

COAGULATION FACTOR XI-MODULATING COMPOSITIONS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 63/515,074, filed July 21, 2023; and U.S. Provisional Application No. 63/583,987, filed September 20, 2023. The disclosure of each of the prior applications is considered part of and is incorporated by reference in its entirety in the disclosure of this application.

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SUMMARY

 The present disclosure provides compounds, compositions, and methods for modulating the expression or activity of Coagulation Factor XI (Factor XI or FXI). In certain embodiments, the compounds, compositions, and methods can be used to reduce the expression of FXI mRNA in a cell or animal. In certain embodiments, the compounds, compositions, and methods can be used to reduce the amount of FXI protein in a cell or animal.

 In certain embodiments, the animal has a FXI related disease, disorder or condition. In certain embodiments, the disease, disorder or condition is a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease) or pancreatitis. In certain embodiments, the disease, disorder or condition is a disease, disorder or condition that is treated with anticoagulant therapy. In certain embodiments, the animal is in need of anticoagulant therapy. Certain compounds, compositions and methods provided herein are directed to treating a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic

disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity),
5 infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease) or pancreatitis in an animal or otherwise treating an animal in need of anticoagulant therapy. In certain embodiments, the compounds and compositions provided herein are potent and tolerable and inhibit FXI expression, which can be used to
10 treat, prevent, ameliorate, or slow progression of a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g.,
15 multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g.,
20 Graves' disease) or pancreatitis in an animal or otherwise treat an animal in need of anticoagulant therapy.

In certain embodiments, the compounds and compositions comprise one or more features that are effective for increasing potency. In certain embodiments, the compounds and compositions comprise one or more features that are effective for increasing tolerability.
25 In certain embodiments, compounds and compositions comprise one or more features that are effective for targeting the compound or composition to a cell or tissue. In certain embodiments, the compounds and compositions are more potent, have greater duration of action or have greater therapeutic value than compounds publicly disclosed.

30 BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying Drawings, which constitute a part of this specification, illustrate embodiments of the disclosure.

FIG. 1 shows the structure of compound RD4581 comprising a first modified oligonucleotide of IA1342 (SEQ ID NO: 535) and a second modified oligonucleotide of IS1733 (SEQ ID NO: 797).

5 **FIG. 2** shows the structure of compound RD4595 comprising a first modified oligonucleotide of IA1356 (SEQ ID NO: 549) and a second modified oligonucleotide of IS1747 (SEQ ID NO: 811).

FIG. 3 shows the structure of compound RD4622 comprising a first modified oligonucleotide of IA1383 (SEQ ID NO: 576) and a second modified oligonucleotide of IS1774 (SEQ ID NO: 838).

10 **FIG. 4** shows the structure of compound RD4626 comprising a first modified oligonucleotide of IA1387 (SEQ ID NO: 580) and a second modified oligonucleotide of IS1778 (SEQ ID NO: 842).

FIG. 5 shows the structure of compound RD4627 comprising a first modified oligonucleotide of IA1388 (SEQ ID NO: 581) and a second modified oligonucleotide of
15 IS1779 (SEQ ID NO: 843).

FIG. 6 shows the structure of compound RD4630 comprising a first modified oligonucleotide of IA1391 (SEQ ID NO: 584) and a second modified oligonucleotide of IS1782 (SEQ ID NO: 846).

FIG. 7 shows the structure of compound RD4636 comprising a first modified
20 oligonucleotide of IA1397 (SEQ ID NO: 590) and a second modified oligonucleotide of IS1788 (SEQ ID NO: 852).

FIG. 8 shows the structure of compound RD4663 comprising a first modified oligonucleotide of IA1424 (SEQ ID NO: 617) and a second modified oligonucleotide of IS1815 (SEQ ID NO: 879).

25 **FIG. 9** shows the structure of compound RD4692 comprising a first modified oligonucleotide of IA1453 (SEQ ID NO: 646) and a second modified oligonucleotide of IS1844 (SEQ ID NO: 908).

FIG. 10 shows the structure of compound RD4707 comprising a first modified oligonucleotide of IA1468 (SEQ ID NO: 661) and a second modified oligonucleotide of
30 IS1859 (SEQ ID NO: 923).

FIG. 11 shows the structure of compound RD4708 comprising a first modified oligonucleotide of IA1469 (SEQ ID NO: 662) and a second modified oligonucleotide of IS1860 (SEQ ID NO: 924).

FIG. 12 shows the structure of compound RD4730 comprising a first modified oligonucleotide of IA1491 (SEQ ID NO: 684) and a second modified oligonucleotide of IS1882 (SEQ ID NO: 946).

5 **FIG. 13** shows the structure of compound RD4740 comprising a first modified oligonucleotide of IA1501 (SEQ ID NO: 694) and a second modified oligonucleotide of IS1892 (SEQ ID NO: 956).

FIG. 14 shows the structure of compound RD4749 comprising a first modified oligonucleotide of IA1510 (SEQ ID NO: 703) and a second modified oligonucleotide of IS1901 (SEQ ID NO: 965).

10 **FIG. 15** shows the structure of compound RD4751 comprising a first modified oligonucleotide of IA1512 (SEQ ID NO: 705) and a second modified oligonucleotide of IS1903 (SEQ ID NO: 967).

FIG. 16 shows the structure of compound RD4754 comprising a first modified oligonucleotide of IA1515 (SEQ ID NO: 708) and a second modified oligonucleotide of IS1906 (SEQ ID NO: 970).

FIG. 17 shows the structure of compound RD4783 comprising a first modified oligonucleotide of IA1544 (SEQ ID NO: 737) and a second modified oligonucleotide of IS1935 (SEQ ID NO: 999).

20 **FIG. 18** shows the structure of compound RD4791 comprising a first modified oligonucleotide of IA1552 (SEQ ID NO: 745) and a second modified oligonucleotide of IS1943 (SEQ ID NO: 1007).

FIG. 19 shows the structure of compound RD4811 comprising a first modified oligonucleotide of IA1572 (SEQ ID NO: 765) and a second modified oligonucleotide of IS1963 (SEQ ID NO: 1027).

25 **FIG. 20** shows the structure of compound RD4812 comprising a first modified oligonucleotide of IA1573 (SEQ ID NO: 766) and a second modified oligonucleotide of IS1964 (SEQ ID NO: 1028).

FIG. 21 shows the structure of compound RD5030 comprising a first modified oligonucleotide of IA1635 (SEQ ID NO: 1086) and a second modified oligonucleotide of IS2026 (SEQ ID NO: 1100).

FIG. 22 shows the structure of compound RD5031 comprising a first modified oligonucleotide of IA1636 (SEQ ID NO: 1087) and a second modified oligonucleotide of IS2027 (SEQ ID NO: 1101).

FIG. 23 shows the structure of compound RD5032 comprising a first modified oligonucleotide of IA1637 (SEQ ID NO: 1088) and a second modified oligonucleotide of IS2028 (SEQ ID NO: 1102).

FIG. 24 shows the structure of compound RD5033 comprising a first modified oligonucleotide of IA1638 (SEQ ID NO: 1089) and a second modified oligonucleotide of IS2029 (SEQ ID NO: 1103).

FIG. 25 shows the structure of compound RD5034 comprising a first modified oligonucleotide of IA1639 (SEQ ID NO: 1090) and a second modified oligonucleotide of IS2030 (SEQ ID NO: 1104).

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DETAILED DESCRIPTION

It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only and are not restrictive of the embodiments, as claimed. 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, treatises, and GenBank, NCBI and other sequence reference records are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their entirety as of the date of filing this application.

Compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Oligomeric compounds referenced by Compound Number or Ref ID NO indicate a combination of nucleobase sequence, chemical modification, and motif.

Herein, the use of the singular includes the plural unless specifically stated otherwise. For example, the articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element, e.g., a plurality of elements. 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 and is used interchangeably with, the phrase “including but not limited to”.

Definitions

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

“Coagulation Factor XI,” used interchangeably with the term “FXI,” refers to any nucleic acid or protein of FXI. Exemplary nucleotide and amino acid sequences of FXI can be found, for example, at GenBank Accession No. NM_000128.4 (incorporated herein as SEQ ID NO: 1), nucleotides 5001 to 28718 of NG_008051.1 (incorporated herein as SEQ ID NO: 2), NM_001354804.2 (incorporated herein as SEQ ID NO: 3). Additional examples of FXI sequences are readily available through publicly available databases, e.g., GenBank, UniProt, and OMIM. Further information on FXI can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term=FXI. FXI, as used herein, also refers to variations of the FXI gene including variants provided in the SNP database. Numerous sequence variations within the FXI gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, e.g., www.ncbi.nlm.nih.gov/snp/?term=FXI). “FXI mRNA” means an mRNA encoding a FXI protein. FXI may be referred to in either upper or lower case.

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

“2’-O-methoxyethyl” or “2’-MOE” means a 2’-O(CH₂)₂-OCH₃ modification. A 2’-O-methoxyethyl modified sugar is a modified sugar with 2’-O(CH₂)₂-OCH₃ in the place of the 2’-OH group of a ribosyl ring.

“5’ start site” means the nucleotide of the target nucleic acid or region which is aligned to the 3’-most nucleoside of an antisense oligonucleotide.

“3’ stop site” means the nucleotide of the target nucleic acid or region which is aligned to the 5’-most nucleoside of an antisense oligonucleotide.

“About” means within $\pm 10\%$ of a value. For example, if it is stated, “a compound achieved about 70% inhibition of FXI”, it is implied that FXI levels are inhibited within a range of 60% and 80%. When about is present before a series of numbers or a range, it is understood that “about” can modify each of the numbers in the series or range.

“Administer” or “administering” refers to routes of introducing a compound or composition provided herein to an individual to perform its intended function. An example, routes of administration that can be used include, but are not limited to, parenteral administration, such as subcutaneous, intravenous, or intramuscular injection or infusion.

“Ameliorate” refers to an improvement or 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 or severity of one or more indicators of a condition or disease. The progression or 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 oligonucleotide” or “antisense strand” means an oligonucleotide which includes a region that is complementary to a target nucleic acid, e.g., a FXI RNA or a region thereof.

“Complementarity” in reference to an oligonucleotide means the nucleobase sequence of such oligonucleotide or one or more regions thereof that is complementary to the nucleobase sequence of another oligonucleotide or nucleic acid or one or more regions thereof when the two nucleobase sequences are aligned in opposing directions. Complementary nucleobases, as described herein, are limited to the following pairs: adenine (A) and thymine (T), adenine (A) and uracil (U), and cytosine (C) and guanine (G) unless otherwise specified. Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside and may include one or more nucleobase mismatches. By contrast, “fully complementary” or “100% complementary” in reference to oligonucleotides means that such oligonucleotides have nucleobase matches at each nucleoside without any nucleobase mismatches.

“Composition” or “pharmaceutical composition” means a mixture of substances suitable for administering to an individual. For example, a composition may comprise one or more compounds or salt thereof and a sterile aqueous solution.

“Co-administration” means administration of two or more compounds in any manner in which the pharmacological effects of both are manifest in the patient. Co-administration does not require both compounds to be administered in a single pharmaceutical composition, in the same dosage form, by the same route of administration, or at the same time. The effects of both compounds need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive. Co-administration includes parallel or sequential administration of the one or more compounds.

“Conjugate group” means a group of atoms that is attached to an oligonucleotide. A conjugate group is optionally attached to an oligonucleotide through a conjugate linker. A conjugate group may, for example, alter the distribution, targeting, or half-life of a compound into which it is incorporated. Conjugate groups include targeting moieties.

“Conjugate linker” means a group of atoms comprising at least one bond that connects a linked moiety to an oligonucleotide.

“Identity” in reference to an oligonucleotide means the nucleobase sequence of such oligonucleotide or one or more regions thereof that matches the nucleobase sequence of another oligonucleotide or nucleic acid or one or more regions thereof. Identity of an oligonucleotide to another oligonucleotide or nucleic acid need not require each nucleobase to match and may include one or more different nucleobases. By contrast, “fully identical” or “100% identity” in reference to oligonucleotides means that such oligonucleotides have the same nucleobase at each relative position over its length as the other oligonucleotide or nucleic acid.

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

“Inhibiting the expression or activity” with reference to a target nucleic acid or protein means to reduce or block the expression or activity of such target relative to the expression or activity in an untreated or control sample and does not necessarily indicate a total elimination of expression or activity.

As used herein, the term “internucleoside linkage” is the covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein, “modified internucleoside linkage” means any internucleoside linkage other than a phosphodiester internucleoside linkage. “Phosphorothioate internucleoside linkage” is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations as further described below. Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present

disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

The term “isotopic variant” refers to a therapeutic agent (e.g., a compound and/or modified oligonucleotide disclosed herein) that contains an unnatural proportion of an isotope at one or more of the atoms that constitute such a therapeutic agent. In certain embodiments, an “isotopic variant” of a therapeutic agent contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (H), deuterium (^2H), tritium (^3H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine 123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, an “isotopic variant” of a therapeutic agent contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (H), deuterium (^2H), tritium (^3H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine 123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I).

It will be understood that, in a therapeutic agent (e.g., a compound and/or modified oligonucleotide disclosed herein), any hydrogen can be ^2H , for example, or any carbon can be ^{13}C , for example, or any nitrogen can be ^{15}N , for example, or any oxygen can be ^{18}O , for example, where feasible according to the judgment of one of skill. In certain embodiments, an “isotopic variant” of a therapeutic agent contains unnatural proportions of deuterium (D).

“Mismatch” or “non-complementary” means a nucleobase of a first oligonucleotide or nucleic acid that is not complementary to the corresponding nucleobase of a second oligonucleotide or nucleic acid when the first oligonucleotide/nucleic acid and second oligonucleotide/nucleic acid are aligned in an antiparallel orientation. For example, nucleobases including, but not limited to, a universal nucleobase, inosine, and hypoxanthine, are capable of hybridizing with at least one nucleobase but are still mismatched or non-complementary with respect to the nucleobase to which they are hybridized. As another

example, a nucleobase of a first oligonucleotide/nucleic acid that is not capable of hybridizing to the corresponding nucleobase of a second oligonucleotide/nucleic acid when the first and second oligonucleotides are aligned in an antiparallel orientation is a mismatch or non-complementary nucleobase.

5 “Modified oligonucleotide” means an oligonucleotide, wherein at least one sugar, nucleobase, or internucleoside linkage is modified.

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

 “Motif” means the pattern of unmodified and modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

15 “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. As used herein a “naturally occurring nucleobase” is adenine (A), thymine (T),
20 cytosine (C), uracil (U), and guanine (G). A “modified nucleobase” is a naturally occurring nucleobase that is chemically modified. A “universal base” or “universal nucleobase” is a nucleobase other than a naturally occurring nucleobase and modified nucleobase and is capable of pairing with any nucleobase.

 “Nucleobase sequence” means the order of contiguous nucleobases in a nucleic acid
25 or oligonucleotide independent of any sugar or internucleoside linkage.

 “Nucleoside” means a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. “Modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. Modified nucleosides include abasic nucleosides, which lack a nucleobase.

30 “Oligomeric Compound” means a compound comprising one or more oligonucleotides and optionally one or more additional features, such as a conjugate group or terminal group. Examples of oligomeric compounds include single-stranded and double-stranded compounds, such as, oligonucleotides, antisense oligonucleotides, interfering RNA compounds (RNAi compounds), microRNA targeting oligonucleotides, occupancy-based

compounds (e.g., mRNA processing or translation blocking compounds and splicing compounds). RNAi compounds include double-stranded compounds (e.g., short-interfering RNA (siRNA) and double-stranded RNA (dsRNA)) and single-stranded compounds (e.g., single-stranded siRNA (ssRNA), single-stranded RNAi (ssRNAi), short hairpin RNA (shRNA) and microRNA mimics) which work at least in part through the RNA-induced silencing complex (RISC) pathway resulting in sequence specific degradation and/or sequestration of a target nucleic acid through a process known as RNA interference (RNAi). The term “RNAi compound” is meant to be equivalent to other terms used to describe nucleic acid compounds that are capable of mediating sequence-specific RNA interference, for example, interfering RNA (iRNA), iRNA agent, RNAi agent, short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically modified siRNA, and others. Additionally, the term “RNAi” is meant to be equivalent to other terms used to describe sequence-specific RNA interference.

The term “oligomeric duplex” means a duplex formed by two oligomeric compounds having complementary nucleobase sequences. Each oligomeric compound of an oligomeric duplex may be referred to as a “duplexed oligomeric compound.” The oligonucleotides of each oligomeric compound of an oligomeric duplex may include non-complementary overhanging nucleosides. In some embodiments, the terms “duplexed oligomeric compound” and “modified oligonucleotide” are used interchangeably. In other embodiments, the terms “oligomeric duplex” and “compound” are used interchangeably.

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

“Pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to an individual. In certain embodiments, a pharmaceutically acceptable carrier or diluent aids the administration of a compound to and absorption by an individual and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, and the like. For example, a pharmaceutically acceptable carrier can be a sterile aqueous solution,

such as PBS or water-for-injection. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present disclosure.

“Pharmaceutically acceptable salt” means or refers to physiologically and pharmaceutically acceptable salts of compounds, such as oligomeric compounds or oligonucleotides, i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein, a pharmaceutically acceptable salt is any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. The pharmaceutically acceptable salts of the therapeutic agents disclosed herein include salts that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds or modified oligonucleotides described herein.

When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent.

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent.

Thus, the compounds of the present disclosure may exist as salts, such as with pharmaceutically acceptable acids. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Such salts include, but are not limited to: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; or (2) salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminum ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminum, lithium, zinc,

and barium hydroxide, ammonia, or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chlorprocaine, 5 diethanolamine, procaine, N-benzylphenethylamine, N-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like (see, for example, Berge et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977, 66, 1-19).

Pharmaceutically acceptable salts further include, by way of example only and 10 without limitation, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, sulfamate, nitrate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, 15 lactate, malonate, succinate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, citrate, benzoate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4- 20 methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, tert-butylacetate, lauryl sulfate, gluconate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate, and the like. In some embodiments, the pharmaceutically acceptable salt of the compounds and modified oligonucleotides disclosed herein is a sodium or a potassium salt. In some embodiments, the 25 pharmaceutically acceptable salt of the compounds and modified oligonucleotides disclosed herein is a sodium salt.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, 30 such as solubility in polar solvents. In embodiments, compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain

physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present disclosure.

5 “Pharmaceutical agent” means a compound that provides a therapeutic benefit when administered to an individual.

“Phosphorothioate linkage” means a modified phosphate linkage in which one of the non-bridging oxygen atoms is replaced with a sulfur atom.

10 “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 oligonucleotide.

“Prevent” refers to delaying or forestalling the onset, development or progression of a disease, disorder, or condition for a period of time.

15 “RNA interference compound” or “RNAi compound” means a compound that acts, at least in part, through an RNA-induced silencing complex (RISC) pathway or Ago2, but not through RNase H, to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi compounds include, but are not limited to double-stranded siRNA, single-stranded siRNA, and microRNA, including microRNA mimics.

