    a 5' wing segment consisting of five linked nucleosides; and

    a 3' wing segment consisting of five linked nucleosides;

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

4. A compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence consisting of the nucleobase sequence recited in SEQ ID NO: 598, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein the 5' wing segment comprises a 2'-O-methoxyethyl sugar, 2'-O-methoxyethyl sugar, and cEt sugar in the 5' to 3' direction; wherein the 3' wing segment comprises a cEt sugar, cEt sugar, and 2'-O-methoxyethyl sugar in the 5' to 3' direction; wherein each internucleoside linkage of the modified oligonucleotide is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

5. A compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence consisting of the nucleobase sequence recited in SEQ ID NO: 549, wherein the modified oligonucleotide has:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of three 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 cEt sugar; wherein each internucleoside linkage of the modified oligonucleotide is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

6. The compound of claim 1, wherein the modified oligonucleotide is at least 80%, at least 95% or 100% complementary to SEQ ID NO: 1.

7. A composition comprising the compound of any one of claims 1-6 or a salt thereof and a pharmaceutically acceptable carrier.

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8. A method of treating a disease associated with dysregulation of the complement alternative pathway in a subject comprising administering to the subject the compound of any one of claims 1-6 or the composition of claim 7, thereby treating the disease.

9. The method of claim 8, wherein the complement alternative pathway is activated greater than normal.

10. The method of claim 8 or 9, wherein the disease is macular degeneration, age related macular degeneration (AMD), wet AMD, dry AMD, or Geographic Atrophy.

11. The method of claim 8 or 9, wherein the disease is a kidney disease, lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS).

12. Use of a compound of any one of claims 1-6 or the composition of claim 7 in the manufacture of a medicament for treating a disease associated with dysregulation of the complement alternative pathway.

13. The use of claim 12, wherein the complement alternative pathway is activated greater than normal.

14. The use of claim 12 or 13, wherein the disease is macular degeneration, age related macular degeneration (AMD), wet AMD, dry AMD, or Geographic Atrophy.

15. The use of claim 12 or 13, wherein the disease is a kidney disease, lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS).

16. A compound of any one of claims 1-6, or the composition of claim 7, for use in treating a disease associated with dysregulation of the complement alternative pathway.

17. The compound or composition for use according to claim 16, wherein the complement alternative pathway is activated greater than normal.

18. The compound or composition for use according to claim 16 or 17, wherein the disease is macular degeneration, age related macular degeneration (AMD), wet AMD, dry AMD, or Geographic Atrophy.

19. The compound or composition for use according to claim 16 or 17, wherein the disease is a kidney disease, lupus nephritis, systemic lupus erythematosus (SLE), dense deposit disease (DDD), C3 glomerulonephritis (C3GN), CFHR5 nephropathy, or atypical hemolytic uremic syndrome (aHUS).

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aat gga act ggg act aac acc tat gca gcc cta aac agt gtc tat ctc        813
Asn Gly Thr Gly Thr Asn Thr Tyr Ala Ala Leu Asn Ser Val Tyr Leu
180                 185                 190                 195

atg atg aac aat caa atg caa ctc ctt ggc atg aaa acg atg gcc tgg        861
Met Met Asn Asn Gln Met Gln Leu Leu Gly Met Lys Thr Met Ala Trp
                200                 205                 210

cag gaa atc cga cat gcc atc atc ctt ctg aca gat gga aag tcc aat        909
Gln Glu Ile Arg His Ala Ile Ile Leu Leu Thr Asp Gly Lys Ser Asn
            215                 220                 225

atg ggt ggc tct ccc aaa aca gct gtt gac caa atc aga gag atc ttg        957
Met Gly Gly Ser Pro Lys Thr Ala Val Asp Gln Ile Arg Glu Ile Leu
        230                 235                 240

aat atc aac cag aag agg aat gac tat ctg gac atc tat gcc atc ggg       1005
Asn Ile Asn Gln Lys Arg Asn Asp Tyr Leu Asp Ile Tyr Ala Ile Gly
    245                 250                 255