20 “Sense oligonucleotide” or “sense strand” means the strand of a double-stranded compound that includes a region that is substantially complementary to a region of the antisense strand of the compound.

“Specifically inhibit” with reference to a target nucleic acid or protein means to reduce or block expression or activity of the target nucleic acid or protein while minimizing or eliminating effects on non-target nucleic acids or proteins.

25 “Subunit” with reference to an oligonucleotide means a nucleotide, nucleoside, nucleobase or sugar or a modified nucleotide, nucleoside, nucleobase or sugar as provided herein.

“Target nucleic acid,” “target RNA,” and “nucleic acid target” all mean a nucleic acid capable of being targeted by compounds described herein.

30 “Target region” means a portion of a target nucleic acid to which one or more compounds is targeted.

“Targeting moiety” means a conjugate group that provides an enhanced affinity for a selected target, e.g., molecule, cell or cell type, compartment, e.g., a cellular or organ

compartment, tissue, organ or region of the body, as, e.g., compared to a compound absent such a moiety.

“Terminal group” means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.

5 “Therapeutically effective amount” or “effective amount” means an amount of a compound, pharmaceutical agent, or composition that provides a therapeutic benefit to an individual. A “therapeutically effective amount” or “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat, prevent or ameliorate a
10 disease or reduce one or more symptoms of a disease or condition). An example of a “therapeutically effective amount” or “effective amount” is an amount sufficient to contribute to the treatment, prevention, amelioration, or reduction of a symptom or symptoms of a disease. A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of
15 the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The term “therapeutically effective amount,” as used herein, refers to that
20 amount of the therapeutic agent sufficient to provide a therapeutic benefit to an individual, such as treating, preventing or ameliorating the disease or disorder or symptom thereof, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as “-fold”
25 increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

The terms “treating” or “treatment” refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the
30 injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters, including the results of a physical examination. The term “treating” and conjugations thereof, may include prevention of an injury, pathology,

condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

“Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, “treatment” as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms, fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

“Treating” and “treatment” as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient. “Treat” refers to administering a compound or pharmaceutical composition to an animal in order to effect an alteration or improvement of a disease, disorder, or condition in the animal.

Certain compounds of the present disclosure possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those that are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic and optically pure

forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

As used herein, the term “isomers” refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

The term “tautomer,” as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure (i.e., the R and S configurations for each asymmetric center). Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

As used herein, “chirally enriched population” means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are compounds comprising modified oligonucleotides.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure.

As used herein, “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center having a random

stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (S) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (R) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the results of a synthetic method that is not designed to control the stereochemical configuration. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.

Certain Embodiments

10 In certain aspects, the disclosure relates to methods, compounds and compositions for inhibiting FXI. In certain embodiments, FXI is specifically inhibited. In certain embodiments, FXI is specifically degraded. In certain embodiments, FXI expression is inhibited. In certain embodiments, FXI translation is inhibited. In certain embodiments, FXI activity is inhibited. In certain embodiments, FXI expression, translation, or activity is reduced by at least 10% relative to the expression, translation, or activity in an untreated or control sample. For example, in certain embodiments, FXI expression, translation, or activity is reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 10-50%, 25-50%, 25-75%, 50-75%, 50-99%, or 75-99% relative to the expression, translation, or activity in an untreated or control sample. In certain embodiments, FXI expression, translation, or activity is reduced as measured by any suitable assay, including but not limited to, an immunoassay, a hybridization-based assay, or a sequencing-based assay (e.g., RNA-Seq).

In certain aspects, the disclosure relates to compounds targeted to a FXI nucleic acid. In certain embodiments, the FXI nucleic acid has the sequence set forth in GENBANK Accession No. NM_000128.4 (incorporated herein as SEQ ID NO: 1), nucleotides 5001 to 28718 of NG_008051.1 (incorporated herein as SEQ ID NO: 2), NM_001354804.2 (incorporated herein as SEQ ID NO: 3).

In certain embodiments, the compound is an oligomeric compound. In certain embodiments, the compound is single-stranded. In certain embodiments, the compound is double-stranded.

Certain embodiments provide a compound comprising a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at

least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139.

Certain embodiments provide a compound comprising a modified oligonucleotide
5 (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139.

Certain embodiments provide a compound comprising a modified oligonucleotide
10 having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139.

In certain embodiments, the modified oligonucleotide is at least 80%, at least 85%, at least 90%, or at least 95% complementary to SEQ ID NO: 1 or 3 or the complement thereof.

15 In certain embodiments, the modified oligonucleotide comprises at least one modification selected from a modified internucleoside linkage, a modified sugar, and a modified nucleobase. In certain embodiments, the compound is double-stranded.

Certain embodiments provide a compound comprising a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having
20 a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides
25 in length) having a region of complementarity to the first modified oligonucleotide.

In certain embodiments, the compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase
30 sequences provided in Tables 2 or 3, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide.

Certain embodiments provide a compound comprising a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having

a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any one SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 11, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 273. In certain embodiments, the first modified oligonucleotide consists of IA1342 (SEQ ID NO: 535), and the second modified oligonucleotide consists of IS1733 (SEQ ID NO: 797). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 1.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 25, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified
5 oligonucleotide has a nucleobase sequence of SEQ ID NO: 287. In certain embodiments, the first modified oligonucleotide consists of IA1356 (SEQ ID NO: 549), and the second modified oligonucleotide consists of IS1747 (SEQ ID NO: 811). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 2.

10 Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 52, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 314. In certain embodiments, the
15 first modified oligonucleotide consists of IA1383 (SEQ ID NO: 576), and the second modified oligonucleotide consists of IS1774 (SEQ ID NO: 838). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 3.

Certain embodiments provide a compound comprising a first modified
20 oligonucleotide having a nucleobase sequence of SEQ ID NO: 56, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 318. In certain embodiments, the first modified oligonucleotide consists of IA1387 (SEQ ID NO: 580), and the second
25 modified oligonucleotide consists of IS1778 (SEQ ID NO: 842). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 4.

Certain embodiments provide a compound comprising a first modified
oligonucleotide having a nucleobase sequence of SEQ ID NO: 57, and a second modified
30 oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 319. In certain embodiments, the first modified oligonucleotide consists of IA1388 (SEQ ID NO: 581), and the second modified oligonucleotide consists of IS1779 (SEQ ID NO: 843). In certain embodiments, the

compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 5.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 60, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 322. In certain embodiments, the first modified oligonucleotide consists of IA1391 (SEQ ID NO: 584), and the second modified oligonucleotide consists of IS1782 (SEQ ID NO: 846). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 6.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 66, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 328. In certain embodiments, the first modified oligonucleotide consists of IA1397 (SEQ ID NO: 590), and the second modified oligonucleotide consists of IS1788 (SEQ ID NO: 852). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 7.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 93, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 355. In certain embodiments, the first modified oligonucleotide consists of IA1424 (SEQ ID NO: 617), and the second modified oligonucleotide consists of IS1815 (SEQ ID NO: 879). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 8.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 122, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 384. In certain embodiments, the

first modified oligonucleotide consists of IA1453 (SEQ ID NO: 646), and the second modified oligonucleotide consists of IS1844 (SEQ ID NO: 908). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 9.

5 Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 137, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 399. In certain embodiments, the
10 first modified oligonucleotide consists of IA1468 (SEQ ID NO: 661), and the second modified oligonucleotide consists of IS1859 (SEQ ID NO: 923). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 10.

 Certain embodiments provide a compound comprising a first modified
15 oligonucleotide having a nucleobase sequence of SEQ ID NO: 138, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 400. In certain embodiments, the first modified oligonucleotide consists of IA1469 (SEQ ID NO: 662), and the second
20 modified oligonucleotide consists of IS1860 (SEQ ID NO: 924). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 11.

 Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 160, and a second modified
25 oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 422. In certain embodiments, the first modified oligonucleotide consists of IA1491 (SEQ ID NO: 684), and the second modified oligonucleotide consists of IS1882 (SEQ ID NO: 946). In certain embodiments, the
30 compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 12.

 Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 170, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to

the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 432. In certain embodiments, the first modified oligonucleotide consists of IA1501 (SEQ ID NO: 694), and the second modified oligonucleotide consists of IS1892 (SEQ ID NO: 956). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 13.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 179, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 441. In certain embodiments, the first modified oligonucleotide consists of IA1510 (SEQ ID NO: 703), and the second modified oligonucleotide consists of IS1901 (SEQ ID NO: 965). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 14.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 181, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 443. In certain embodiments, the first modified oligonucleotide consists of IA1512 (SEQ ID NO: 705), and the second modified oligonucleotide consists of IS1903 (SEQ ID NO: 967). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 15.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 184, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 446. In certain embodiments, the first modified oligonucleotide consists of IA1515 (SEQ ID NO: 708), and the second modified oligonucleotide consists of IS1906 (SEQ ID NO: 970). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 16.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 213, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified
5 oligonucleotide has a nucleobase sequence of SEQ ID NO: 475. In certain embodiments, the first modified oligonucleotide consists of IA1544 (SEQ ID NO: 737), and the second modified oligonucleotide consists of IS1935 (SEQ ID NO: 999). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 17.

10 Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 221, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 483. In certain embodiments, the
15 first modified oligonucleotide consists of IA1552 (SEQ ID NO: 745), and the second modified oligonucleotide consists of IS1943 (SEQ ID NO: 1007). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 18.

Certain embodiments provide a compound comprising a first modified
20 oligonucleotide having a nucleobase sequence of SEQ ID NO: 241, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 503. In certain embodiments, the first modified oligonucleotide consists of IA1572 (SEQ ID NO: 765), and the second
25 modified oligonucleotide consists of IS1963 (SEQ ID NO: 1027). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 19.

Certain embodiments provide a compound comprising a first modified
oligonucleotide having a nucleobase sequence of SEQ ID NO: 242, and a second modified
30 oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 504. In certain embodiments, the first modified oligonucleotide consists of IA1573 (SEQ ID NO: 766), and the second modified oligonucleotide consists of IS1964 (SEQ ID NO: 1028). In certain embodiments,

the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 20.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 1058, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 1072. In certain embodiments, the first modified oligonucleotide consists of IA1635 (SEQ ID NO: 1086), and the second modified oligonucleotide consists of IS2026 (SEQ ID NO: 1100). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 21.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 1059, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 1073. In certain embodiments, the first modified oligonucleotide consists of IA1636 (SEQ ID NO: 1087), and the second modified oligonucleotide consists of IS2027 (SEQ ID NO: 1101). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 22.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 1060, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 1074. In certain embodiments, the first modified oligonucleotide consists of IA1637 (SEQ ID NO: 1088), and the second modified oligonucleotide consists of IS2028 (SEQ ID NO: 1102). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 23.

Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 1061, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 1075. In certain embodiments, the

first modified oligonucleotide consists of IA1638 (SEQ ID NO: 1089), and the second modified oligonucleotide consists of IS2029 (SEQ ID NO: 1103). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 24.

5 Certain embodiments provide a compound comprising a first modified oligonucleotide having a nucleobase sequence of SEQ ID NO: 1062, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the second modified oligonucleotide has a nucleobase sequence of SEQ ID NO: 1076. In certain embodiments, the
10 first modified oligonucleotide consists of IA1639 (SEQ ID NO: 1090), and the second modified oligonucleotide consists of IS2030 (SEQ ID NO: 1104). In certain embodiments, the compound has the chemical structure, or a pharmaceutically acceptable salt or stereoisomer thereof, as shown in FIG. 25.

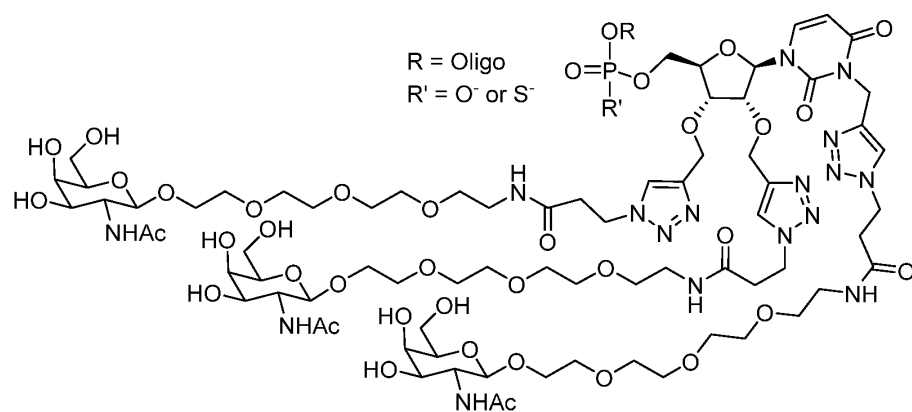
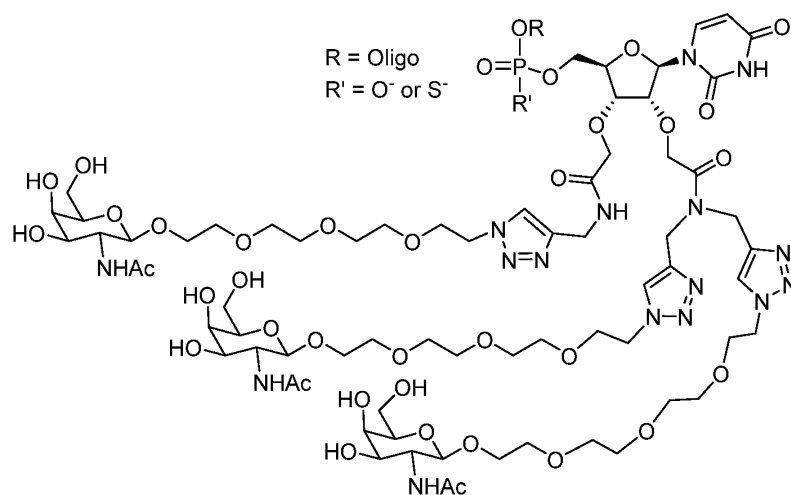
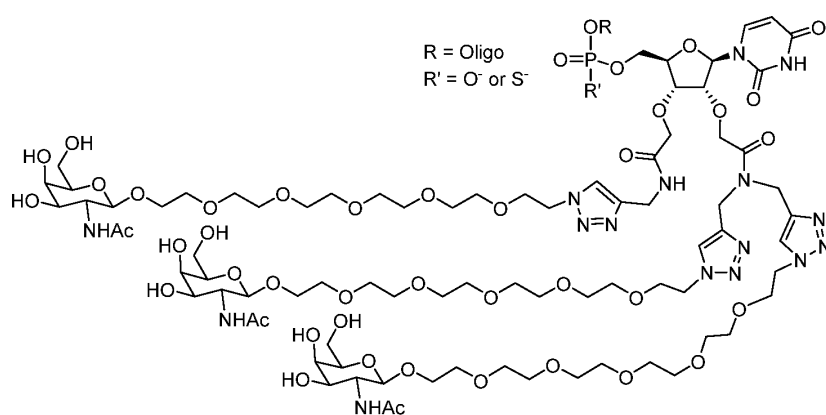
 In certain embodiments, the modified oligonucleotide or first modified
15 oligonucleotide of any preceding compound has at least 80%, at least 85%, at least 90%, or at least 95% complementarity or identity to SEQ ID NO: 1 or 3 over its length. In certain embodiments, the modified oligonucleotide or first modified oligonucleotide has at least 1, at least 2, at least 3 mismatches to a region of SEQ ID NO: 1 or 3 or the complement thereof. In certain embodiments, the region of complementarity between the first modified
20 oligonucleotide or first strand and the second modified oligonucleotide or second strand is 14 to 30 linked nucleosides in length. In certain embodiments, the region of complementarity between the first modified oligonucleotide or first strand and the second modified oligonucleotide or second strand is 14 to 23 linked nucleosides in length. In certain
25 embodiments, the region of complementarity between the first modified oligonucleotide or first strand and the second modified oligonucleotide or second strand is 19 to 23 linked nucleosides in length. In certain embodiments, the region of complementarity between the first modified oligonucleotide or first strand and the second modified oligonucleotide or second strand is 21 to 23 linked nucleosides in length. In certain embodiments, the first modified oligonucleotide is fully complementary to the second modified oligonucleotide.

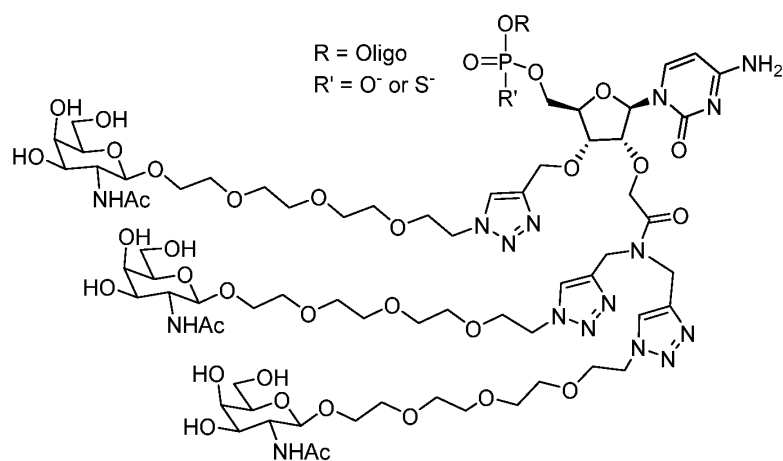
30 In certain embodiments, the modified oligonucleotide or first modified oligonucleotide of any preceding compound comprises at least one modification selected from a modified internucleoside linkage, a modified sugar, and a modified nucleobase. In certain embodiments, the second modified oligonucleotide of any preceding compound comprises at least one modification selected from the group consisting of a modified

internucleoside linkage, a modified sugar, and a modified nucleobase. In certain
embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside
linkage or a methylphosphonate internucleoside linkage. In certain embodiments, the
phosphorothioate internucleoside linkage or methylphosphonate internucleoside linkage is at
5 the 3' terminus of the first or second modified oligonucleotide or at the 5' terminus of the
first modified oligonucleotide. In certain embodiments, the modified sugar comprises a
modification selected from the group consisting of a halogen, an alkoxy group and a bicyclic
sugar. In certain embodiments, the modified sugar comprises a 2'-F modification. In certain
embodiments, the modified sugar comprises a 2'-OMe modification. In certain embodiments,
10 each nucleoside of the first modified oligonucleotide comprises a modified sugar. In certain
embodiments, each nucleoside of the second modified oligonucleotide comprises a modified
sugar. In certain embodiments, the modified sugar comprises a modification selected from the
group consisting of a halogen, an alkoxy group and a bicyclic sugar or a combination thereof.
In certain embodiments, the modified sugar comprises a modification selected from the group
15 consisting of 2'-MOE, 2'-F, and 2'-OMe or a combination thereof. In certain embodiments,
the first modified oligonucleotide comprises no more than ten 2'-F sugar modifications. In
certain embodiments, the second modified oligonucleotide comprises no more than five 2'-F
sugar modifications.

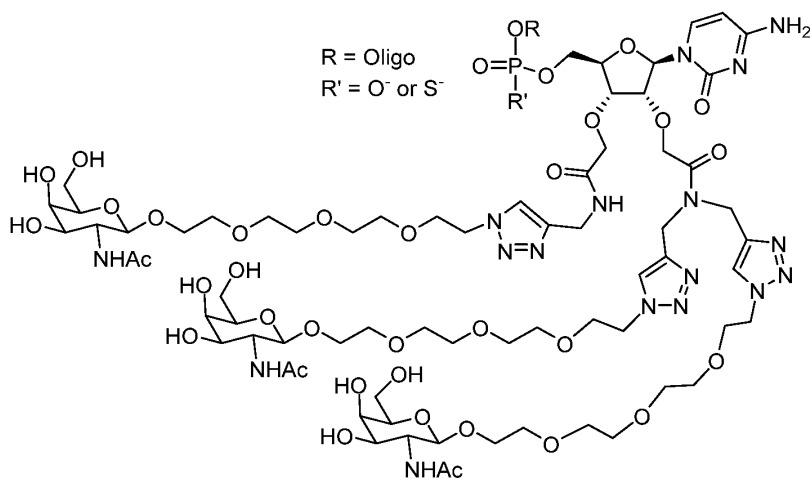
In certain embodiments, the compound of any preceding embodiment comprises a
20 conjugate group. In certain embodiments, the conjugate group is attached to the 5' end of the
modified oligonucleotide. In certain embodiments, the conjugate group is a targeting moiety.
In certain embodiments, the targeting moiety comprises one or more GalNAc. In certain
embodiments, the modified oligonucleotide is the second modified oligonucleotide or sense
oligonucleotide. In certain embodiments, the one or more GalNAc is attached to the 2' or 3'
25 position of the ribosyl ring. In certain embodiments, the one or more GalNAc is attached to
the 5' nucleoside of the modified oligonucleotide. In certain embodiments, the 5' nucleoside
of a modified oligonucleotide is selected from the following Formulae or a salt, solvate, or
hydrate thereof, wherein R is the portion of the modified oligonucleotide other than the 5'
nucleoside:

30

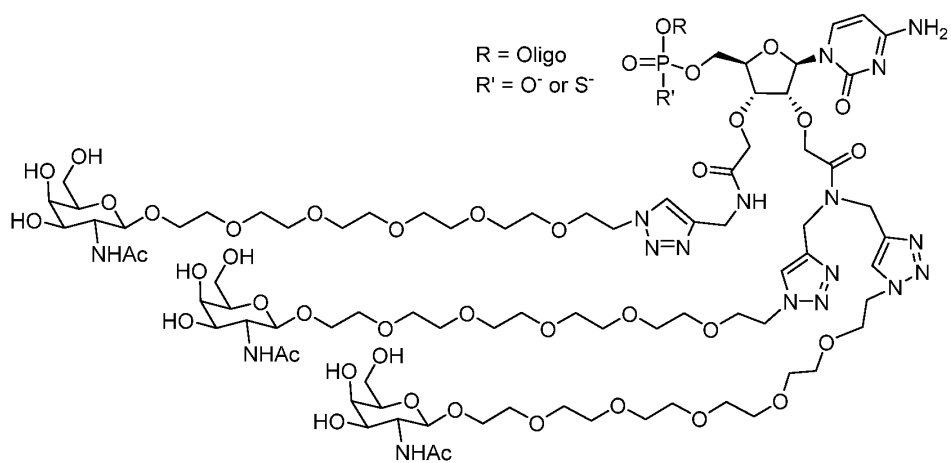
**Formula I****Formula II****Formula III**

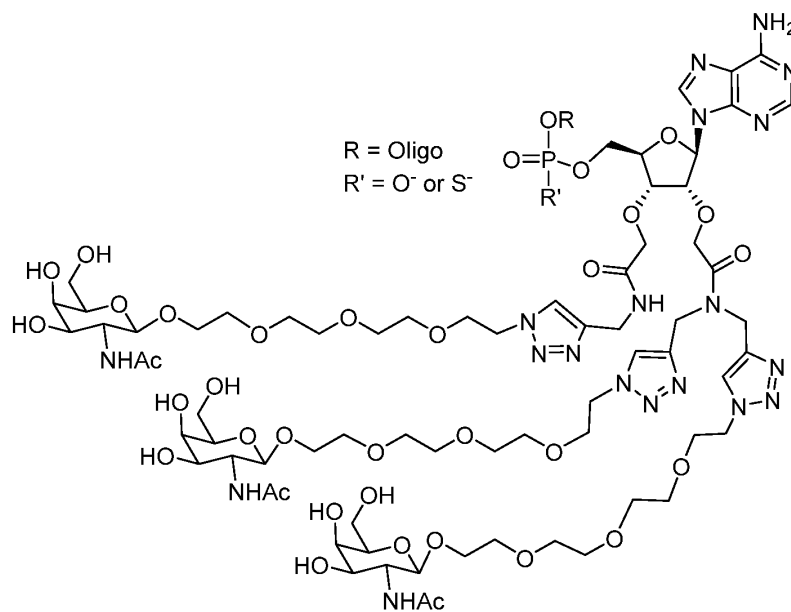


Formula IV

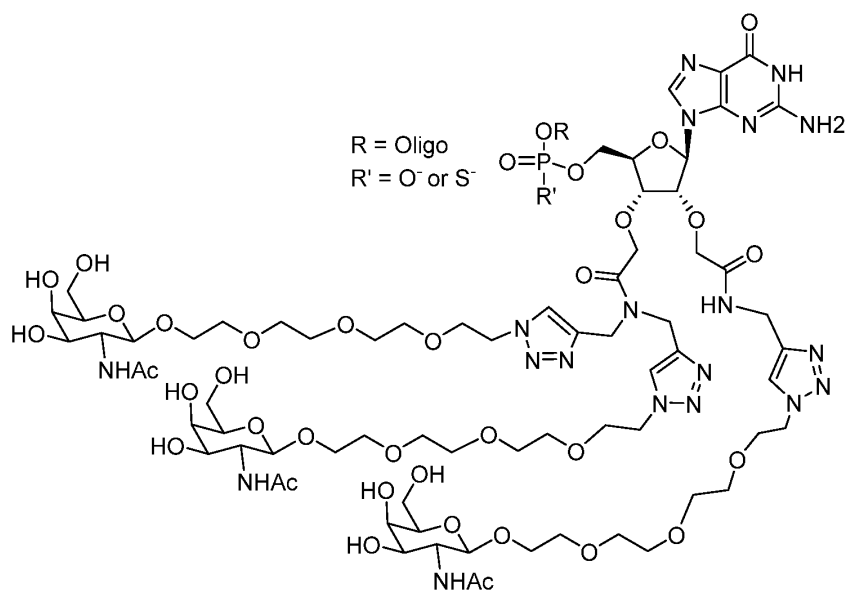


Formula V



Formula VI**Formula VII**

5

**Formula VIII**

In certain embodiments, R' is O. In certain embodiments, R' is S. In certain
 10 embodiments, the 5' nucleoside of the modified oligonucleotide is Formula I and R' is O. In

certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula I and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula II and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula II and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula III and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula III and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula IV and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula IV and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula V and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula V and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VI and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VI and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VII and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VII and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VIII and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VIII and R' is S.

Certain embodiments provide a compound comprising a first modified oligonucleotide selected from the group consisting of any one of Ref ID NOs: IA1341-IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and IA1729-IA1731, and a second modified oligonucleotide 14 to 21 linked nucleosides in length fully complementary to the first modified oligonucleotide.

Certain embodiments provide a compound comprising a first modified oligonucleotide selected from the group consisting of any one of Ref ID NOs: IA1341-IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and IA1729-IA1731, and a second modified oligonucleotide selected from the group consisting of Ref ID NOs: IS1732-IS1993, IS2026-IS2030, IS2043-IS2045, IS2047, IS2052-IS2056, IS2142, and IS2148-2150. In certain embodiments, the compound comprises a first modified oligonucleotide consisting of IA1341-IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and IA1729-IA1731, and a second modified oligonucleotide consisting of IS1732-IS1993, IS2026-IS2030, IS2043-IS2045, IS2047, IS2052-IS2056, IS2142, and IS2148-2150.

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1342 (SEQ ID NO: 535), and a second modified oligonucleotide consisting of IS1733 (SEQ ID NO: 797) (see FIG. 1).

5 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1356 (SEQ ID NO: 549), and a second modified oligonucleotide consisting of IS1747 (SEQ ID NO: 811) (see FIG. 2).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1383 (SEQ ID NO: 576), and a second modified oligonucleotide consisting of IS1774 (SEQ ID NO: 838) (see FIG. 3).

10 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1387 (SEQ ID NO: 580), and a second modified oligonucleotide consisting of IS1778 (SEQ ID NO: 842) (see FIG. 4).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1388 (SEQ ID NO: 581), and a second modified oligonucleotide consisting of IS1779 (SEQ ID NO: 843) (see FIG. 5).

15 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1391 (SEQ ID NO: 584), and a second modified oligonucleotide consisting of IS1782 (SEQ ID NO: 846) (see FIG. 6).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1397 (SEQ ID NO: 590), and a second modified oligonucleotide consisting of IS1788 (SEQ ID NO: 852) (see FIG. 7).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1424 (SEQ ID NO: 617), and a second modified oligonucleotide consisting of IS1815 (SEQ ID NO: 879) (see FIG. 8).

25 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1453 (SEQ ID NO: 646), and a second modified oligonucleotide consisting of IS1844 (SEQ ID NO: 908) (see FIG. 9).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1468 (SEQ ID NO: 661), and a second modified oligonucleotide consisting of IS1859 (SEQ ID NO: 923) (see FIG. 10).

30 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1469 (SEQ ID NO: 662), and a second modified oligonucleotide consisting of IS1860 (SEQ ID NO: 924) (see FIG. 11).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1491 (SEQ ID NO: 684), and a second modified oligonucleotide consisting of IS1882 (SEQ ID NO: 946) (see FIG. 12).

5 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1501 (SEQ ID NO: 694) and a second modified oligonucleotide consisting of IS1892 (SEQ ID NO: 956) (see FIG. 13).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1510 (SEQ ID NO: 703), and a second modified oligonucleotide consisting of IS1901 (SEQ ID NO: 965) (see FIG. 14).

10 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1512 (SEQ ID NO: 705), and a second modified oligonucleotide consisting of IS1903 (SEQ ID NO: 967) (see FIG. 15).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1515 (SEQ ID NO: 708), and a second modified oligonucleotide consisting of IS1906 (SEQ ID NO: 970) (see FIG. 16).

15 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1544 (SEQ ID NO: 737), and a second modified oligonucleotide consisting of IS1935 (SEQ ID NO: 999) (see FIG. 17).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1552 (SEQ ID NO: 745), and a second modified oligonucleotide consisting of IS1943 (SEQ ID NO: 1007) (see FIG. 18).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1572 (SEQ ID NO: 765), and a second modified oligonucleotide consisting of IS1963 (SEQ ID NO: 1027) (see FIG. 19).

25 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1573 (SEQ ID NO: 766), and a second modified oligonucleotide consisting of IS1964 (SEQ ID NO: 1028) (see FIG. 20).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1635 (SEQ ID NO: 1086), and a second modified oligonucleotide consisting of IS2026 (SEQ ID NO: 1100) (see FIG. 21).

30 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1636 (SEQ ID NO: 1087), and a second modified oligonucleotide consisting of IS2027 (SEQ ID NO: 1101) (see FIG. 22).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1637 (SEQ ID NO: 1088), and a second modified oligonucleotide consisting of IS2028 (SEQ ID NO: 1102) (see FIG. 23).

5 Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1638 (SEQ ID NO: 1089), and a second modified oligonucleotide consisting of IS2029 (SEQ ID NO: 1103) (see FIG. 24).

Certain embodiments provide a compound comprising a first modified oligonucleotide consisting of IA1639 (SEQ ID NO: 1090), and a second modified oligonucleotide consisting of IS2030 (SEQ ID NO: 1104) (see FIG. 25).

10 In certain embodiments, provided herein is a population of modified oligonucleotides, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom. In certain embodiments, provided herein is a population of compounds, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

15 In certain embodiments, the compound of any foregoing embodiment is in a pharmaceutically acceptable salt form. In certain embodiments, the pharmaceutically acceptable salt is a sodium salt. In certain embodiments, the pharmaceutically acceptable salt is a potassium salt.

20 Certain embodiments provide a composition comprising the compound of any one of the foregoing embodiments and a pharmaceutically acceptable carrier.

Certain embodiments provide a composition comprising a compound of any preceding embodiment, for use in therapy.

25 Certain embodiments provide a method of treating, preventing, or ameliorating a disease, disorder or condition associated with FXI in an individual comprising administering to the individual a compound targeted to FXI, thereby treating, preventing, or ameliorating the disease.

30 In certain embodiments, the compound or composition of any foregoing embodiment is administered to an individual. In certain embodiments, the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or

condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the disease, disorder or condition is treatable with anticoagulant therapy. In certain embodiments, the individual is in need of anticoagulant therapy.

In certain embodiments, administering the compound inhibits or reduces or improves a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an animal.

In certain embodiments, a compound or composition comprising a compound of any preceding embodiment is administered to an individual in a therapeutically effective amount. In certain embodiments, a compound or composition comprising a compound of any preceding embodiment is administered to an individual at a dosage level sufficient to deliver about 1 to 100 mg/kg of body weight of the individual. In certain embodiments, a compound or composition comprising a compound of any preceding embodiment is administered to an individual at a fixed dose of about 25 mg to about 1,000 mg. In certain embodiments, the compound or composition is administered to the individual one or more times in a day up to the dosage level or fixed dose.

In certain embodiments, a compound or composition comprising a compound of any preceding embodiment is administered to an individual daily, weekly, monthly, quarterly or yearly. In certain embodiments, a compound or composition comprising a compound of any preceding embodiment is administered to an individual about once per quarter (i.e., once every three months) to about once per year. In certain embodiments, a compound or composition comprising a compound of any preceding embodiment is administered to an individual about once per quarter, about once every six months or about once per year.

Certain embodiments provide a method of inhibiting expression of FXI in a cell comprising contacting the cell with a compound targeted to FXI, thereby inhibiting expression of FXI in the cell. In certain embodiments, the cell is in the liver of an individual. In certain embodiments, the individual has, or is at risk of having, a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis or is otherwise in need of anticoagulant therapy.

Certain embodiments provide a method of reducing or inhibiting a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an individual, comprising administering a compound targeted to FXI to the individual, thereby reducing or inhibiting a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity),

infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in the individual. In certain embodiments, the individual has, or is at risk of having, a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound is a compound targeted to FXI. In certain embodiments, the compound is any of the foregoing compounds. In certain embodiments, the compound or composition is administered parenterally.

Certain embodiments provide use of a compound targeted to FXI for treating, preventing, or ameliorating a disease, disorder or condition associated with FXI. In certain embodiments, the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound is a compound targeted to FXI. In certain embodiments, the compound is any of the foregoing compounds.

Certain embodiments provide use of a compound targeted to FXI in the manufacture of a medicament for treating, preventing, or ameliorating a disease, disorder or condition associated with FXI. In certain embodiments, the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease,

disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound is a compound targeted to FXI. In certain embodiments, the compound is any of the foregoing compounds.

Certain Indications

In certain aspects, the disclosure relates to methods of inhibiting FXI expression, which can be useful for treating, preventing, or ameliorating a disease associated with FXI in an individual, by administration of a compound that targets FXI. In certain embodiments, the compound can be a FXI specific inhibitor. In certain embodiments, the compound can be an antisense oligonucleotide, an oligomeric compound, or an oligonucleotide targeted to FXI.

In certain aspects, the disclosure relates to treating, preventing, or ameliorating a disease, disorder or condition associated with FXI. In certain embodiments, diseases, disorders or conditions associated with FXI treatable, preventable, and/or ameliorable with the methods provided herein include a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. Certain compounds provided herein are directed to compounds and compositions that reduce a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack,

stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an animal.

10 In certain embodiments, a method of treating, preventing, or ameliorating a disease associated with FXI in an individual comprises administering to the individual a compound comprising a FXI specific inhibitor, thereby treating, preventing, or ameliorating the disease. In certain embodiments, the individual is identified as having, or at risk of having, a disease associated with FXI. In certain embodiments, the disease is a FXI related disease. In certain

15 embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides) in length having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at

20 least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of

25 any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequences of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and

30 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound

can be single-stranded or double-stranded. In certain embodiments, a single-stranded compound can be 14 to 30, 14 to 23, 14 to 20, 16 to 20, or 14 to 16, linked nucleosides in length. In certain embodiments, a single-stranded compound can be 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, linked nucleosides in length. In certain embodiments, a double-stranded compound can comprise two oligonucleotides of the same or different lengths, as described elsewhere herein. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, administering the compound improves, preserves, or prevents a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-

dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an animal.

- 5 In certain embodiments, a method of treating, preventing, or ameliorating a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an
- 10 autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis,
- 15 endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an animal comprises administering to the individual a compound comprising a FXI specific inhibitor, thereby treating, preventing, or ameliorating a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an
- 20 inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral
- 25 infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the FXI specific inhibitor is a compound provided herein. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an
- 30 oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071,

1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising

the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified

5 oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to

10 the first modified oligonucleotide. In certain embodiments, administering the compound improves, preserves, or prevents a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or

15 condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an animal. In certain embodiments, the individual is identified as having, or at risk of having, a disease associated with FXI.

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In certain embodiments, a method of inhibiting expression of FXI in an individual having, or at risk of having, a disease associated with FXI comprises administering to the

25 individual a compound comprising a FXI specific inhibitor, thereby inhibiting expression of FXI in the individual. In certain embodiments, administering the compound inhibits expression of FXI in the liver. In certain embodiments, the disease is a FXI related disease. In certain embodiments, the individual has, or is at risk of having, a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or

30 condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-

dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound

5 comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23

10 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-

15 271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain

20 embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any one of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-

25 1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a

30 nucleobase sequence of any one of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an

antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23
5 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first
10 modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having
15 a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length
20 having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, administering the compound improves, preserves, or prevents a FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial
25 fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity),
30 infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.

In certain embodiments, a method of inhibiting expression of FXI in a cell comprises contacting the cell with a compound comprising a FXI specific inhibitor, thereby inhibiting

expression of FXI in the cell. In certain embodiments, the cell is a hepatocyte. In certain embodiments, the cell is in the liver. In certain embodiments, the cell is in the liver of an individual who has, or is at risk of having, a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound

comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

30 In certain embodiments, a method of reducing or inhibiting a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune

disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an individual having, or at risk of having, a disease associated with FXI comprises administering to the individual a compound comprising a FXI specific inhibitor, thereby reducing or inhibiting a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in the individual. In certain embodiments, the individual has, or is at risk of having, a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous

nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first

modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified

5 oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and

10 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the compound is administered to the individual parenterally. In certain embodiments, the individual is identified as having, or at risk of having, a disease associated with FXI.