gtg ggc aag ctg gat gtg gac tgg aga gaa ctg aat gag ctg ggg tcc       1053
Val Gly Lys Leu Asp Val Asp Trp Arg Glu Leu Asn Glu Leu Gly Ser
260                 265                 270                 275

aag aag gat ggc gag agg cat gcc ttc att ctg cag gac aca aag gct       1101
Lys Lys Asp Gly Glu Arg His Ala Phe Ile Leu Gln Asp Thr Lys Ala
                280                 285                 290

ctg cac cag gtc ttt gaa cat atg ctg gat gtc tcc aag ctc aca gac       1149
Leu His Gln Val Phe Glu His Met Leu Asp Val Ser Lys Leu Thr Asp
            295                 300                 305

acc atc tgc ggg gtg ggg aac atg tca gca aac gcc tct gac caa gag       1197
Thr Ile Cys Gly Val Gly Asn Met Ser Ala Asn Ala Ser Asp Gln Glu
        310                 315                 320

agg aca ccc tgg cat gtc act att aag ccc aag agc caa gag acc tgc       1245
Arg Thr Pro Trp His Val Thr Ile Lys Pro Lys Ser Gln Glu Thr Cys
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    325                 330                 335

cgg gga gcc ctc atc tcc gac caa tgg gtc ctg aca gcg gct cac tgc       1293
Arg Gly Ala Leu Ile Ser Asp Gln Trp Val Leu Thr Ala Ala His Cys
340                 345                 350                 355

ttc cgc gat ggc aac gac cac tcc cta tgg agg gtc aat gtg gga gac       1341
Phe Arg Asp Gly Asn Asp His Ser Leu Trp Arg Val Asn Val Gly Asp
                360                 365                 370

ccc aaa tcc cag tgg ggc aaa gaa ttc ctt att gag aag gca gtg att       1389
Pro Lys Ser Gln Trp Gly Lys Glu Phe Leu Ile Glu Lys Ala Val Ile
            375                 380                 385

tcc cca gga ttt gat gtc ttt gcc aaa aag aac cag gga atc ctg gag       1437
Ser Pro Gly Phe Asp Val Phe Ala Lys Lys Asn Gln Gly Ile Leu Glu
        390                 395                 400

ttc tat ggt gat gac atc gcc ctg ctg aag ctg gcc cag aaa gta aag       1485
Phe Tyr Gly Asp Asp Ile Ala Leu Leu Lys Leu Ala Gln Lys Val Lys
    405                 410                 415

atg tcc acc cat gcc agg ccc atc tgc ctt ccc tgc acc atg gag gcc       1533
Met Ser Thr His Ala Arg Pro Ile Cys Leu Pro Cys Thr Met Glu Ala
420                 425                 430                 435

aat ctg gct ctg cgg aga cct caa ggc agc acc tgt agg gac cat gag       1581
Asn Leu Ala Leu Arg Arg Pro Gln Gly Ser Thr Cys Arg Asp His Glu
                440                 445                 450

aat gaa ctg ctg aac aaa cag agt gtt cct gct cat ttt gtc gcc ttg       1629
Asn Glu Leu Leu Asn Lys Gln Ser Val Pro Ala His Phe Val Ala Leu
            455                 460                 465

aat ggg agc aaa ctg aac att aac ctt aag atg gga gtg gag tgg aca       1677
Asn Gly Ser Lys Leu Asn Ile Asn Leu Lys Met Gly Val Glu Trp Thr
        470                 475                 480

agc tgt gcc gag gtc gtc tcc caa gaa aaa acc atg ttc ccc aac ttg       1725
Ser Cys Ala Glu Val Val Ser Gln Glu Lys Thr Met Phe Pro Asn Leu
    485                 490                 495

aca gat gtc agg gag gtg gtg aca gac cag ttt cta tgc agt ggg acc       1773
Thr Asp Val Arg Glu Val Val Thr Asp Gln Phe Leu Cys Ser Gly Thr
500                 505                 510                 515