15 Certain embodiments are drawn to a compound comprising a FXI specific inhibitor for use in treating a disease, disorder or condition associated with FXI. In certain embodiments, the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an

20 inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral

25 infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a

30 modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-

1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any one of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-

271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound
5 comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide. In certain embodiments, the
10 compound is administered to the individual parenterally.

Certain embodiments are drawn to a compound comprising a FXI specific inhibitor for use in reducing or inhibiting a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory
15 disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial
20 infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30,
25 for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a
30 compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the

group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

Certain embodiments are drawn to the use of a compound comprising a FXI specific inhibitor for the manufacture or preparation of a medicament for treating a disease associated with FXI. Certain embodiments are drawn to the use of a compound comprising a FXI specific inhibitor for the preparation of a medicament for treating a disease, disorder or condition associated with FXI. In certain embodiments, the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof. In certain embodiments, the disease, disorder or condition is a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes

mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or

oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

Certain embodiments are drawn to the use of a compound comprising a FXI specific inhibitor for the manufacture or preparation of a medicament for reducing or inhibiting a FXI related disease, disorder or condition or a symptom thereof in an individual having, or at risk of having, a FXI related disease, disorder or condition or a symptom thereof associated with FXI. In certain embodiments, the FXI related disease, disorder or condition is a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.

Certain embodiments are drawn to use of a compound comprising a FXI specific inhibitor for the preparation of a medicament for treating a disease, disorder or condition associated with FXI. In certain embodiments, the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof or a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis. In certain embodiments, the compound comprises an antisense oligonucleotide targeted to FXI. In certain embodiments, the compound comprises an oligonucleotide targeted to FXI. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, a compound comprises a modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, a compound

comprises a modified oligonucleotide selected from the group consisting of the nucleobase sequence of any of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139. In certain embodiments, the compound comprises a first modified oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second modified oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139. In any of the foregoing embodiments, the compound can be single-stranded or double-stranded. In any of the foregoing embodiments, the compound can be an antisense oligonucleotide or oligomeric compound. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide (e.g., of 14 to 30, for example, 14 to 23, linked nucleosides in length) having a region of complementarity to the first modified oligonucleotide. In certain embodiments, a compound comprises a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

In any of the foregoing methods or uses, the compound can be an oligomeric compound. In any of the foregoing methods or uses, the compound can be single-stranded or double-stranded. In any of the foregoing methods or uses, the compound can be targeted to FXI. In certain embodiments, the compound comprises or consists of a modified oligonucleotide. In certain embodiments, the compound comprises one or more modified

oligonucleotides. In certain embodiments, the compound comprises a first modified oligonucleotide and a second modified oligonucleotide. In certain embodiments, a modified oligonucleotide is 8 to 80 linked nucleosides in length, 10 to 30 linked nucleosides in length, 14 to 30 linked nucleosides in length, 14 to 23 linked nucleosides in length, or 19 to 23 linked nucleosides in length. In certain embodiments, a modified oligonucleotide is at least 80%, at least 85%, at least 90%, at least 95% or 100% complementary to any of the nucleobase sequences recited in SEQ ID NOs: 1 and 3, or the complement thereof, over its length. In certain embodiments, a modified oligonucleotide comprises at least one modified internucleoside linkage, at least one modified sugar and/or at least one modified nucleobase.

10 In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, the modified sugar is a bicyclic sugar, 2'-MOE, 2'-F, or 2'-OMe. In certain embodiments, the modified nucleobase is a 5-methylcytosine. In any of the foregoing embodiments, each modified oligonucleotide is independently 12 to 30, 14 to 30, 14 to 25, 14 to 24, 14 to 23, 16 to 23, 17 to 23, 18 to 23, 19 to 23, 19 to 22, or 19 to 20 linked nucleosides in length. In certain embodiments, a modified oligonucleotide has at least 1, at least 2, at least 3 mismatches to a region of SEQ ID NO: 1 and 3.

In any of the foregoing methods or uses, the compound comprises a first and second modified oligonucleotide, wherein there is a region of complementarity between a first modified oligonucleotide and a second modified oligonucleotide. In certain embodiments, the region of complementarity between the first oligonucleotide and the second oligonucleotide is 14 to 23, 19 to 23, or 21 to 23 linked nucleosides in length. In certain embodiments, the first modified oligonucleotide is fully complementary to the second modified oligonucleotide. In certain embodiments, the first modified oligonucleotide comprises at least one modification selected from a modified internucleoside linkage, a modified sugar, and a modified nucleobase. In certain embodiments, the second modified oligonucleotide comprises at least one modification selected from the group consisting of a modified internucleoside linkage, a modified sugar, and a modified nucleobase. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage or a methylphosphonate internucleoside linkage. In certain embodiments, the modified internucleoside linkage is at the 3' terminus of the first or second modified oligonucleotide or at the 5' terminus of the first or second modified oligonucleotide. In certain embodiments, the first or second modified oligonucleotide comprises one or more modified sugars. In certain embodiments, each nucleoside of the first or second modified

oligonucleotide comprises a modified sugar. In certain embodiments, the modified sugar comprises a modification selected from the group consisting of a halogen, an alkoxy group and a bicyclic sugar. In certain embodiments, the modified sugar comprises a modification selected from group consisting of 2'-MOE, 2'-F, and 2'-OMe or a combination thereof. In
5 certain embodiments, the first or second modified oligonucleotide comprises no more than ten 2'-F sugar modifications. In certain embodiments, the first or second modified oligonucleotide comprises no more than five 2'-F sugar modifications.

In any of the forgoing methods or uses, a compound comprises a conjugate group. In certain embodiments, the conjugate group is attached to the 5' end of a modified
10 oligonucleotide. In certain embodiments, the conjugate group is a targeting moiety. In certain embodiments, the targeting moiety comprises one or more GalNAc. In certain embodiments, the one or more GalNAc is attached to the 2' or 3' position of the ribosyl ring. In certain embodiments, the one or more GalNAc is attached to the 5' nucleoside of the modified oligonucleotide. In certain embodiments, the 5' nucleoside of a modified
15 oligonucleotide is selected from Formulae I -VIII, or a salt, solvate, or hydrate thereof, wherein R is the modified oligonucleotide other than the 5' nucleoside. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula I and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula I and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula II
20 and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula II and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula III and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula III and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula IV and R' is O. In certain
25 embodiments, the 5' nucleoside of the modified oligonucleotide is Formula IV and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula V and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula V and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VI and R' is O. In certain embodiments, the 5' nucleoside of the modified
30 oligonucleotide is Formula VI and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VII and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VII and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VIII and R' is O.

In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VIII and R' is S.

In any of the foregoing methods or uses, the compound comprises a first modified oligonucleotide selected from the group consisting of any one of Ref ID NOs: IA1341-
5 IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and IA1729-
IA1731, and a second modified oligonucleotide 14 to 23 linked nucleosides in length fully
complementary to the first modified oligonucleotide. In certain embodiments, the compound
comprises a first modified oligonucleotide selected from the group consisting of Ref ID NOs:
10 IA1341-IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and
IA1729-IA1731, and a second modified oligonucleotide selected from the group consisting of
Ref ID NOs: IS1732-IS1993, IS2026-IS2030, IS2043-IS2045, IS2047, IS2052-IS2056,
IS2142, and IS2148-2150. In certain embodiments, the compound comprises a first modified
oligonucleotide selected from any of the Ref ID NOs listed in Table 3 and a second modified
oligonucleotide selected from any of the Ref ID NOs listed in Table 3. In certain
15 embodiments, the compound is in a pharmaceutically acceptable salt form. In certain
embodiments, the pharmaceutically acceptable salt is a sodium salt. In certain embodiments,
the pharmaceutically acceptable salt is a potassium salt. In certain embodiments, a
composition comprises the compound of any one of the foregoing embodiments and a
pharmaceutically acceptable carrier.

20 In any of the foregoing methods or uses, a compound or composition comprising a
compound of any preceding embodiment is administered to an individual in a therapeutically
effective amount. In certain embodiments, a compound or composition comprising a
compound of any preceding embodiment is administered to an individual at a dosage level
sufficient to deliver about 1 to 100 mg/kg of body weight of the individual. In certain
25 embodiments, a compound or composition comprising a compound of any preceding
embodiment is administered to an individual at a fixed dose of about 25 mg to about 1,000
mg. In certain embodiments, the composition is administered to the individual one or more
times in a day up to the dosage level or fixed dose.

In any of the foregoing methods or uses, a compound or composition comprising a
30 compound of any preceding embodiment is administered to an individual daily, weekly,
monthly, quarterly or yearly. In certain embodiments, a compound or composition
comprising a compound of any preceding embodiment is administered to an individual about
once per quarter (i.e., once every three months) to about once per year. In certain
embodiments, a compound or composition comprising a compound of any preceding

embodiment is administered to an individual about once per quarter, about once every six months or about once per year.

Certain Compounds

5 In certain aspects, the disclosure relates to a compound that comprises or consists of an oligomeric compound. In certain embodiments, the oligomeric compound comprises a nucleobase sequence complementary to that of a target nucleic acid.

 In certain aspects, the disclosure relates to a compound that comprises or consists of a modified oligonucleotide. In certain embodiments, the modified oligonucleotide has a
10 nucleobase sequence complementary to that of a target nucleic acid.

 In certain aspects, the disclosure relates to a compound that comprises or consists of an antisense oligonucleotide. In certain embodiments, the antisense oligonucleotide has a nucleobase sequence complementary to that of a target nucleic acid.

 In certain aspects, the disclosure relates to a compound that is a single-stranded
15 compound. In certain embodiments, the single-stranded compound comprises or consists of an oligomeric compound. In certain embodiments, such an oligomeric compound comprises or consists of an oligonucleotide and optionally a conjugate group. In certain embodiments, the oligonucleotide is a modified oligonucleotide. In certain embodiments, the oligonucleotide is an antisense oligonucleotide. In certain embodiments, the oligonucleotide
20 or modified oligonucleotide of a single-stranded compound comprises a self-complementary nucleobase sequence.

 In certain aspects, the disclosure relates to a compound that is a double-stranded compound. In certain embodiments, the double-stranded compound comprises or consists of an oligomeric compound. In certain embodiments, the double-stranded compound comprises
25 a first oligonucleotide and a second oligonucleotide. In certain embodiments, the first oligonucleotide has a region complementarity to a target nucleic acid and the second oligonucleotide has a region complementarity to the first modified oligonucleotide. In certain embodiments, the double-stranded compound comprises a modified oligonucleotide. In certain embodiments, the modified oligonucleotide has a region complementarity to a target
30 nucleic acid. In certain embodiments, the double-stranded compound comprises a first modified oligonucleotide and a second modified oligonucleotide. In certain embodiments, the first modified oligonucleotide has a region complementarity to a target nucleic acid and the second modified oligonucleotide has a region complementarity to the first modified oligonucleotide. In certain embodiments, an oligonucleotide or modified oligonucleotide of a

double-stranded compound is an RNA oligonucleotide. In such embodiments, the thymine nucleobase in the modified oligonucleotide is replaced by a uracil nucleobase.

In certain embodiments, a compound described herein comprises a conjugate group.

In certain embodiments, the first oligonucleotide or first modified oligonucleotide of a double-stranded compound comprises a conjugate group. In certain embodiments, the second oligonucleotide or second modified oligonucleotide of a double-stranded compound comprises a conjugate group. In certain embodiments, a first oligonucleotide or first modified oligonucleotide and a second oligonucleotide or second modified oligonucleotide of a double-stranded compound each comprises a conjugate group.

In certain embodiments, a compound is 14-30 linked nucleosides in length. In certain embodiments, the first oligonucleotide or first modified oligonucleotide of a double-stranded compound is 14-30 linked nucleosides in length. In certain embodiments, the second oligonucleotide or second modified oligonucleotide is 14-30 linked nucleosides in length. In certain embodiments, the oligonucleotides or modified oligonucleotides of a double-stranded compound are blunt ended at one or both ends of the compound. In certain embodiments, the oligonucleotides or modified oligonucleotides of a double-stranded compound include non-complementary overhanging nucleosides at one or both ends of the compound.

In certain embodiments, a compound has a nucleobase sequence comprising at least 14 contiguous nucleobases of any of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, one of the oligonucleotides or modified oligonucleotides of a double-stranded compound has a nucleobase sequence comprising at least 14 contiguous nucleobases of any of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139.

Examples of single-stranded and double-stranded compounds include, but are not limited to, oligonucleotides, antisense oligonucleotides, siRNAs, microRNA targeting oligonucleotides, occupancy-based compounds (e.g., mRNA processing or translation blocking compounds and splicing compounds), and single-stranded RNAi compounds (e.g. small hairpin RNAs (shRNAs), single stranded siRNAs (ssRNAs) and microRNA mimics).

In certain embodiments, a compound described herein has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target region of a target nucleic acid to which it is targeted.

In certain embodiments, a compound described herein comprises an oligonucleotide 12 to 30 linked subunits in length. In certain embodiments, a compound described herein

comprises an oligonucleotide 12 to 23 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide 14 to 30 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide 14 to 23 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 15 to 30 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 15 to 23 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 16 to 30 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 16 to 23 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 17 to 30 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 17 to 23 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 18 to 30 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 18 to 23 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 19 to 30 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 19 to 23 linked subunits in length. In other words, such oligonucleotides are 12 to 30 linked subunits, 12 to 23 linked subunits, 14 to 30 linked subunits, 14 to 23 linked subunits, 15 to 30 linked subunits, 15 to 23 linked subunits, 16 to 30 linked subunits, 16 to 23 linked subunits, 17 to 30 linked subunits, 17 to 23 linked subunits, 18 to 30 linked subunits, 18 to 23 linked subunits, 19 to 30 linked subunits or 19 to 23 linked subunits, respectively. In certain embodiments, a compound described herein comprises an oligonucleotide 14 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 16 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 17 linked subunits in length. In certain embodiments, compound described herein comprises an oligonucleotide 18 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 19 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 20 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 21 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 22 linked subunits in length. In certain embodiments, a compound described herein comprises an oligonucleotide 23 linked subunits in length. In other embodiments, a compound described herein comprises an oligonucleotide 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 23, 18 to 24, 18 to 25, 18 to 50, 19 to 23, 19 to 30, 19 to 50, 20 to 23 or 20 to 30 linked subunits. In certain such embodiments, the compound described herein comprises an oligonucleotide 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 linked subunits in length, or a range defined by any two of the above values.

In certain embodiments, the compound may further comprise an additional moiety, such as a conjugate group or delivery moiety. In certain embodiments, such compounds are oligomeric compounds, and the additional moiety is attached to an oligonucleotide. In certain embodiments, a conjugate group is attached to a nucleoside of an oligonucleotide.

In certain embodiments, compounds may be shortened or truncated. For example, one or more subunits may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation) of an oligonucleotide.

In certain embodiments, compounds may be lengthened. For example, one or more subunits may be attached to the 3' end or 5' end of an oligonucleotide. In certain embodiments, at least one subunit (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more subunits) is attached to the 5' end of an oligonucleotide. In certain embodiments, at least one subunit (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more subunits) is attached to the 3' end of an oligonucleotide. In certain embodiments, at least one or more subunits may be attached to the 3' end or 5' end of an oligonucleotide of a double-stranded compound creating a 3' and/or 5' end overhang. In certain embodiments, at least one subunit (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more subunits) is attached to the 5' end of both oligonucleotides of a double-stranded compound. In certain embodiments, at least one subunit (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more subunit) is attached to the 3' end of both oligonucleotides of a double-stranded compound. In certain embodiments, subunits are attached to both oligonucleotides of a double-stranded compound at the same end (e.g., that subunits are attached to the 3' end of one of the oligonucleotides and subunits are attached to the 5' end of the other oligonucleotide). In certain embodiments, when subunits are attached to both oligonucleotides of a double-stranded compound at the same end, the number of

subunits attached to each oligonucleotide may be the same or may be different. In certain embodiments, when subunits are attached to both oligonucleotides of a double-stranded compound at the same end, the number of subunits attached to each oligonucleotide is the same. In certain embodiments, when subunits are attached to both oligonucleotides of a double-stranded compound at the same end, the number of subunits attached to each oligonucleotide is different. This scenario, where subunits are attached to both oligonucleotides of a double-stranded compound at the same end, may occur at one or both ends of a double-stranded compound. In certain embodiments, the subunits attached to the 3' and/or 5' end are modified.

10 In certain embodiments, compounds described herein are oligonucleotides. In certain embodiments, compounds described herein are modified oligonucleotides. In certain embodiments, compounds described herein are antisense oligonucleotides. In certain embodiments, compounds described herein are oligomeric compounds. In certain embodiments, compounds described herein are RNAi compounds. In certain embodiments, compounds described herein are siRNA compounds.

In certain embodiments, a compound described herein can comprise any of the oligonucleotide sequences targeted to FXI described herein. In certain embodiments, the compound can be double-stranded.

20 In certain embodiments, the compound comprises an oligonucleotide comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 contiguous nucleobase portion of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139. In certain embodiments, the compound comprises a second oligonucleotide. In certain embodiments, the compound comprises a first oligonucleotide comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 contiguous nucleobase portion of any of SEQ ID NOs: 10-271, 534-795, 1058-1071, 1086-1099, 1121-1124, or 1131-1134, and a second oligonucleotide comprising at least an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 contiguous nucleobase portion of any of SEQ ID NOs: 272-533, 796-1057, 1072-1085, 1100-1113, 1126-1129, or 1136-1139.

30 In certain embodiments, the compound comprises ribonucleotides in which the oligonucleotide has uracil (U) in place of thymine (T) for any of the sequences provided here. In certain embodiments, the compound comprises deoxyribonucleotides in which the oligonucleotide has thymine (T) in place of uracil (U) for any of the sequences provided here.

Certain Mechanisms

In certain embodiments, compounds described herein comprise or consist of modified oligonucleotides. In certain embodiments, compounds described herein comprise or consist of antisense oligonucleotides. In certain embodiments, compounds comprise or consist of
5 oligomeric compounds. In certain embodiments, compounds described herein are capable of hybridizing to a target nucleic acid. In certain embodiments, compounds described herein selectively affect one or more target nucleic acid. Such compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to
10 one or more non-target nucleic acid in such a way that results in a significant undesired activity.

In certain embodiments, hybridization of a compound described herein to a target nucleic acid results in recruitment of one or more proteins that cause the cleavage of the target nucleic acid. For example, certain compounds described herein or a portion of the
15 compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain compounds described herein result in cleavage of the target nucleic acid by Argonaute. Compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA) or single-stranded (ssRNA).

20 In certain embodiments, hybridization of compounds described herein to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain such embodiments, hybridization of the compound to the target nucleic acid results in the alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of the compound to a target nucleic acid results in inhibition of a binding interaction between
25 the target nucleic acid and a protein or other nucleic acid. In certain such embodiments, hybridization of the compound to the target nucleic acid results in the alteration of RNA processing. In certain such embodiments, hybridization of the compound to a target nucleic acid results in alteration of translation of the target nucleic acid.

Activities resulting from the hybridization of a compound to a target nucleic acid may
30 be observed directly or indirectly. In certain embodiments, observation or detection of an activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein, and/or a phenotypic change in a cell or animal.

Certain Modifications

In certain aspects, the disclosure relates to compounds that comprise or consist of oligonucleotides. Oligonucleotides consist of linked nucleosides. In certain embodiments, oligonucleotides may be unmodified RNA or DNA or may be modified. In certain
 5 embodiments, the oligonucleotides are modified oligonucleotides. In certain embodiments, the modified oligonucleotides comprise at least one modified sugar, modified nucleobase or modified internucleoside linkage relative to an unmodified RNA or DNA. In certain
 10 embodiments, an oligonucleotide has a modified nucleoside. A modified nucleoside may comprise a modified sugar, a modified nucleobase or both a modified sugar and a modified nucleobase. Modified oligonucleotides may also include end modifications, e.g., 5'-end
 modifications and 3'-end modifications.

Sugar Modifications and Motifs

In certain embodiments, a modified sugar is a substituted furanosyl sugar or non-bicyclic modified sugar. In certain embodiments, a modified sugar is a bicyclic or tricyclic
 15 modified sugar. In certain embodiments, a modified sugar is a sugar surrogate. A sugar surrogate may comprise one or more substitutions described herein.

In certain embodiments, a modified sugar is a substituted furanosyl or non-bicyclic modified sugar. In certain embodiments, the furanosyl sugar is a ribosyl sugar. In certain
 20 embodiments, the furanosyl sugar comprises one or more substituent groups, including, but not limited to, substituent groups at the 2', 3', 4', and 5' positions.

In certain embodiments, substituents at the 2' position include, but are not limited to, F and OCH₃ ("OMe", "O-methyl" or "methoxy"). In certain embodiments, substituent groups at the 2' position suitable for non-bicyclic modified sugars include, but are not limited to, halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, F, Cl, Br, SCH₃, SOCH₃, SO₂CH₃,
 25 ONO₂, NO₂, N₃, and NH₂. In certain embodiments, substituent groups at the 2' position include, but are not limited to, O-(C₁-C₁₀) alkoxy, alkoxyalkyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, O-alkyl-O-alkyl, alkynyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. In certain embodiments, substituent groups at the 2' position
 30 include, but are not limited to, alkaryl, aralkyl, O-alkaryl, and O-aralkyl. In certain embodiments, these 2' substituent groups can be further substituted with one or more substituent groups independently selected from hydroxyl, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl, and alkynyl. In certain
 embodiments, substituent groups at the 2' position include, but are not limited to,

O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nCH₃, O(CH₂)_nONH₂, O(CH₂)_nNH₂, O(CH₂)_nSCH₃, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are independently from 1 to about 10. In certain embodiments, substituent groups at the 2' position include, but are not limited to, OCH₂CH₂OCH₃ ("MOE"), O(CH₂)₂ON(CH₃)₂ ("DMAOE"),

5 O(CH₂)₂O(CH₂)₂N(CH₃)₂ ("DMAEOE"), and OCH₂C(=O)-N(H)CH₃ ("NMA").

In certain embodiments, substituent groups at the 4' position suitable for non-bicyclic modified sugars include, but are not limited to, alkoxy (e.g., methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. In certain embodiments, substituent groups at the 5' position suitable for non-bicyclic modified sugars include, but are not limited to,

10 methyl ("Me") (R or S), vinyl, and methoxy. In certain embodiments, substituents described herein for the 2', 4' and 5' position can be added to other specific positions on the sugar. In certain embodiments, such substituents may be added to the 3' position of the sugar on the 3' terminal nucleoside or the 5' position of the 5' terminal nucleoside. In certain embodiments, a non-bicyclic modified sugar may comprise more than one non-bridging sugar substituent. In

15 certain such embodiments, non-bicyclic modified sugars substituents include, but are not limited to, 5'-Me-2'-F, 5'-Me-2'-OMe (including both R and S isomers). In certain embodiments, modified sugar substituents include those described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.

In certain embodiments, a modified sugar is a bicyclic sugar. A bicyclic sugar is a

20 modified sugar comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, a bicyclic sugar comprises a bridging substituent that bridges two atoms of the furanosyl ring to form a second ring. In certain embodiments, a bicyclic sugar does not comprise a furanosyl moiety. A "bicyclic nucleoside" ("BNA") is a nucleoside having a

25 bicyclic sugar. In certain embodiments, the bicyclic sugar comprises a bridge between the 4' and 2' furanose ring atoms. In certain embodiments, the bicyclic sugar comprises a bridge between the 5' and 3' furanose ring atoms. In certain such embodiments, the furanose ring is a ribose ring. In certain embodiments, 4' to 2' bridging substituents include, but are not limited to, 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' ("constrained ethyl" or "cEt" when in the S

30 configuration), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof (e.g., U.S. Patent No. 7,399,845), 4'-C(CH₃)(CH₃)-O-2' and analogs thereof (e.g., U.S. Patent No. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (e.g., U.S. Patent No. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (e.g., U.S. Patent Publication

No. 2004/0171570), 4'-CH₂-N(R)-O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group (e.g., U.S. Patent No. 7,427,672), 4'-CH₂-C(H)(CH₃)-2' (e.g., Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134), and 4'-CH₂-C(=CH₂)-2' and analogs thereof (e.g., U.S. Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein

5 by reference. Additional representative U.S. Patents and U.S. Patent Publications that teach the preparation of bicyclic nucleic acid nucleotides include, but are not limited to, the following: U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133; 7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US

10 2009/0012281, US 2013/0190383; and WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference. Any 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 e.g., WO 99/14226). Specified bicyclic nucleosides herein are in the β -D configuration, unless otherwise specified.

15 In certain embodiments, a modified sugar is a sugar surrogate. In certain embodiments, a sugar surrogate has the oxygen atom replaced, e.g., with a sulfur, carbon or nitrogen atom. In certain such embodiments, the sugar surrogate may also comprise bridging and/or non-bridging substituents as described herein. In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. In certain such embodiments, the sugar

20 surrogate comprises a cyclobutyl moiety in place of the pentofuranosyl sugar. In certain embodiments, the sugar surrogate comprises a six membered ring in place of the pentofuranosyl sugar. In certain embodiments, the sugar surrogate comprises a tetrahydropyran ("THP") in place of the pentofuranosyl sugar. In certain embodiments, the sugar surrogate comprises a morpholino in place of the pentofuranosyl sugar. Representative

25 US patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Patent Nos. 4,981,957; 5,118,800; 5,166,315; 5,185,444; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,700,920; 7,875,733; 7,939,677; 8,088,904; 8,440,803; and 9,005,906, the entire contents of

30 each of the foregoing are hereby incorporated herein by reference.

In some embodiments, sugar surrogates comprise acyclic moieties. In certain embodiments, the sugar surrogate is an unlocked nucleic acid ("UNA"). A UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses a monomer where the

bonds between C1'-C4' have been removed (i.e. the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e. the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed. Representative U.S. publications that teach the preparation of UNA include, but are not limited to, U.S. Patent No. 8,314,227; and U.S. Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference. In certain embodiments, sugar surrogates comprise peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (see, e.g., Kumar et al., Org. Biomol. Chem., 2013, 11, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., US2013/130378, the entire contents of which is hereby incorporated herein by reference. Many other bicyclic and tricyclic sugar and sugar surrogate ring systems are known in the art that can be used in modified nucleosides.

In certain aspects, the disclosure relates to compounds comprising at least one oligonucleotide wherein the nucleosides of such oligonucleotide comprise one or more types of modified sugars and/or unmodified sugars arranged along the oligonucleotide or region thereof in a defined pattern or "sugar motif". In certain instances, such sugar motifs include, but are not limited to, any of the patterns of sugar modifications described herein.

In certain embodiments, an oligonucleotide comprises a gapmer sugar motif. A gapmer oligonucleotide comprises or consists of a region having two external "wing" regions and a central or internal "gap" region. The gap and wing regions form a contiguous sequence of nucleosides, wherein the majority of nucleoside sugars of each of the wings differ from the majority of nucleoside sugars of the gap. In certain embodiments, the wing regions comprise a majority of modified sugars and the gap comprises a majority of unmodified sugars. In certain embodiments, the nucleosides of the gap are deoxynucleosides. Compounds with a gapmer sugar motif are described in, for example US Patent 8,790,919, the entire contents of which is hereby incorporated herein by reference.

In certain embodiments, one or both oligonucleotides of a double-stranded compound comprise a triplet sugar motif. An oligonucleotide with a triplet sugar motif comprises three identical sugar modifications on three consecutive nucleosides. In certain embodiments, the triplet is at or near the cleavage site of the oligonucleotide. In certain embodiments, an oligonucleotide of a double-stranded compound may contain more than one triplet sugar motif. In certain embodiments, the identical sugar modification of the triplet sugar motif is a 2'-F modification. Compounds with a triplet sugar motif are disclosed, for example, in US Patent 10,668,170, the entire contents of which is incorporated herein by reference.

In certain embodiments, one or both oligonucleotides of a double-stranded compound comprise a quadruplet sugar motif. An oligonucleotide with a quadruplet sugar motif comprises four identical sugar modifications on four consecutive nucleosides. In certain embodiments, the quadruplet is at or near the cleavage site. In certain embodiments, an oligonucleotide of a double-stranded compound may contain more than one quadruplet sugar motif. In certain embodiments, the identical sugar modification of the quadruplet sugar motif is a 2'-F modification. For a double-stranded compound having a duplex region of 19-23 nucleotides in length, the cleavage site of the antisense oligonucleotide is typically around the 10, 11, and 12 positions from the 5'-end. In certain embodiments, the quadruplet sugar motif is at the 8, 9, 10, 11 positions; the 9, 10, 11, 12 positions; the 10, 11, 12, 13 positions; the 11, 12, 13, 14 positions; or the 12, 13, 14, 15 positions of the sense oligonucleotide, counting from the first nucleoside of the 5'-end of the sense oligonucleotide, or, the count starting from the first paired nucleotide within the duplex region from the 5'-end of the sense oligonucleotide. In certain embodiments, the quadruplet sugar motif is at the 8, 9, 10, 11 positions; the 9, 10, 11, 12 positions; the 10, 11, 12, 13 positions; the 11, 12, 13, 14 positions; or the 12, 13, 14, 15 positions of the antisense oligonucleotide, counting from the first nucleoside of the 5'-end of the antisense oligonucleotide, or, the count starting from the first paired nucleotide within the duplex region from the 5'-end of the antisense oligonucleotide. The cleavage site may change according to the length of the duplex region of the double-stranded compound and may change the position of the quadruplet accordingly.

In certain embodiments, an oligonucleotide comprises an alternating sugar motif. In certain embodiments, one or both oligonucleotides of a double-stranded compound comprise an alternating sugar motif. An oligonucleotide with an alternating sugar motif comprises at least two different sugar modifications wherein one or more consecutive nucleosides comprising a first sugar modification alternates with one or more consecutive nucleosides comprising a second sugar modification and one or more consecutive nucleosides comprising a third sugar modification, etc. For example, if A, B and C each represent one type of modification to the nucleoside, the alternating motif can be "ABABABABABAB...", "AABBAABBAABB...", "AABAABAABAAB...", "AAABAABAAAB...", "AAABBBAAABBB...", or "ABCABCABCABC..." etc. In certain embodiments, the alternating sugar motif is repeated for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleobases along an oligonucleotide. In certain embodiments, the alternating sugar motif is comprised of two different sugar modifications.

In certain embodiments, the alternating sugar motif comprises 2'-OMe and 2'-F sugar modifications.

In certain embodiments, each nucleoside of an oligonucleotide is independently modified with one or more sugar modifications provided herein. In certain embodiments, each oligonucleotide of a double-stranded compound independently has one or more sugar motifs provided herein. In certain embodiments, an oligonucleotide containing a sugar motif, is fully modified in that each nucleoside other than the nucleosides comprising the sugar motif comprises a sugar modification.

Nucleobase Modifications and Motifs

In certain embodiments, compounds described herein comprise modified oligonucleotides. In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides that do not comprise a nucleobase, referred to as an abasic nucleoside.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, 5-methylcytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl ($C\equiv C-CH_3$) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly, 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-dezaadenine, 3-deazaguanine, 3-dezaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one, and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example, 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone.

Further nucleobases include those disclosed in U.S. Patent 3,687,808; Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859; Kroschwitz, J.L., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, dsRNA Research and Applications, pages 289-302; Antisense Research and Applications, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; Antisense Drug Technology, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443 (Chapters 6 and 15), each of which are hereby incorporated herein by reference.

Publications that teach the preparation of certain of the above noted modified nucleobases, as well as other modified nucleobases include without limitation, US Applications 2003/0158403 and 2003/0175906; U.S. Patents 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,434,257; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,645,985; 5,681,941; 5,811,534; 5,750,692; 5,948,903; 5,587,470; 5,457,191; 5,763,588; 5,830,653; 5,808,027; 6,005,096; 6,015,886; 6,147,200; 6,166,197; 6,166,199; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

In certain embodiments, compounds described herein comprise oligonucleotides. In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methylcytosines.

In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments, the block is within 3 nucleosides of the 3'-end of the oligonucleotide. In certain embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments, the block is within 3 nucleosides of the 5'-end of the oligonucleotide.

Internucleoside Linkage Modifications and Motifs

A 3' to 5' phosphodiester linkage is the naturally occurring internucleoside linkage of RNA and DNA. In certain embodiments, compounds described herein have one or more modified, i.e. non-naturally occurring, internucleoside linkages. Certain non-naturally occurring internucleoside linkages may impart desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases. Representative phosphorus-containing modified internucleoside linkages include, but are not limited to, phosphotriesters, alkylphosphonates (e.g. methylphosphonates), phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include, but are not limited to, methylenemethylimino (-CH₂-N(CH₃)-O-CH₂), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH₂-O-); and N,N'-dimethylhydrazine (-CH₂-N((CH₃)-N((CH₃)-). Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art. Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), methoxypropyl, and thioformacetal (3'-S-CH₂-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See, for example: Carbohydrate Modifications in Antisense Research; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts.

In certain embodiments, compounds provided herein comprise at least one modified internucleoside linkage. A modified internucleoside linkage may be placed at any position of an oligonucleotide. For double-stranded compounds, a modified internucleoside linkage may be placed within the sense oligonucleotide, antisense oligonucleotide, or both oligonucleotides of the double-stranded compound.

In certain embodiments, the internucleoside linkage modification may occur on every nucleoside of an oligonucleotide. In certain embodiments, internucleoside linkage modifications may occur in an alternating pattern along an oligonucleotide. In certain embodiments, essentially each internucleoside linking group is a phosphate internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate (P=S). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is independently selected from a

phosphorothioate and phosphate internucleoside linkage. In certain embodiments, the pattern of the internucleoside linkage modification on each oligonucleotide of a double-stranded compound is the same. In certain embodiments, the pattern of the internucleoside linkage modification on each oligonucleotide of a double-stranded compound is different. In certain
5 embodiments, a double-stranded compound comprises 6-8 modified internucleoside linkages. In certain embodiments, the 6-8 modified internucleoside linkages are phosphorothioate internucleoside linkages or alkylphosphonate internucleoside linkages. In certain embodiments, the sense oligonucleotide comprises at least two modified internucleoside linkages at either or both the 5'-end and the 3'-end. In certain such embodiments, the
10 modified internucleoside linkages are phosphorothioate internucleoside linkages or alkylphosphonate internucleoside linkages. In certain embodiments, the antisense oligonucleotide comprises at least two modified internucleoside linkages at either or both the 5'-end and the 3'-end. In certain such embodiments, the modified internucleoside linkages are phosphorothioate internucleoside linkages or alkylphosphonate internucleoside linkages.
15 In certain embodiments, a double-stranded compound comprises an overhang region. In certain embodiments, a double-stranded compound comprises a phosphorothioate or alkylphosphonate internucleoside linkage modification in the overhang region. In certain embodiments, a double-stranded compound comprises a phosphorothioate or alkylphosphonate internucleotide linkage linking the overhang nucleotide with a paired
20 nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleoside linkages between the terminal three nucleosides, in which two of the three nucleosides are overhang nucleosides, and the third is a paired nucleoside next to the overhang nucleoside. These terminal three nucleosides may be at the 3'-end of the antisense oligonucleotide, the 3'-end of the sense oligonucleotide, the 5'-end of the antisense
25 oligonucleotide, or the 5'end of the antisense oligonucleotide.

In certain embodiments, modified oligonucleotides comprise one or more internucleoside linkages having chiral centers. Representative chiral internucleoside linkages include, but are not limited to, alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having chiral centers can be prepared as
30 populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides

can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. As is well understood by those of skill in the art, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 99% of the molecules in the population. Such enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, e.g., methods described in Oka et al., JACS 125, 8307 (2003), Wan et al. Nuc. Acid. Res. 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (Sp) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (Rp) configuration.

Conjugate Groups

In certain embodiments, the compounds described herein comprise or consist of one or more oligonucleotides and, optionally, one or more conjugate groups. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, a conjugate group is attached at the 3' end of an oligonucleotide. In certain embodiments, a conjugate group is attached at the 5' end of an oligonucleotide. In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups.

In certain embodiments, conjugate groups are terminal groups attached to either or both ends of an oligonucleotide. In certain such embodiments, terminal groups are attached at the 3' end of an oligonucleotide. In certain such embodiments, terminal groups are attached at

the 5' end of an oligonucleotide. In certain embodiments, terminal groups include, but are not limited to, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified, such as an overhang.

- 5 In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including, but not limited to, pharmacodynamics, pharmacokinetics, stability, activity, half-life, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In certain embodiments, conjugate groups enhance the affinity of a compound for a selected target, e.g., molecule, cell or cell type, compartment,
- 10 e.g., a cellular or organ compartment, tissue, organ or region of the body, as, e.g., compared to a compound absent such a conjugate group. In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, e.g., fluorophores or reporter groups that enable detection of the oligonucleotide.

- In certain embodiments, conjugate groups include, but are not limited to, intercalators,
- 15 reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterol, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

- In certain embodiments, conjugate groups include an active drug substance, for
- 20 example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial, or an antibiotic.

- In certain embodiments, conjugate groups are targeting moieties. In certain
- 25 embodiments, a targeting moiety includes, but is not limited to, a lectin, glycoprotein, lipid, protein, peptide, peptide mimetic, receptor ligand, antibody, thyrotropin, melanotropin, surfactant protein A, carbohydrate, carbohydrate derivative, modified carbohydrate, carbohydrate cluster, polysaccharide, modified polysaccharide, or polysaccharide derivative, mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine
- 30 (GalNAc), N-acetylglucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, vitamin A, biotin, or an RGD peptide or RGD peptide mimetic.