cag gag gat gag agt ccc tgc aag ggt gtg acc acc act cca ttg tct       1821
Gln Glu Asp Glu Ser Pro Cys Lys Gly Val Thr Thr Thr Pro Leu Ser
                520                 525                 530

tcg gcc cag cct caa gga tcc tgc tct ctg gag ggg gta gag atc aaa       1869
Ser Ala Gln Pro Gln Gly Ser Cys Ser Leu Glu Gly Val Glu Ile Lys
            535                 540                 545

ggt ggc tcc ttc cga ctt ctc caa gag ggc cag gca ctg gaa tac gtg       1917
Gly Gly Ser Phe Arg Leu Leu Gln Glu Gly Gln Ala Leu Glu Tyr Val
        550                 555                 560

tgt cct tct ggc ttc tac ccg tac cct gtg cag aca cgt acc tgc aga       1965
Cys Pro Ser Gly Phe Tyr Pro Tyr Pro Val Gln Thr Arg Thr Cys Arg
    565                 570                 575

tcc acg ggg tcc tgg agc acc ctg cag act caa gat cga aaa act gtc       2013
Ser Thr Gly Ser Trp Ser Thr Leu Gln Thr Gln Asp Arg Lys Thr Val
580                 585                 590                 595

aag aag gca gag tgc aga gca atc cgc tgt cca cga cca cag gac ttc       2061
Lys Lys Ala Glu Cys Arg Ala Ile Arg Cys Pro Arg Pro Gln Asp Phe
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                600                 605                 610

gag aac ggg gaa tac cgg ccc cgg tct ccc tac tac aat gtg agt gat       2109
Glu Asn Gly Glu Tyr Arg Pro Arg Ser Pro Tyr Tyr Asn Val Ser Asp
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gag atc tct ttc cac tgc tat gac ggt tac act ctc cgg ggc tct gcc       2157
Glu Ile Ser Phe His Cys Tyr Asp Gly Tyr Thr Leu Arg Gly Ser Ala
        630                 635                 640

aat cgc acc tgc caa gtg aat ggc cgg tgg agt ggg cag aca gcg atc       2205
Asn Arg Thr Cys Gln Val Asn Gly Arg Trp Ser Gly Gln Thr Ala Ile
    645                 650                 655

tgt gac aac gga gcg ggg tac tgc tcc aac cca ggc atc ccc att ggc       2253
Cys Asp Asn Gly Ala Gly Tyr Cys Ser Asn Pro Gly Ile Pro Ile Gly
660                 665                 670                 675

aca agg aag gtg ggc agc cgg tac cgc ctt gaa gac agc gtc acc tac       2301
Thr Arg Lys Val Gly Ser Arg Tyr Arg Leu Glu Asp Ser Val Thr Tyr
                680                 685                 690

cac tgc agc cgg ggg ctt acc ctg cgt ggc tcc cag cgg cga aca tgt       2349
His Cys Ser Arg Gly Leu Thr Leu Arg Gly Ser Gln Arg Arg Thr Cys
            695                 700                 705

cag gaa ggt ggc tct tgg agc ggg acg gag cct tcc tgc caa gac tcc       2397
Gln Glu Gly Gly Ser Trp Ser Gly Thr Glu Pro Ser Cys Gln Asp Ser
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ttc atg tac gac acc cct caa gag gtg gcc gaa gct ttc ctg tct tcc       2445
Phe Met Tyr Asp Thr Pro Gln Glu Val Ala Glu Ala Phe Leu Ser Ser
    725                 730                 735

ctg acg gag acc ata gaa gga gtc gat gcc gag gat ggg cac agc cca       2493
Leu Thr Glu Thr Ile Glu Gly Val Asp Ala Glu Asp Gly His Ser Pro
740                 745                 750                 755

ggg gaa caa cag aag cgg agg atc atc cta gac cct tca ggc tcc atg       2541
Gly Glu Gln Gln Lys Arg Arg Ile Ile Leu Asp Pro Ser Gly Ser Met
                760                 765                 770