In certain embodiments, conjugate groups may include, but are not limited to, the conjugate groups described in the following references such as cholesterol (e.g., Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553-6556), cholic acid (e.g., Manoharan et al., *Biorg. Med. Chem. Lett.*, 1994, 4:1053-1060), thioether, e.g., hexyl-S-tritylthiol (e.g., Manoharan et al., *Ann. NY. Acad. Sci.*, 1992, 660:306-309; Manoharan et al., *Biorg. Med. Chem. Lett.*, 1993, 3:2765-2770), thiocholesterol (e.g., Oberhauser et al., *Nucl. Acids Res.*, 1992, 20:533-538), aliphatic chains, e.g., do-decan-diol or undecyl residues (e.g., 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), phospholipids, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (e.g., Manoharan et al., *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18:3777-3783), polyamines or a polyethylene glycol chains (e.g., Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14:969-973), adamantane acetic acid (e.g., Manoharan et al., *Tetrahedron Lett.*, 1995, 36:3651-3654), palmityl (e.g., Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264:229-237), octadecylamine or hexylamino-carbonyloxycholesterol moiety (e.g., Crooke et al. *J. Pharmacol. Exp. Ther.*, 1996, 277:923-937), tocopherol (e.g., Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, 4, e220 and Nishina et al., *Molecular Therapy*, 2008, 16:734-740), GalNAc and other carbohydrates (e.g., Maier et al., *Bioconjugate Chemistry*, 2003, 14, 18-29; Rensen et al., *J. Med. Chem.* 2004, 47, 5798-5808; WO2009/073809 and US Patents 8,106,022; 8,450,467 and 8,828,957; and WO2014/179445; WO2014/179620 and US Patents 9,127,276; 9,181,549 and 10,844,379) each of which is incorporated herein by reference in its entirety.

Conjugate groups may be attached to oligonucleotides through conjugate linkers. In certain embodiments, a conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units or combination of such repeating units. In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain embodiments, a conjugate linker comprises at least one phosphorus group. In certain embodiments, a conjugate linker comprises at least one phosphate group. In certain embodiments, a conjugate linker includes at least one neutral linking group. In certain embodiments, conjugate linkers include, but are not limited to, pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEx or AHA). Other conjugate linkers include, but are not limited to, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-

C₁₀ alkenyl, or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, and alkynyl. In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, such linker-nucleosides may be modified or unmodified nucleosides. It is typically desirable for linker-nucleosides to be cleaved from the compound after it reaches a target tissue. Accordingly, linker-nucleosides herein can be linked to one another and to the remainder of the compound through cleavable bonds. Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which a compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid.

In certain embodiments, conjugate groups and conjugate linkers as well as other modifications include, without limitation, those described in the following references: US 5,994,517; US 6,300,319; US 6,660,720; US 6,906,182; US 7,262,177; US 7,491,805; US 8,106,022; US 7,723,509; US 9,127,276; US 2006/0148740; US 2011/0123520; WO2013/033230; WO2012/037254, Biessen et al., *J. Med. Chem.* 1995, 38, 1846-1852; Lee et al., *Bioorganic & Medicinal Chemistry* 2011, 19, 2494-2500; Rensen et al., *J. Biol. Chem.* 2001, 276, 37577-37584; Rensen et al., *J. Med. Chem.* 2004, 47, 5798-5808; Slidregt et al., *J. Med. Chem.* 1999, 42, 609-618; Valentijn et al., *Tetrahedron*, 1997, 53, 759-770; Lee, *Carbohydr Res*, 1978, 67, 509-514; Connolly et al., *J Biol Chem*, 1982, 257, 939-945; Pavia et al., *Int J Pep Protein Res*, 1983, 22, 539-548; Lee et al., *Biochem*, 1984, 23, 4255-4261; Lee et al., *Glycoconjugate J*, 1987, 4, 317-328; Toyokuni et al., *Tetrahedron Lett*, 1990, 31, 2673-2676; Biessen et al., *J Med Chem*, 1995, 38, 1538-1546; Valentijn et al., *Tetrahedron*, 1997, 53, 759-770; Kim et al., *Tetrahedron Lett*, 1997, 38, 3487-3490; Lee et al., *Bioconjug Chem*, 1997, 8, 762-765; Kato et al., *Glycohiol*, 2001, 11, 821-829; Rensen et al., *J Biol Chem*, 2001, 276, 37577-37584; Lee et al., *Methods Enzymol*, 2003, 362, 38-43; Westerlind et al., *Glycoconj J*, 2004, 21, 227-241; Lee et al., *Bioorg Med Chem Lett*, 2006, 16(19), 5132-5135; Maierhofer et al., *Bioorg Med Chem*, 2007, 15, 7661-7676; Khorev et al., *Bioorg Med Chem*, 2008, 16, 5216-5231; Lee et al., *Bioorg Med Chem*, 2011, 19, 2494-2500; Kornilova et al., *Analyt Biochem*, 2012, 425, 43-46; Pujol et al., *Angew Chemie Int Ed Engl*,

2012, 51, 7445-7448; Biessen et al., J Med Chem, 1995, 38, 1846-1852; Sliedregt et al., J Med Chem, 1999, 42, 609-618; Rensen et al., J Med Chem, 2004, 47, 5798-5808; Rensen et al., Arterioscler Thromb Vase Biol, 2006, 26, 169-175; van Rossenberg et al., Gene Ther, 2004, 11, 457-464; Sato et al., J Am Chem Soc, 2004, 126, 14013-14022; Lee et al., J Org Chem, 2012, 77, 7564-7571; Biessen et al., FASEB J, 2000, 14, 1784-1792; Rajur et al., Bioconjug Chem, 1997, 8, 935-940; Duff et al., Methods Enzymol, 2000, 313, 297-321; Maier et al., Bioconjug Chem, 2003, 14, 18-29; Jayaprakash et al., Org Lett, 2010, 12, 5410-5413; Manoharan, Antisense Nucleic Acid Drug Dev, 2002, 12, 103-128; Merwin et al., Bioconjug Chem, 1994, 5, 612-620; Tomiya et al., Bioorg Med Chem, 2013, 21, 5275-5281;

10 International applications WO1998/013381; WO2011/038356; WO1997/046098; WO2008/098788; WO2004/101619; WO2012/037254; WO2011/120053; WO2011/100131; WO2011/163121; WO2012/177947; WO2013/033230; WO2013/075035; WO2012/083185; WO2012/083046; WO2009/082607; WO2009/134487; WO2010/144740; WO2010/148013; WO1997/020563; WO2010/088537; WO2002/043771; WO2010/129709; WO2012/068187;

15 WO2009/126933; WO2004/024757; WO2010/054406; WO2012/089352; WO2012/089602; WO2013/166121; WO2013/165816; U.S. Patents 4,751,219; 7,582,744; 8,552,163; 8,137,695; 6,908,903; 6,383,812; 7,262,177; 6,525,031; 5,994,517; 6,660,720; 6,300,319; 7,723,509; 8,106,022; 7,491,805; 7,491,805; 8,541,548; 8,344,125; 8,313,772; 8,349,308; 8,450,467; 8,501,930; 8,158,601; 7,262,177; 6,906,182; 6,620,916; 8,435,491; 8,404,862;

20 7,851,615; Published U.S. Patent Application Publications US2011/0097264; US2011/0097265; US2013/0004427; US2003/0119724; US2011/0207799; US2012/0035115; US2012/0230938; US2005/0164235; US2006/0183886; US2012/0136042; US2012/0095075; US2013/0109817; US2006/0148740; US2008/0206869; US2012/0165393; US2012/0101148; US2013/0121954;

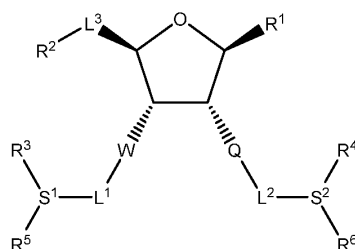
25 US2011/0123520; US2003/0077829; US2008/0108801; and US2009/0203132; each of which is incorporated herein by reference in its entirety.

Certain Targeting Moieties

In certain embodiments, a compound provided herein comprises a conjugate group. In certain embodiments, an oligonucleotide provided herein comprises a conjugate group. In certain embodiments, the conjugate group is a targeting moiety. In certain embodiments, the targeting moiety comprises one or more GalNAc. In certain embodiments, the one or more GalNAc are attached to one or more positions on a furanose ring. In certain embodiments, the one or more GalNAc are attached to the 2' or 3' position on a furanose ring. In certain embodiments, the furanose ring is a subunit of the oligonucleotide. In certain embodiments,

the furanose ring is the 5' nucleoside sugar of an oligonucleotide. In certain embodiments, the furanose ring is the 5' nucleoside sugar of a sense oligonucleotide. In certain embodiments, a compound or oligonucleotide comprises one or more subunits with the following formula or a salt, solvate, or hydrate thereof:

5



Formula IX

wherein:

- R^1 is H, adenine, guanine, thymine, cytosine, uracil, carbocyclyl, heterocyclyl, aryl,
 10 heteroaryl, or a nucleobase isostere;
 R^2 is the oligonucleotide sequence;
 L^1 is alkyl, or alkyl-C(=O)-NH-alkyl;
 L^2 is alkyl, or alkyl-C(=O)-NH-alkyl;
 L^3 is a bond, a phosphodiester bond, a phosphorothioate bond, a triazole, a tetrazole,
 15 an amide, a reverse-amide, a carbamate, a carbonate, urea, O, S, S(=O), S(=O)₂, NH,
 substituted N group, alkyl, alkenyl, dienyl, alkynyl, heteroalkyl, phosphate;
 R^3 is H, -C(=O)-NH-(CH₂CH₂O)_j-GalNAc, or -C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc;
 R^4 is H, -C(=O)-NH-(CH₂CH₂O)_k-GalNAc, or -C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-
 20 GalNAc;
 R^5 is -C(=O)-NH-(CH₂CH₂O)_m-GalNAc, or -C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc;
 R^6 is -C(=O)-NH-(CH₂CH₂O)_n-GalNAc, or -C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc;
 25 W and Q are each independently O, NH, CH₂, or CH₂O;
 S^1 and S^2 are each independently C(R^7) or N, wherein each instance of R^7 is independently H, alkyl, heteroalkyl, or halogen;
 j is an integer 1-10, inclusive;
 k is an integer 1-10, inclusive;

m is an integer 1-10, inclusive; and

n is an integer 1-10, inclusive.

In certain embodiments, R^3 , R^4 , R^5 , and R^6 are the same. In certain embodiments, R^3 , R^5 , and R^6 are the same. In certain embodiments, R^3 or R^4 is H.

5 In certain embodiments, L^1 and L^2 are the same.

In certain embodiments, L^1 and L^2 are each independently alkyl; R^3 is H, $-C(=O)-NH-(CH_2CH_2O)_j-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^4 is H, $-C(=O)-NH-(CH_2CH_2O)_k-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^5 is $-C(=O)-NH-(CH_2CH_2O)_m-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; and R^6 is $-C(=O)-NH-(CH_2CH_2O)_n-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$.

10 In certain embodiments, L^1 and L^2 are each independently alkyl- $C(=O)-NH-alkyl$; R^3 is H, $-C(=O)-NH-(CH_2CH_2O)_j-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^4 is H, $-C(=O)-NH-(CH_2CH_2O)_k-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^5 is

15 $-C(=O)-NH-(CH_2CH_2O)_m-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; and R^6 is $-C(=O)-NH-(CH_2CH_2O)_n-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$.

In certain embodiments, R^4 is H.

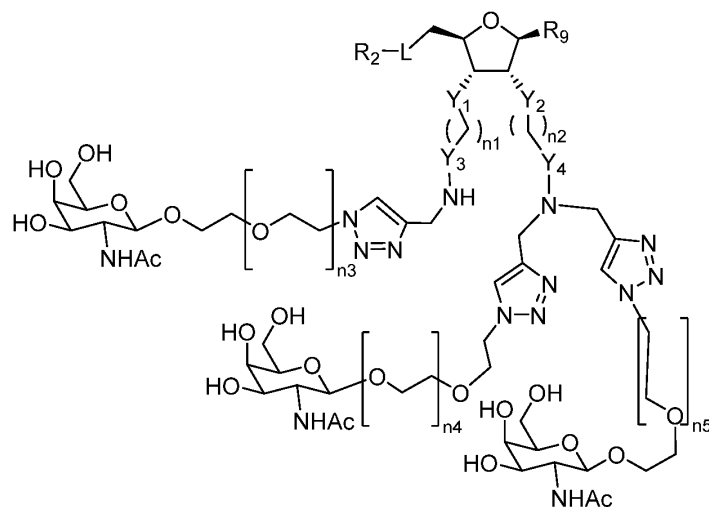
In certain embodiments, L^1 and L^2 are each independently alkyl; R^3 is $-C(=O)-NH-(CH_2CH_2O)_j-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^4 is H; R^5 is $-C(=O)-NH-(CH_2CH_2O)_m-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; and R^6 is $-C(=O)-NH-(CH_2CH_2O)_n-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$.

20 In certain embodiments, L^1 and L^2 are each independently alkyl- $C(=O)-NH-alkyl$; R^3 is $-C(=O)-NH-(CH_2CH_2O)_j-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^4 is H; R^5 is $-C(=O)-NH-(CH_2CH_2O)_m-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; and R^6 is $-C(=O)-NH-(CH_2CH_2O)_n-GalNAc$, or $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$.

25 In certain embodiments, R^3 is $-C(=O)-NH-(CH_2CH_2O)_j-GalNAc$; R^4 is H; R^5 is $-C(=O)-NH-(CH_2CH_2O)_m-GalNAc$; and R^6 is $-C(=O)-NH-(CH_2CH_2O)_n-GalNAc$.

30 In certain embodiments, R^3 is $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; R^4 is H; R^5 is $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$; and R^6 is $-C(=O)-NH-alkyl-NH-C(=O)-alkyl-O-GalNAc$.

In certain embodiments, a compound or oligonucleotide comprises one or more subunits with the following formula or a salt, solvate, or hydrate thereof:

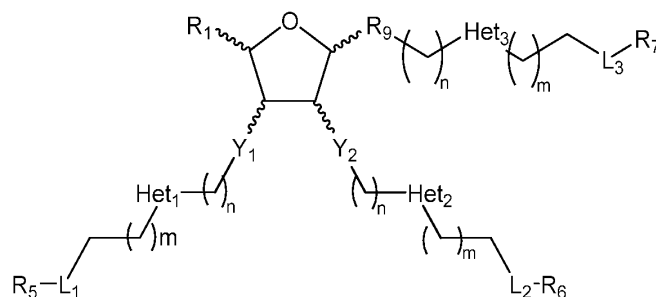


Formula X

wherein:

- 5 R⁹ is H, adenine, guanine, thymine, cytosine, or uracil, or adenine, guanine, thymine, cytosine, or uracil, each comprising a Protecting Group (PG), a modified nucleobase, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or a nucleobase isostere;
- 10 L is a bond, a phosphodiester bond, a phosphorothioate bond, a triazole, a tetrazole, an amide, a reverse-amide, a carbamate, a carbonate, urea, alkyl, or heteroalkyl;
- R² is the oligonucleotide sequence;
- Y₁ is O, CH₂, CH₂O, or optionally substituted NH;
- Y₂ is O, CH₂, CH₂O, or optionally substituted NH;
- 15 Y₃ is CO, SO₂, P(O)O, CH₂-O-C(O), CH₂-NH-C(O), CH₂-NH-SO₂, or CH₂;
- Y₄ is CO, SO₂, P(O)O, CH₂-O-C(O), CH₂-NH-C(O), CH₂-NH-SO₂, or CH₂;
- n₂ is 0, 1, 2, 3, 4, 5, or 6; and
- each n₁, n₃, n₄ and n₅ is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

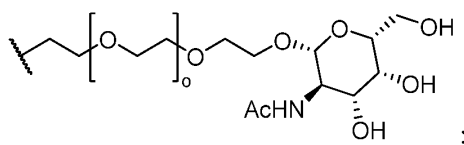
- 20 In certain embodiments, a compound or oligonucleotide comprises one or more subunits with the following formula or a salt, solvate, or hydrate thereof:



Formula XI

wherein:

- 5 each n is independently 1, 2, 3, 4, or 5;
 each m is independently 0, 1, 2, 3, 4, 5, or 6;
 each o is independently 0, 1, 2, 3, 4, 5, or 6;
 each of L₁, L₂, and L₃ is independently absent, C(=O), or C(=O)NH;
 each Y₁ is independently O, CH(R^a), S, S(=O), S(=O)₂, NH, substituted N group, NHC(=O),
 10 C(=O)NH, P(=O)₂-O-, P(=O)(=S)-O, P(=S)₂-O-, -O-P(=O)₂-O-, -O-P(=O)(=S)-O-,
 -O-P(=S)₂-O-, -O-P(=O)₂-, -O-P(=O)(=S)-, -O-P(=S)₂-;
 each Y₂ is independently O, CH(R^b), S, S(=O), S(=O)₂, NH, substituted N group, NHC(=O),
 C(=O)NH, P(=O)₂-O-, P(=O)(=S)-O, P(=S)₂-O-, -O-P(=O)₂-O-, -O-P(=O)(=S)-O-,
 -O-P(=S)₂-O-, -O-P(=O)₂-, -O-P(=O)(=S)-, -O-P(=S)₂-;
 15 each of Het₁, Het₂, and Het₃ is independently optionally substituted heteroaryl or optionally substituted heterocyclyl;
 R¹ is the oligonucleotide sequence linked by a bond, a phosphodiester bond, a phosphorothioate bond, a triazole, a tetrazole, an amide, a reverse-amide, a carbamate, a carbonate, urea, alkyl, or heteroalkyl;



- 20 each R₅, R₆, and R₇ is independently
 R₉ is optionally substituted heterocyclyl;
 each R^a is independently H, alkyl, halo, OR^c, or SR^c;
 each R^b is independently H, alkyl, halo, OR^c, or SR^c; and
 each R^c is independently H or alkyl.

25

In certain embodiments, the subunit is selected from Formulae I through VIII or a salt, solvate, or hydrate thereof, wherein R is the modified oligonucleotide other than the 5' nucleoside. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula I and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula I and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula II and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula II and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula III and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula III and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula IV and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula IV and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula V and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula V and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VI and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VI and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VII and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VII and R' is S. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VIII and R' is O. In certain embodiments, the 5' nucleoside of the modified oligonucleotide is Formula VIII and R' is S.

Target Nucleic Acids and Target Regions

In certain embodiments, compounds described herein comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain embodiments, the target nucleic acid is non-coding. In certain such embodiments, the target nucleic acid is selected from an mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is an mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain such embodiments, the target region is entirely within an exon. In certain such embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

In certain embodiments, compounds disclosed herein hybridize with a FXI nucleic acid. The most common mechanism of hybridization involves hydrogen bonding between complementary nucleobases of the nucleic acid molecules. Hybridization can occur under varying conditions. Hybridization 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 hybridizes specifically to a target nucleic acid are well known in the art. In certain embodiments, the compounds provided herein specifically hybridize with a FXI nucleic acid.

Nucleotide sequences that encode FXI include, without limitation, the following:

- 10 GENBANK Accession Nos. NM_000128.4 (incorporated herein as SEQ ID NO: 1),
nucleotides 5001 to 28718 of NG_008051.1 (incorporated herein as SEQ ID NO: 2),
NM_001354804.2 (incorporated herein as SEQ ID NO: 3).