aac atc tac ctg gtg cta gat gga tca gac agc att ggg gcc ggc aac       2589
Asn Ile Tyr Leu Val Leu Asp Gly Ser Asp Ser Ile Gly Ala Gly Asn
            775                 780                 785

ttc aca gga gcc aaa aag tgt cta gtc aac tta att gag aag gtg gca       2637
Phe Thr Gly Ala Lys Lys Cys Leu Val Asn Leu Ile Glu Lys Val Ala
        790                 795                 800

agt tat ggt gtg aag cca aga tat gct cta gtg aca tat gcc aca tac       2685
Ser Tyr Gly Val Lys Pro Arg Tyr Ala Leu Val Thr Tyr Ala Thr Tyr
    805                 810                 815

ccc aga att tgg gtc aaa gtg tct gac caa gag agc agc aat gca gac       2733
Pro Arg Ile Trp Val Lys Val Ser Asp Gln Glu Ser Ser Asn Ala Asp
820                 825                 830                 835

tgg gtc acg aag aag ctc agt gaa atc aat tat gaa gac cac aag ttg       2781
Trp Val Thr Lys Lys Leu Ser Glu Ile Asn Tyr Glu Asp His Lys Leu
                840                 845                 850

aag tca ggg act aac acc aag agg gcc ctc cag gca gtg tac agc atg       2829
Lys Ser Gly Thr Asn Thr Lys Arg Ala Leu Gln Ala Val Tyr Ser Met
            855                 860                 865

atg agt tgg cca gag gac atc cct cct gaa ggc tgg aac cgc acc cgc       2877
Met Ser Trp Pro Glu Asp Ile Pro Pro Glu Gly Trp Asn Arg Thr Arg
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        870                 875                 880

cat gtc atc atc ctc atg acc gat gga ttg cac aac atg ggc ggg gac       2925
His Val Ile Ile Leu Met Thr Asp Gly Leu His Asn Met Gly Gly Asp
    885                 890                 895

cca att act gtc att gat gag atc cgg gac ttg tta tac atc ggc aag       2973
Pro Ile Thr Val Ile Asp Glu Ile Arg Asp Leu Leu Tyr Ile Gly Lys
900                 905                 910                 915

gat cgt aaa aac ccg agg gag gat tat ctg gat gtc tat gtg ttt ggg       3021
Asp Arg Lys Asn Pro Arg Glu Asp Tyr Leu Asp Val Tyr Val Phe Gly
                920                 925                 930

gtt gga cct ttg gtg gac caa gtg aac atc aat gct ttg gct tcc aag       3069
Val Gly Pro Leu Val Asp Gln Val Asn Ile Asn Ala Leu Ala Ser Lys
            935                 940                 945

aaa gac aat gag caa cat gtg ttc aaa gtc aag gat atg gaa aac ctg       3117
Lys Asp Asn Glu Gln His Val Phe Lys Val Lys Asp Met Glu Asn Leu
        950                 955                 960

gaa gac gtt ttc ttc caa atg att gat gaa agc cag tct ctg agt ctc       3165
Glu Asp Val Phe Phe Gln Met Ile Asp Glu Ser Gln Ser Leu Ser Leu
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tgt ggc atg gtt tgg gaa cac agc aag ggt acc gat tac cac aag caa       3213
Cys Gly Met Val Trp Glu His Ser Lys Gly Thr Asp Tyr His Lys Gln
980                 985                 990                 995

cca tgg cag gcc aag  atc tca gtc act cgc  cct tcg aag gga cat         3258
Pro Trp Gln Ala Lys  Ile Ser Val Thr Arg  Pro Ser Lys Gly His
                1000                1005                1010

gag agc tgt atg ggg  gct gtg gtg tct gag  tac ttt gtg ctg aca         3303
Glu Ser Cys Met Gly  Ala Val Val Ser Glu  Tyr Phe Val Leu Thr
                1015                1020                1025