Complementarity

- 15 Oligonucleotides provided herein may have a defined percent complementarity to a particular nucleic acid, target region, oligonucleotide, or portion thereof. Non-complementary nucleobases may be tolerated provided that the oligonucleotide remains able to specifically hybridize to the nucleic acid, oligonucleotide, or portion thereof. In certain embodiments, the oligonucleotides provided herein, or a specified portion thereof are at least, or are up to 70%,
20 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%,
or 100% complementary to a target nucleic acid, a target region, an oligonucleotide or specified portion thereof. In certain embodiments, the oligonucleotides provided herein, or a specified portion thereof, are 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, 95% to 100%, or any number in between these ranges, complementary to a target
25 nucleic acid, a target region, an oligonucleotide or specified portion thereof. Percent complementarity of an oligonucleotide with a target nucleic acid, a target region, an oligonucleotide or specified portion thereof can be determined using routine methods. For example, an oligonucleotide in which 18 of 20 nucleobases of the oligonucleotide are complementary to a target region, and would therefore specifically hybridize, would
30 represent 90 percent complementarity. In this example, the remaining non-complementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an oligonucleotide which is 18 nucleobases in length having four non-complementary 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. Percent complementarity of an oligonucleotide with a region of a target nucleic acid, a target region, an oligonucleotide or specified portion thereof can be determined routinely using BLAST programs (basic local alignment search tools) known in the art. In certain embodiments, oligonucleotides described
5 herein, or specified portions thereof, are fully complementary (i.e. 100% complementary) to a target nucleic acid, a target region, an oligonucleotide or specified portion thereof. For example, an oligonucleotide may be fully complementary to a target nucleic acid, a target region, an oligonucleotide, or specified portion thereof. As used herein, “fully complementary” means each nucleobase of an oligonucleotide is complementary to the
10 corresponding nucleobase of a target nucleic acid, a target region, an oligonucleotide, or a specified portion thereof. For example, a 20 nucleobase oligonucleotide 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 compound. “Fully complementary” can also be used in reference to a specified portion of
15 the first and/or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase oligonucleotide can be “fully complementary” to a 20 nucleobase region of a target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase compound 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
20 nucleobase portion of the compound. At the same time, the entire 30 nucleobase compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the compound are also complementary to the target sequence.

In certain embodiments, oligonucleotides described herein comprise one or more mismatched nucleobases relative to a target nucleic acid, a target region, an oligonucleotide
25 or a specified portion thereof. In certain embodiments, oligonucleotides described herein that are, or are up to 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 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, or specified portion thereof. In certain embodiments, oligonucleotides described herein that are, or are up to 14, 15, 16, 17,
30 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, a target region, an oligonucleotide, or specified portion thereof. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 from the 5'-end of the oligonucleotide. In

certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, 13 or 14 from the 3'-end of the oligonucleotide. In certain embodiments, the mismatch forms a wobble base pair with a corresponding nucleobase on the target nucleic acid. For example, in certain embodiments, the mismatch forms a wobble base pair selected from hypoxanthine (nucleobase of inosine) and uracil (I:U base pair); guanine and uracil (G:U base pair); hypoxanthine and adenine (I:A base pair); and hypoxanthine and cytosine (I:C base pair). Accordingly, in certain embodiments, a mismatched nucleobase on an oligonucleotide comprises hypoxanthine, guanine, or uracil.

In certain embodiments, oligonucleotides described herein may be complementary to a portion of a nucleic acid. As used herein, "portion" refers to a defined number of contiguous nucleobases within a region of a nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an oligonucleotide. In certain embodiments, the oligonucleotides are complementary to at least an 8 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 9 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 10 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least an 11 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 12 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 13 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 14 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 15 nucleobase portion of a nucleic acid. In certain embodiments, the oligonucleotides are complementary to at least a 16 nucleobase portion of a nucleic acid. Also contemplated are oligonucleotides that are complementary to at least a 9, 10, 17, 18, 19, 20, 21, 22, 23 or more nucleobase portion of a nucleic acid, or a range defined by any two of these values. In certain embodiments, the oligonucleotide is an antisense oligonucleotide. 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. In certain embodiments, the oligonucleotide is a sense oligonucleotide. In certain embodiments, a portion of the sense oligonucleotide is compared to an equal length portion of an antisense oligonucleotide. 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 of a sense oligonucleotide is compared to an equal length portion of an antisense oligonucleotide.

Identity

5 The oligonucleotides provided herein may also have a defined percent identity to a particular nucleic acid, target region, oligonucleotide, or specified portion thereof. As used herein, an oligonucleotide is identical to a sequence disclosed herein if it has the same nucleobase pairing ability. For example, a DNA which contains thymidine in place of uracil in a disclosed RNA sequence would be considered identical to the RNA sequence since both
10 uracil and thymidine pair with adenine. Shortened and lengthened versions of the compounds described herein as well as compounds having non-identical bases relative to the compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the compound. Percent identity of an oligonucleotide is calculated according to the number of bases that have identical base pairing relative to the sequence to
15 which it is being compared. In certain embodiments, oligonucleotides described herein, or portions thereof, are, or are at least, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the nucleic acids, oligonucleotides, or a portion thereof, disclosed herein. In certain embodiments, oligonucleotides described herein are about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%,
20 94%, 95%, 96%, 97%, 98%, or 99% identical, or any percentage between such values, to a particular nucleic acid or oligonucleotide, or portion thereof.

 In certain embodiments, an oligonucleotide may have one or more mismatched nucleobases. In certain such embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 from the 5'-end of the oligonucleotide. In certain such embodiments, the
25 mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, 13 or 14 from the 3'-end of the oligonucleotide. In certain embodiments, a portion of the 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. In certain embodiments, the oligonucleotide is a
30 sense oligonucleotide. In certain embodiments, a portion of the sense 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.

Pharmaceutical Compositions and Formulations

Compounds described herein may be admixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered. Certain embodiments provide pharmaceutical compositions comprising one or more compounds or a salt thereof. In certain embodiments, the compounds are antisense oligonucleotides. In certain embodiments, the compounds are oligomeric compounds. In certain embodiments, the compounds comprise or consist of one or more modified oligonucleotides. In certain such embodiments, the pharmaceutical composition comprises one or more compound and a suitable pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises one or more compound and a sterile saline solution. In certain embodiments, such pharmaceutical composition consists of one compound and a sterile saline solution. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises one or more compound and sterile water. In certain embodiments, a pharmaceutical composition consists of one compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises one or more compounds and phosphate-buffered saline (PBS). In certain embodiments, a pharmaceutical composition consists of one compound and sterile PBS. In certain embodiments, the sterile PBS is pharmaceutical grade PBS.

A compound described herein targeted to FXI can be utilized in pharmaceutical compositions by combining the compound with a suitable pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutically acceptable diluent is water, such as sterile water suitable for injection. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising a compound targeted to FXI and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is water. In certain embodiments, the compound comprises or consists of one or more modified oligonucleotide provided herein.

Pharmaceutical compositions comprising compounds provided herein encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. In certain embodiments,

the compounds are antisense oligonucleotides. In certain embodiments, the compounds are oligomeric compounds. In certain embodiments, the compound comprises or consists of one or more modified oligonucleotide. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. A prodrug can include the incorporation of additional nucleosides at one or both ends of a compound which are cleaved by endogenous nucleases within the body, to form the active compound. In certain embodiments, the compounds or compositions further comprise a pharmaceutically acceptable carrier or diluent.

EXAMPLES

The following examples describe the process to identify lead compounds targeted to FXI. Certain compounds are distinguished as having high potency and tolerability.

The following examples serve only to illustrate the compounds described herein and are not intended to limit the same. The following examples and related sequence listing accompanying this filing may identify sequence as either "RNA" or "DNA"; however, as disclosed herein, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that the designation of a sequence as "RNA" or "DNA" is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH for the natural 2'-H of DNA) or as an RNA having a modified base (methylated uracil for natural uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to, those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to, such nucleic acids having modified nucleobases.

Each of the references recited in the present application is incorporated herein by reference in its entirety.

Table 1
Chemical Nomenclature

Abbreviation	Structure
'm'	2'-O-methyl sugar modification (e.g., mA, mG, mC, mU)
'f'	2'-F sugar modification (e.g., fA, fG, fC, fU)
'*'	phosphorothioate internucleoside linkage
'.'	Phosphate internucleoside linkage

'dQ'	inverted abasic deoxyribose
'H1'	Formula I
'H2'	Formula II
'H4'	Formula III
'H9'	Formula VI
'H7'	Formula V
'Hd'	Formula VII
'Hl'	Formula VIII

Table 2
Compound Sequence and Targeting Position on SEQ ID NO: 1

Compound Number	Seq ID NO: 1 Start Site	Seq ID NO: 1 Stop Site	Antisense Sequence (5'-3')	SEQ ID NO:	Sense Sequence (5'-3')	SEQ ID NO:
RD4580	18	40	UCUUCAUCCUCCUCUGAAUGAGC	10	CUCAUUCAGAGGAGGAUGAAGA	272
RD4581	96	118	AGAAAAUCAUCCUGAAAAGACCU	11	GGUCUUUUCAGGAUGAUUUUCU	273
RD4582	350	372	UCUUGGCAGUGUUUCUGUAAACAC	12	UGUUACAGAAACACUGCCAAGA	274
RD4583	351	373	UUCUUGGCAGUGUUUCUGUAACA	13	GUUACAGAAACACUGCCAAGAA	275
RD4584	352	374	ACUCUUGGCAGUGUUUCUGUAAAC	14	UUACAGAAACACUGCCAAGAGU	276
RD4585	353	375	UACUCUUGGCAGUGUUUCUGUAA	15	UACAGAAACACUGCCAAGAGUA	277
RD4586	354	376	UCACUCUUGGCAGUGUUUCUGUA	16	ACAGAAACACUGCCAAGAGUGA	278
RD4587	355	377	UUCACUCUUGGCAGUGUUUCUGU	17	CAGAAACACUGCCAAGAGUGAA	279
RD4588	399	421	UUGAGCAUUGCUUGAAAGAAUAC	18	UAUUCUUUCAAGCAAUGCUCAA	280
RD4589	407	429	UAUUUGGUGUGAGCAUUGCUUGA	19	CAAGCAAUGCUCACACCAAUA	281
RD4590	408	430	UUUUUGGUGUGAGCAUUGCUUG	20	AAGCAAUGCUCACACCAAUA	282
RD4591	417	439	UGCAAGCGCUUAUUUGGUGUGAG	21	UCACACCAAUAAGCGCUUGCA	283
RD4592	418	440	UUGCAAGCGCUUAUUUGGUGUGA	22	CACACCAAUAAGCGCUUGCAA	284
RD4593	419	441	UUUGCAAGCGCUUAUUUGGUGUG	23	ACACCAAUAAGCGCUUGCAA	285

RD4594	420	442	UGUUGCAAGCGCUUAUUUGGUGU	24	CACCAAUAAGCGCUUGCAACA	286
RD4595	421	443	UUGUUGCAAGCGCUUAUUUGGUG	25	ACCAAUAAGCGCUUGCAACAA	287
RD4596	422	444	UUUGUUGCAAGCGCUUAUUUGGU	26	CCAAUAAGCGCUUGCAACAAA	288
RD4597	423	445	UUUUGUUGCAAGCGCUUAUUUGG	27	CAAUAAGCGCUUGCAACAAAA	289
RD4598	424	446	UCUUUGUUGCAAGCGCUUAUUUG	28	AAUAAGCGCUUGCAACAAAGA	290
RD4599	425	447	UUCUUUGUUGCAAGCGCUUAUUU	29	AAUAAGCGCUUGCAACAAAGAA	291
RD4600	426	448	UGUCUUUGUUGCAAGCGCUUAUU	30	AUAAGCGCUUGCAACAAAGACA	292
RD4601	427	449	AUGUCUUUGUUGCAAGCGCUUAU	31	UAAGCGCUUGCAACAAAGACAU	293
RD4602	428	450	AAUGUCUUUGUUGCAAGCGCUUA	32	AAGCGCUUGCAACAAAGACAUU	294
RD4603	429	451	AAAUGUCUUUGUUGCAAGCGCUU	33	AGCGCUUGCAACAAAGACAUUU	295
RD4604	436	458	UCCACAUAAAUGUCUUUGUUGCA	34	GCAACAAAGACAUUUUUGUGGA	296
RD4605	437	459	UCCACAUAAAUGUCUUUGUUGC	35	CAACAAAGACAUUUUUGUGGAA	297
RD4606	441	463	UUAGGUCCACAUAAAUGUCUUUG	36	AAAGACAUUUUUGUGGACCUGAA	298
RD4607	442	464	UCUAGGUCCACAUAAAUGUCUUU	37	AAGACAUUUUUGUGGACCUGAGA	299
RD4608	446	468	UAUGUCUAGGUCCACAUAAAUGU	38	CAUUUAUGUGGACCUGAGACUA	300
RD4609	447	469	UCAUGUCUAGGUCCACAUAAAUG	39	AUUUAUGUGGACCUGAGACAUGA	301
RD4610	448	470	UUCAUGUCUAGGUCCACAUAAAU	40	UUUAUGUGGACCUGAGACAUGAA	302
RD4611	453	475	UGCCCUUCAUGUCUAGGUCCACA	41	GUGGACCUGAGACAUGAAGGGCA	303
RD4612	458	480	UUUUUAUGCCCUUCAUGUCUAGGU	42	CCUAGACAUGAAGGGCAUAAAA	304
RD4613	494	516	UCAUUCUUGAGCACUCUUGGCAA	43	UGCCAAGAGUGCUCAGAAUGA	305
RD4614	505	527	UAUCUUUCUUGGCAUUCUUGAGC	44	CUCAAGAAUGCCAAGAAAGAUA	306
RD4615	507	529	UGCAUCUUUCUUGGCAUUCUUGA	45	CAAGAAUGCCAAGAAAGAUGCA	307

RD4616	510	532	UCGUGCAUCUUUCUUGGCAUUCU	46	GAAUGCCAAGAAAGAUGCACGA	308
RD4617	511	533	UCCGUGCAUCUUUCUUGGCAUUC	47	AAUGCCAAGAAAGAUGCACGGA	309
RD4618	512	534	AUCCGUGCAUCUUUCUUGGCAUU	48	AUGCCAAGAAAGAUGCACGGAU	310
RD4619	513	535	UAUCCGUGCAUCUUUCUUGGCAU	49	UGCCAAGAAAGAUGCACGGAUA	311
RD4620	514	536	UCAUCCGUGCAUCUUUCUUGGCA	50	GCCAAGAAAGAUGCACGGAUGA	312
RD4621	538	560	UACGUGAAAAAGUGGCAGUGGAC	51	UCCACUGCCACUUUUUCACGUA	313
RD4622	583	605	AGACAAAUGUUACGAUGCUCAG	52	UGGAGCAUCGUAACAUUUGUCU	314
RD4623	584	606	UAGACAAAUGUUACGAUGCUGCA	53	GGAGCAUCGUAACAUUUGUCUA	315
RD4624	585	607	UUAGACAAAUGUUACGAUGCUC	54	GAGCAUCGUAACAUUUGUCUAA	316
RD4625	586	608	AGUAGACAAAUGUUACGAUGCUC	55	AGCAUCGUAACAUUUGUCUACU	317
RD4626	587	609	UAGUAGACAAAUGUUACGAUGCU	56	GCAUCGUAACAUUUGUCUACUA	318
RD4627	588	610	UCAGUAGACAAAUGUUACGAUGC	57	CAUCGUAACAUUUGUCUACUGA	319
RD4628	589	611	UUCAGUAGACAAAUGUUACGAUG	58	AUCGUAACAUUUGUCUACUGAA	320
RD4629	590	612	UUUCAGUAGACAAAUGUUACGAU	59	UCGUAACAUUUGUCUACUGAAA	321
RD4630	592	614	UGCUUCAGUAGACAAAUGUUACG	60	GUAACAUUUGUCUACUGAAGCA	322
RD4631	593	615	UUGCUUCAGUAGACAAAUGUUAC	61	UAACAUUUGUCUACUGAAGCAA	323
RD4632	598	620	UGGGUGUGCUUCAGUAGACAAAU	62	UUUGUCUACUGAAGCACACCCA	324
RD4633	599	621	UUGGGUGUGCUUCAGUAGACAAA	63	UUGUCUACUGAAGCACACCCAA	325
RD4634	600	622	UUUGGGUGUGCUUCAGUAGACAA	64	UGUCUACUGAAGCACACCCAAA	326
RD4635	601	623	UUUUGGGUGUGCUUCAGUAGACA	65	GUCUACUGAAGCACACCCAAAA	327
RD4636	667	689	UCACAGGAUUUCAGUGAAAAUCC	66	GAUUUUCACUGAAAUCCUGUGA	328
RD4637	668	690	UGCACAGGAUUUCAGUGAAAAUC	67	AUUUUCACUGAAAUCCUGUGCA	329

RD4638	669	691	UUGCACAGGAUUUCAGUGAAAAU	68	UUUUCACUGAAAUCCUGUGCAA	330
RD4639	670	692	AGUGCACAGGAUUUCAGUGAAAA	69	UUUUCACUGAAAUCCUGUGCACU	331
RD4640	671	693	AAGUGCACAGGAUUUCAGUGAAA	70	UUCACUGAAAUCCUGUGCACUU	332
RD4641	672	694	AAAGUGCACAGGAUUUCAGUGAA	71	UCACUGAAAUCCUGUGCACUUU	333
RD4642	673	695	UAAAGUGCACAGGAUUUCAGUGA	72	CACUGAAAUCCUGUGCACUUUA	334
RD4643	681	703	UCAGAUUAGAAAGUGCACAGGAU	73	UCCUGUGCACUUUCUAAUCUGA	335
RD4644	682	704	UCCAGAUUAGAAAGUGCACAGGA	74	CCUGUGCACUUUCUAAUCUGGA	336
RD4645	683	705	AGCCAGAUUAGAAAGUGCACAGG	75	CUGUGCACUUUCUAAUCUGGCU	337
RD4646	798	820	ACAAGCAACCGGAUGAUGAGUG	76	ACUCAUCAUCCCGGUUGCUUGU	338
RD4647	803	825	AAAAACAAGCAACCGGAUGAU	77	UCAUCCCGGUUGCUUGUUUUUU	339
RD4648	804	826	UAAAAACAAGCAACCGGAUGA	78	CAUCCCGGUUGCUUGUUUUUUUA	340
RD4649	805	827	UUAAAAACAAGCAACCGGAUG	79	AUCCCGGUUGCUUGUUUUUUUAA	341
RD4650	806	828	UGUAAAAACAAGCAACCGGAU	80	UCCCGGUUGCUUGUUUUUUUACA	342
RD4651	807	829	AGGUAAAAACAAGCAACCGGA	81	CCCGGUUGCUUGUUUUUUUACCU	343
RD4652	808	830	AAGGUAAAAACAAGCAACCGG	82	CCGUUGCUUGUUUUUUUACCUU	344
RD4653	809	831	UAAGGUAAAAACAAGCAACCG	83	CGGUUGCUUGUUUUUUUACCUUA	345
RD4654	810	832	AGAAGGUAAAAACAAGCAACCG	84	GGUUGCUUGUUUUUUUACCUUCU	346
RD4655	811	833	AAGAAGGUAAAAACAAGCAACC	85	GUUGCUUGUUUUUUUACCUUCUU	347
RD4656	812	834	AAAGAAGGUAAAAACAAGCAAC	86	UUGCUUGUUUUUUUACCUUCUUU	348
RD4657	815	837	UGAAAAGAAGGUAAAAACAAGC	87	CUUGUUUUUUUACCUUCUUUUA	349
RD4658	816	838	UGGAAAAGAAGGUAAAAACAAG	88	UUGUUUUUUUACCUUCUUUUCCA	350
RD4659	817	839	UGGAAAAGAAGGUAAAAACAA	89	UGUUUUUUUACCUUCUUUUCCCA	351