gca gca cat tgt ttt  act gtg gac gac aag  gaa cac tca atc aag         3348
Ala Ala His Cys Phe  Thr Val Asp Asp Lys  Glu His Ser Ile Lys
                1030                1035                1040

gtc agc gtg gga ggg  aag aag cgg gac ctg  gag ata gaa aaa gtc         3393
Val Ser Val Gly Gly  Lys Lys Arg Asp Leu  Glu Ile Glu Lys Val
                1045                1050                1055

cta ttt cac ccc gac  tac aac att agc gag  aaa aaa gaa gca gga         3438
Leu Phe His Pro Asp  Tyr Asn Ile Ser Glu  Lys Lys Glu Ala Gly
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att cct gaa ttt tat  gac tat gac gtt gcc  ctg atc aag ctc aag         3483
Ile Pro Glu Phe Tyr  Asp Tyr Asp Val Ala  Leu Ile Lys Leu Lys
                1075                1080                1085

aat aag ttg aat tat  gac ccg act atc agg  ccc att tgt ctc ccc         3528
Asn Lys Leu Asn Tyr  Asp Pro Thr Ile Arg  Pro Ile Cys Leu Pro
                1090                1095                1100

tgc acc gag gga aca  act cga gct ttg agg  ctt cct cca act acc         3573
Cys Thr Glu Gly Thr  Thr Arg Ala Leu Arg  Leu Pro Pro Thr Thr
                1105                1110                1115

act tgc cag caa cag  aag gaa gag ctg ctc  cct gca cag gat atc         3618
Thr Cys Gln Gln Gln  Lys Glu Glu Leu Leu  Pro Ala Gln Asp Ile
                1120                1125                1130

aaa gct ctg ttt gtg  tct gag gag gag aag  aag ctg act cgg aag         3663
Lys Ala Leu Phe Val  Ser Glu Glu Glu Lys  Lys Leu Thr Arg Lys
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gag gtc tac atc aag  aat ggg gat aag aaa  ggc agc tgt gag aga        3708
Glu Val Tyr Ile Lys  Asn Gly Asp Lys Lys  Gly Ser Cys Glu Arg
                1150                1155                1160

gat gct caa tat gcc  cca ggc tat gac aaa  gtc aag gac atc tcg        3753
Asp Ala Gln Tyr Ala  Pro Gly Tyr Asp Lys  Val Lys Asp Ile Ser
                1165                1170                1175

gag gtg gtc acc cct  cgg ttc ctt tgt act  gga gga gtg agt ccc        3798
Glu Val Val Thr Pro  Arg Phe Leu Cys Thr  Gly Gly Val Ser Pro
                1180                1185                1190

tat gct gac ccc aat  act tgc aga ggt gat  tct ggc ggc ccc ttg        3843
Tyr Ala Asp Pro Asn  Thr Cys Arg Gly Asp  Ser Gly Gly Pro Leu
                1195                1200                1205

ata gtt cac aag aga  agt cgt ttc att caa  gtt ggt gtc atc agc        3888
Ile Val His Lys Arg  Ser Arg Phe Ile Gln  Val Gly Val Ile Ser
                1210                1215                1220

tgg gga gta gtg gat  gtc tgc aaa aac cag  aag cgg caa aag cag        3933
Trp Gly Val Val Asp  Val Cys Lys Asn Gln  Lys Arg Gln Lys Gln
                1225                1230                1235

gta cct gct cac gcc  cga gac ttt cac gtc  aac ctc ttc caa gtg        3978
Val Pro Ala His Ala  Arg Asp Phe His Val  Asn Leu Phe Gln Val
                1240                1245                1250

ctg ccc tgg ctg aag  gag aaa ctc caa gat  gag gat ttg ggt ttt        4023
Leu Pro Trp Leu Lys  Glu Lys Leu Gln Asp  Glu Asp Leu Gly Phe
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Leu

aacactt                                                             4086


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tggggccctc cttcatgaat gttccgggaa gcagtggctg cgtgcgcagg gtaggctggc     240

caggctgcag atgccagagc agattgcata aaaggttagg ggacagtggg aaaggggtgt     300

agccagatcc agcatttggg tttcagtttg gacaggaggt caaataggca cccagagtga     360

cctggagagg gctttgggcc actggactct ctggtgcttt cc atg aca atg gag        414
                                                Met Thr Met Glu
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agc ccc cag ctc tgc ctc gtc ctc ttg gtc tta ggc ttc tcc tct gga        462
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Ser Pro Gln Leu Cys Leu Val Leu Leu Val Leu Gly Phe Ser Ser Gly
5                   10                  15                  20

ggt gtg agc gca act cca gtg ctt gag gcc cgg ccc caa gtc tcc tgc        510
Gly Val Ser Ala Thr Pro Val Leu Glu Ala Arg Pro Gln Val Ser Cys
                25                  30                  35

tct ctg gag gga gta gag atc aaa ggc ggc tcc ttt caa ctt ctc caa        558
Ser Leu Glu Gly Val Glu Ile Lys Gly Gly Ser Phe Gln Leu Leu Gln
            40                  45                  50

ggc ggt cag gcc ctg gag tac cta tgt ccc tct ggc ttc tac cca tac        606
Gly Gly Gln Ala Leu Glu Tyr Leu Cys Pro Ser Gly Phe Tyr Pro Tyr
        55                  60                  65

ccc gtg cag act cga acc tgc aga tcc aca ggc tcc tgg agc gac ctg        654
Pro Val Gln Thr Arg Thr Cys Arg Ser Thr Gly Ser Trp Ser Asp Leu
    70                  75                  80

cag acc cga gac caa aag att gtc cag aag gcg gaa tgc aga gca ata        702
Gln Thr Arg Asp Gln Lys Ile Val Gln Lys Ala Glu Cys Arg Ala Ile
85                  90                  95                  100

cgc tgc cca cga ccg cag gac ttt gaa aat ggg gaa ttc tgg ccc cgg        750
Arg Cys Pro Arg Pro Gln Asp Phe Glu Asn Gly Glu Phe Trp Pro Arg
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tcc ccc ttc tac aac ctg agt gac cag att tct ttt caa tgc tat gat        798
Ser Pro Phe Tyr Asn Leu Ser Asp Gln Ile Ser Phe Gln Cys Tyr Asp
            120                 125                 130

ggt tac gtt ctc cgg ggc tct gct aat cgc acc tgc caa gag aat ggc        846
Gly Tyr Val Leu Arg Gly Ser Ala Asn Arg Thr Cys Gln Glu Asn Gly
        135                 140                 145

cgg tgg gat ggg caa aca gca att tgt gat gat gga gct gga tac tgt        894
Arg Trp Asp Gly Gln Thr Ala Ile Cys Asp Asp Gly Ala Gly Tyr Cys
    150                 155                 160

ccc aat ccc ggt att cct att ggg aca agg aag gtg ggt agc caa tac        942
Pro Asn Pro Gly Ile Pro Ile Gly Thr Arg Lys Val Gly Ser Gln Tyr
165                 170                 175                 180

cgc ctt gaa gac att gtt act tac cac tgc agc cgg gga ctt gtc ctg        990
Arg Leu Glu Asp Ile Val Thr Tyr His Cys Ser Arg Gly Leu Val Leu
                185                 190                 195

cgt ggc tcc cag aag cga aag tgt caa gaa ggt ggc tca tgg agt ggg       1038
Arg Gly Ser Gln Lys Arg Lys Cys Gln Glu Gly Gly Ser Trp Ser Gly
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aca gag cct tcc tgc caa gat tcc ttc atg tat gac agc cct caa gaa       1086
Thr Glu Pro Ser Cys Gln Asp Ser Phe Met Tyr Asp Ser Pro Gln Glu
        215                 220                 225

gtg gcc gaa gca ttc cta tcc tcc ctg aca gag acc atc gaa gga gcc       1134
Val Ala Glu Ala Phe Leu Ser Ser Leu Thr Glu Thr Ile Glu Gly Ala
    230                 235                 240

gat gct gag gat ggg cac agc cca gga gaa cag cag aag agg aag att       1182
Asp Ala Glu Asp Gly His Ser Pro Gly Glu Gln Gln Lys Arg Lys Ile
245                 250                 255                 260

gtc cta gac ccc tcg ggc tcc atg aat atc tac ctg gtg cta gat gga       1230
Val Leu Asp Pro Ser Gly Ser Met Asn Ile Tyr Leu Val Leu Asp Gly
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tca gac agc atc gga agc agc aac ttc aca ggg gct aag cgg tgc ctc       1278
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Ser Asp Ser Ile Gly Ser Ser Asn Phe Thr Gly Ala Lys Arg Cys Leu
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acc aac ttg att gag aag gtg gcg agt tac ggg gtg agg cca cga tat       1326
Thr Asn Leu Ile Glu Lys Val Ala Ser Tyr Gly Val Arg Pro Arg Tyr
        295                 300                 305

ggt ctc ctg aca tat gct aca gtc ccc aaa gtg ttg gtc aga gtg tct       1374
Gly Leu Leu Thr Tyr Ala Thr Val Pro Lys Val Leu Val Arg Val Ser
    310                 315                 320

gat gag agg agt agc gat gcc gac tgg gtc aca gag aag ctc aac caa       1422
Asp Glu Arg Ser Ser Asp Ala Asp Trp Val Thr Glu Lys Leu Asn Gln
325                 330                 335                 340

atc agt tat gaa gac cac aag ctg aag tca ggg acc aac acc aag agg       1470
Ile Ser Tyr Glu Asp His Lys Leu Lys Ser Gly Thr Asn Thr Lys Arg
                345                 350                 355

gct ctc cag gct gtg tat agc atg atg agc tgg gca ggg gat gcc ccg       1518
Ala Leu Gln Ala Val Tyr Ser Met Met Ser Trp Ala Gly Asp Ala Pro
            360                 365                 370

cct gaa ggc tgg aat aga acc cgc cat gtc atc atc att atg act gat       1566
Pro Glu Gly Trp Asn Arg Thr Arg His Val Ile Ile Ile Met Thr Asp
        375                 380                 385

ggc ttg cac aac atg ggt gga aac cct gtc act gtc att cag gac atc       1614
Gly Leu His Asn Met Gly Gly Asn Pro Val Thr Val Ile Gln Asp Ile
    390                 395                 400

cga gcc ttg ctg gac atc ggc agg gat ccc aaa aat ccc agg gag gat       1662
Arg Ala Leu Leu Asp Ile Gly Arg Asp Pro Lys Asn Pro Arg Glu Asp
405                 410                 415                 420

tac ctg gat gtg tat gtg ttt ggg gtc ggg cct ctg gtg gac tcc gtg       1710
Tyr Leu Asp Val Tyr Val Phe Gly Val Gly Pro Leu Val Asp Ser Val
                425                 430                 435

aac atc aat gcc tta gct tcc aaa aag gac aat gag cat cat gtg ttt       1758
Asn Ile Asn Ala Leu Ala Ser Lys Lys Asp Asn Glu His His Val Phe
            440                 445                 450

aaa gtc aag gat atg gaa gac ctg gag aat gtt ttc tac caa atg att       1806
Lys Val Lys Asp Met Glu Asp Leu Glu Asn Val Phe Tyr Gln Met Ile
        455                 460                 465

gat gaa acc aaa tct ctg agt ctc tgt ggc atg gtg tgg gag cat aaa       1854
Asp Glu Thr Lys Ser Leu Ser Leu Cys Gly Met Val Trp Glu His Lys
    470                 475                 480

aaa ggc aac gat tat cat aag caa cca tgg caa gcc aag atc tca gtc       1902
Lys Gly Asn Asp Tyr His Lys Gln Pro Trp Gln Ala Lys Ile Ser Val
485                 490                 495                 500

act cgc cct ctg aaa gga cat gag acc tgt atg ggg gcc gtg gtg tct       1950
Thr Arg Pro Leu Lys Gly His Glu Thr Cys Met Gly Ala Val Val Ser
                505                 510                 515

gag tac ttc gtg ctg aca gca gcg cac tgc ttc atg gtg gat gat cag       1998
Glu Tyr Phe Val Leu Thr Ala Ala His Cys Phe Met Val Asp Asp Gln
            520                 525                 530

aaa cat tcc atc aag gtc agc gtg ggg ggt cag agg cgg gac ctg gag       2046
Lys His Ser Ile Lys Val Ser Val Gly Gly Gln Arg Arg Asp Leu Glu
        535                 540                 545

att gaa gag gtc ctg ttc cac ccc aaa tac aat att aat ggg aaa aag       2094
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Ile Glu Glu Val Leu Phe His Pro Lys Tyr Asn Ile Asn Gly Lys Lys
    550                 555                 560

gca gaa ggg atc cct gag ttc tat gat tat gat gtg gcc cta gtc aag       2142
Ala Glu Gly Ile Pro Glu Phe Tyr Asp Tyr Asp Val Ala Leu Val Lys
565                 570                 575                 580

ctc aag aac aag ctc aag tat ggc cag act ctc agg ccc atc tgt ctc       2190
Leu Lys Asn Lys Leu Lys Tyr Gly Gln Thr Leu Arg Pro Ile Cys Leu
                585                 590                 595

ccc tgc acg gag gga acc aca cga gcc ttg agg ctt cct cag aca gcc       2238
Pro Cys Thr Glu Gly Thr Thr Arg Ala Leu Arg Leu Pro Gln Thr Ala
            600                 605                 610

acc tgc aag cag cac aag gaa cag ttg ctc cct gtg aag gat gtc aaa       2286
Thr Cys Lys Gln His Lys Glu Gln Leu Leu Pro Val Lys Asp Val Lys
        615                 620                 625

gct ctg ttt gta tct gag caa ggg aag agc ctg act cgg aag gag gtg       2334
Ala Leu Phe Val Ser Glu Gln Gly Lys Ser Leu Thr Arg Lys Glu Val
    630                 635                 640

tac atc aag aat ggg gac aag aaa gcc agt tgt gag aga gat gct aca       2382
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645                 650                 655                 660

aag gcc caa ggc tat gag aag gtc aaa gat gcc tct gag gtg gtc act       2430
Lys Ala Gln Gly Tyr Glu Lys Val Lys Asp Ala Ser Glu Val Val Thr
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cca cgg ttc ctc tgc aca gga ggg gtg gat ccc tat gct gac ccc aac       2478
Pro Arg Phe Leu Cys Thr Gly Gly Val Asp Pro Tyr Ala Asp Pro Asn
            680                 685                 690

aca tgc aaa gga gat tcc ggg ggc cct ctc att gtt cac aag aga agc       2526
Thr Cys Lys Gly Asp Ser Gly Gly Pro Leu Ile Val His Lys Arg Ser
        695                 700                 705

cgc ttc att caa gtt ggt gtg att agc tgg gga gta gta gat gtc tgc       2574
Arg Phe Ile Gln Val Gly Val Ile Ser Trp Gly Val Val Asp Val Cys
    710                 715                 720

aga gac cag agg cgg caa cag ctg gta ccc tct tat gcc cgg gac ttc       2622
Arg Asp Gln Arg Arg Gln Gln Leu Val Pro Ser Tyr Ala Arg Asp Phe
725                 730                 735                 740

cac atc aac ctc ttc cag gtg ctg ccc tgg cta aag gac aag ctc aaa       2670
His Ile Asn Leu Phe Gln Val Leu Pro Trp Leu Lys Asp Lys Leu Lys
                745                 750                 755

gat gag gat ttg ggt ttt cta taa agagcttcct gcagggagag tgtgaggaca      2724
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