RD4660	818	840	UUGGGAAAAGAAGGUAAAAACA	90	GUUUUUUACCUUCUUUCCCAA	352
RD4661	819	841	UCUGGGAAAAGAAGGUAAAAAC	91	UUUUUUUACCUUCUUUCCAGA	353
RD4662	825	847	UCCAUUCUGGGAAAAGAAGGUA	92	ACCUUCUUUCCAGGAUGGA	354
RD4663	839	861	UUGAGAUUCUUUGGGCCAUUCCU	93	GGAAUGGCCCAAAGAAUCUCA	355
RD4664	841	863	UUUUGAGAUUCUUUGGGCCAUUC	94	AAUGGCCCAAAGAAUCUCAAAA	356
RD4665	842	864	UCUUUGAGAUUCUUUGGGCCAUU	95	AUGGCCCAAAGAAUCUCAAGA	357
RD4666	844	866	UUUCUUUGAGAUUCUUUGGGCCA	96	GGCCCAAAGAAUCUCAAGAAA	358
RD4667	853	875	AGACAAAGAUUCUUUGAGAUUC	97	AAUCUCAAGAAAUUCUUUGUCU	359
RD4668	855	877	UGAGACAAAGAUUCUUUGAGAU	98	UCUCAAGAAAUUCUUUGUCUCA	360
RD4669	856	878	AGGAGACAAAGAUUCUUUGAGA	99	CUCAAGAAAUUCUUUGUCUCCU	361
RD4670	857	879	AAGGAGACAAAGAUUCUUUGAG	100	UCAAGAAAUUCUUUGUCUCCUU	362
RD4671	858	880	UAAGGAGACAAAGAUUCUUUGA	101	CAAAGAAAUUCUUUGUCUCCUUA	363
RD4672	876	898	AUCCACUCUCAGAUUUUUAAGG	102	CUUAAAACAUCUGAGAGUGGAU	364
RD4673	877	899	AAUCCACUCUCAGAUUUUUAAG	103	UUAAAACAUCUGAGAGUGGAUU	365
RD4674	955	977	AACACUGGGAUGCUGUGCCUGCA	104	GCAGGCACAGCAUCCAGUGUU	366
RD4675	956	978	UAACACUGGGAUGCUGUGCCUGC	105	CAGGCACAGCAUCCAGUGUUA	367
RD4676	957	979	AGAACACUGGGAUGCUGUGCCUG	106	AGGCACAGCAUCCAGUGUUCU	368
RD4677	958	980	UAGAACACUGGGAUGCUGGCCU	107	GGCACAGCAUCCAGUGUUCUA	369
RD4678	959	981	UCAGAACACUGGGAUGCUGGCC	108	GCACAGCAUCCAGUGUUCUGA	370
RD4679	960	982	UGCAGAACACUGGGAUGCUGUGC	109	CACAGCAUCCAGUGUUCUGCA	371
RD4680	964	986	UAAUGGCAGAACACUGGGAUGCU	110	GCAUCCAGUGUUCUGCCAUA	372
RD4681	965	987	AGAAUGGCAGAACACUGGGAUGC	111	CAUCCAGUGUUCUGCCAUAUCU	373

RD4682	966	988	AAGAAUGGCAGAACACUGGGAUG	112	AUCCCAGUGUUCUGCCAUCUUCU	374
RD4683	975	997	UGUAAAAUGAAGAAUGGCAGAAC	113	UUCUGCCAUCUUCUACUUUUUACA	375
RD4684	976	998	UGGUAAAAUGAAGAAUGGCAGAA	114	UCUGCCAUCUUCUACUUUUUACCA	376
RD4685	981	1003	UGUCAUGGUAAAAUGAAGAAUGG	115	CAUUCUUCUACUUUUUACCAUGACA	377
RD4686	982	1004	UUGUCAUGGUAAAAUGAAGAAUG	116	AUUCUUCUACUUUUUACCAUGACAA	378
RD4687	983	1005	AGUGUCAUGGUAAAAUGAAGAAU	117	UUCUUCUACUUUUUACCAUGACACU	379
RD4688	989	1011	UAAAUCAGUGUCAUGGUAAAAUG	118	AUUUUACCAUGACACUGAUUUUA	380
RD4689	990	1012	AGAAAUCAUGUGUCAUGGUAAAAU	119	UUUUACCAUGACACUGAUUUUCU	381
RD4690	991	1013	AAGAAUUCAGUGUCAUGGUAAAA	120	UUUACCAUGACACUGAUUUUCU	382
RD4691	992	1014	UAAGAAUUCAGUGUCAUGGUAAA	121	UUACCAUGACACUGAUUUUCUUA	383
RD4692	1016	1038	AGCAACAAUUAUCCAGUUCUUCUC	122	AGAAGAACUGGAUUAUUGUUGCU	384
RD4693	1017	1039	UAGCAACAAUUAUCCAGUUCUUCU	123	GAAGAACUGGAUUAUUGUUGCUA	385
RD4694	1075	1097	AAAAACUGGCAGCGGACGGCAUU	124	AUGCCGUCCGUGCCAGUUUUU	386
RD4695	1076	1098	AAAAAACUGGCAGCGGACGGCAU	125	UGCCGUCCGUGCCAGUUUUUU	387
RD4696	1077	1099	UAAAAAACUGGCAGCGGACGGCA	126	GCCGUCCGUGCCAGUUUUUUUA	388
RD4697	1078	1100	UUAAAAAACUGGCAGCGGACGGC	127	CCGUCCGUGCCAGUUUUUUUAA	389
RD4698	1079	1101	UGUAAAAAACUGGCAGCGGACGG	128	CGUCCGUGCCAGUUUUUUUACA	390
RD4699	1080	1102	AGGUAAAAAACUGGCAGCGGACG	129	GUCCGUGCCAGUUUUUUUACCU	391
RD4700	1081	1103	UAGGUAAAAAACUGGCAGCGGAC	130	UCCGUGCCAGUUUUUUUACCUA	392
RD4701	1082	1104	AUAGGUAAAAAACUGGCAGCGGA	131	CCGUGCCAGUUUUUUUACCUAU	393
RD4702	1197	1219	AUGUGUAUCCAGAGAUGCCUCCU	132	GGAGGCAUCUCUGGAUACACAU	394
RD4703	1236	1258	UUUUGGUGGUACACUCAUUAUCC	133	GAUAAUGAGUGUACCACCAAAA	395

RD4704	1239	1261	UGAUUUUGGUGGUACACUCAUUA	134	AAUGAGUGUACCACCAAAAUCA	396
RD4705	1240	1262	UUGAUUUUGGUGGUACACUCAUU	135	AUGAGUGUACCACCAAAAUCAA	397
RD4706	1241	1263	UUUGAUUUUGGUGGUACACUCAU	136	UGAGUGUACCACCAAAAUCAAA	398
RD4707	1242	1264	UCUUGAUUUUGGUGGUACACUCA	137	GAGUGUACCACCAAAAUCAAGA	399
RD4708	1243	1265	UGCUUGAUUUUGGUGGUACACUC	138	AGUGUACCACCAAAAUCAAGCA	400
RD4709	1244	1266	UGGCUUGAUUUUGGUGGUACACU	139	GUGUACCACCAAAAUCAAGCCA	401
RD4710	1245	1267	UGGGCUUGAUUUUGGUGGUACAC	140	UGUACCACCAAAAUCAAGCCCA	402
RD4711	1246	1268	UUGGGCUUGAUUUUGGUGGUACA	141	GUACCACCAAAAUCAAGCCCAA	403
RD4712	1247	1269	UCUGGGCUUGAUUUUGGUGGUAC	142	UACCACCAAAAUCAAGCCCAGA	404
RD4713	1248	1270	UCCUGGGCUUGAUUUUGGUGGUA	143	ACCACCAAAAUCAAGCCCAGGA	405
RD4714	1249	1271	AUCCUGGGCUUGAUUUUGGUGGU	144	CCACCAAAAUCAAGCCCAGGAU	406
RD4715	1250	1272	UAUCCUGGGCUUGAUUUUGGUGG	145	CACCAAAAUCAAGCCCAGGAUA	407
RD4716	1251	1273	UGAUCCUGGGCUUGAUUUUGGUG	146	ACCAAAAUCAAGCCCAGGAUCA	408
RD4717	1252	1274	ACGAUCCUGGGCUUGAUUUUGGU	147	CCAAAUCAAGCCCAGGAUCGU	409
RD4718	1253	1275	AACGAUCCUGGGCUUGAUUUUGG	148	CAAAAUCAAGCCCAGGAUCGUU	410
RD4719	1254	1276	UAACGAUCCUGGGCUUGAUUUUG	149	AAAAUCAAGCCCAGGAUCGUUA	411
RD4720	1255	1277	UCAACGAUCCUGGGCUUGAUUUU	150	AAAUCAAGCCCAGGAUCGUUGA	412
RD4721	1256	1278	UCCAACGAUCCUGGGCUUGAUUU	151	AAUCAAGCCCAGGAUCGUUGGA	413
RD4722	1257	1279	UUCCAACGAUCCUGGGCUUGAUU	152	AUCAAGCCCAGGAUCGUUGGAA	414
RD4723	1258	1280	UCUCCAACGAUCCUGGGCUUGAU	153	UCAAGCCCAGGAUCGUUGGAGA	415
RD4724	1259	1281	UCCUCCAACGAUCCUGGGCUUGA	154	CAAGCCCAGGAUCGUUGGAGGA	416
RD4725	1263	1285	UAGUCCUCCAACGAUCCUGGGC	155	CCCAGGAUCGUUGGAGGAACUA	417

RD4726	1264	1286	UCAGUUCCUCCAACGAUCCUGGG	156	CCAGGAUCGUUGGAGGAACUGA	418
RD4727	1330	1352	AGGUGUCUCUGAGUGGGUGAGGU	157	CCUCACCCACUCAGAGACACCU	419
RD4728	1331	1353	UAGGUGUCUCUGAGUGGGUGAGG	158	CUCACCCACUCAGAGACACCUA	420
RD4729	1332	1354	ACAGGUGUCUCUGAGUGGGUGAG	159	UCACCCACUCAGAGACACCUGU	421
RD4730	1354	1376	UUUCCAAUGAUGGAGCCUCCACA	160	GUGGAGGCUCCAUCAUUGGAAA	422
RD4731	1355	1377	UUUCCAAUGAUGGAGCCUCCAC	161	UGGAGGCUCCAUCAUUGGAAAA	423
RD4732	1363	1385	AUCCACUGGUUUCCAAUGAUGGA	162	CCAUCAUUGGAAACCAGUGGAU	424
RD4733	1365	1387	AUAUCCACUGGUUUCCAAUGAUG	163	AUCAUUGGAAACCAGUGGAUUAU	425
RD4734	1367	1389	UAAUAUCCACUGGUUUCCAAUGA	164	CAUUGGAAACCAGUGGAUUAUA	426
RD4735	1393	1415	ACCCCAUAGAAACAGUGAGCGGC	165	CCGCUCACUGUUUCUAUGGGGU	427
RD4736	1394	1416	UACCCCAUAGAAACAGUGAGCGG	166	CGCUCACUGUUUCUAUGGGGUUA	428
RD4737	1395	1417	UUACCCCAUAGAAACAGUGAGCG	167	GCUCACUGUUUCUAUGGGGUAA	429
RD4738	1396	1418	UCUACCCCAUAGAAACAGUGAGC	168	CUCACUGUUUCUAUGGGGUAGA	430
RD4739	1397	1419	UUCUACCCCAUAGAAACAGUGAG	169	UCACUGUUUCUAUGGGGUAGAA	431
RD4740	1398	1420	ACUCUACCCCAUAGAAACAGUGA	170	CACUGUUUCUAUGGGGUAGAGU	432
RD4741	1399	1421	UACUCUACCCCAUAGAAACAGUG	171	ACUGUUUCUAUGGGGUAGAGUA	433
RD4742	1400	1422	UGACUCUACCCCAUAGAAACAGU	172	CUGUUUCUAUGGGGUAGAGUCA	434
RD4743	1401	1423	UUGACUCUACCCCAUAGAAACAG	173	UGUUUCUAUGGGGUAGAGUCAA	435
RD4744	1402	1424	UGUGACUCUACCCCAUAGAAACA	174	GUUUCUAUGGGGUAGAGUCACA	436
RD4745	1403	1425	AGGUGACUCUACCCCAUAGAAAC	175	UUUCUAUGGGGUAGAGUCACCU	437
RD4746	1404	1426	UAGGUGACUCUACCCCAUAGAAA	176	UUCUAUGGGGUAGAGUCACCUA	438
RD4747	1405	1427	UUAGGUGACUCUACCCCAUAGAA	177	UCUAUGGGGUAGAGUCACCUAA	439

RD4748	1406	1428	UUUAGGUGACUCUACCCCAUAGA	178	CUAUGGGGUAGAGUCACCUAAA	440
RD4749	1407	1429	UCUUAGGUGACUCUACCCCAUAG	179	UAUGGGGUAGAGUCACCUAAGA	441
RD4750	1408	1430	AUCUUAGGUGACUCUACCCCAUA	180	AUGGGGUAGAGUCACCUAAGAU	442
RD4751	1409	1431	AAUCUUAGGUGACUCUACCCCAU	181	UGGGGUAGAGUCACCUAAGAUU	443
RD4752	1411	1433	AAAAUCUUAGGUGACUCUACCCC	182	GGGUAGAGUCACCUAAGAUUUU	444
RD4753	1412	1434	UAAAAUCUUAGGUGACUCUACCC	183	GGUAGAGUCACCUAAGAUUUUA	445
RD4754	1413	1435	UCAAAAUCUUAGGUGACUCUACC	184	GUAGAGUCACCUAAGAUUUUGA	446
RD4755	1414	1436	UGCAAAAUCUUAGGUGACUCUAC	185	UAGAGUCACCUAAGAUUUUGCA	447
RD4756	1419	1441	AGACACGCAAAAUUUAGGUGAC	186	UCACCUAAGAUUUUGCGUGUCU	448
RD4757	1480	1502	UCUUGAACCCCAAAGAAAGAUGU	187	CAUCUUUCUUUGGGGUUCAAGA	449
RD4758	1481	1503	UUCUUGAACCCCAAAGAAAGAUG	188	AUCUUUCUUUGGGGUUCAAGAA	450
RD4759	1482	1504	UUUCUUGAACCCCAAAGAAAGAU	189	UCUUUCUUUGGGGUUCAAGAAA	451
RD4760	1483	1505	AUUUCUUGAACCCCAAAGAAAGA	190	CUUUCUUUGGGGUUCAAGAAAU	452
RD4761	1484	1506	UAUUUCUUGAACCCCAAAGAAAG	191	UUUCUUUGGGGUUCAAGAAUA	453
RD4762	1485	1507	UUAUUUCUUGAACCCCAAAGAAA	192	UUCUUUGGGGUUCAAGAAUA	454
RD4763	1486	1508	AUUUUUCUUGAACCCCAAAGAA	193	UCUUUGGGGUUCAAGAAUAU	455
RD4764	1488	1510	UUAUUUUUCUUGAACCCCAAAG	194	UUUGGGGUUCAAGAAUAUA	456
RD4765	1491	1513	UGAUUUAUUUUUCUUGAACCCCA	195	GGGGUUCAAGAAUAUAUAUCA	457
RD4766	1492	1514	UGGAUUUAUUUUUCUUGAACCCC	196	GGGUUCAAGAAUAUAUAUCCA	458
RD4767	1493	1515	AUGGAUUUAUUUUUCUUGAACCC	197	GGUUCAAGAAUAUAUAUCCA	459
RD4768	1542	1564	UUUUCAACAAGGCAUAUCAUAC	198	UAUGAUUUGCCUUGUUGAAAA	460
RD4769	1544	1566	UAGUUUCAACAAGGCAUAUCAU	199	UGAUUUGCCUUGUUGAAACUA	461

RD4770	1545	1567	UCAGUUUCAACAAGGCAAUUCA	200	GAUUAUUGCCUUGUUGAAACUGA	462
RD4771	1546	1568	UCCAGUUUCAACAAGGCAUAUC	201	AUAUUGCCUUGUUGAAACUGGA	463
RD4772	1547	1569	UUCCAGUUUCAACAAGGCAUAU	202	UAUUGCCUUGUUGAAACUGGAA	464
RD4773	1548	1570	UUUCCAGUUUCAACAAGGCAUA	203	AUUGCCUUGUUGAAACUGGAAA	465
RD4774	1550	1572	UGUUUCCAGUUUCAACAAGGCAA	204	UGCCUUGUUGAAACUGGAAACA	466
RD4775	1551	1573	UGGUUUCAGUUUCAACAAGGCA	205	GCCUUGUUGAAACUGGAAACCA	467
RD4776	1555	1577	ACUGUGGUUCCAGUUUCAACAA	206	UGUUGAAACUGGAAACCACAGU	468
RD4777	1556	1578	UACUGUGGUUCCAGUUUCAACA	207	GUUGAAACUGGAAACCACAGUA	469
RD4778	1557	1579	UCACUGUGGUUCCAGUUUCAAC	208	UUGAAACUGGAAACCACAGUGA	470
RD4779	1558	1580	UUCACUGUGGUUCCAGUUUCAA	209	UGAAACUGGAAACCACAGUGAA	471
RD4780	1560	1582	AAUUCACUGUGGUUCCAGUUUC	210	AAACUGGAAACCACAGUGAAUU	472
RD4781	1561	1583	UAAUUCACUGUGGUUCCAGUUU	211	AACUGGAAACCACAGUGAAUUA	473
RD4782	1562	1584	UUAUUCACUGUGGUUCCAGUU	212	ACUGGAAACCACAGUGAAUUAA	474
RD4783	1566	1588	UUGUGUAAUUCACUGUGGUUCC	213	GAAACCACAGUGAAUUACACAA	475
RD4784	1567	1589	UCUGUGUAAUUCACUGUGGUUUC	214	AAACCACAGUGAAUUACACAGA	476
RD4785	1568	1590	AUCUGUGUAAUUCACUGUGGUUU	215	AACCACAGUGAAUUACACAGAU	477
RD4786	1581	1603	UGGGUCGUUGAGAAUCUGUGUAA	216	UACACAGAUUCUACACGACCCA	478
RD4787	1582	1604	AUGGGUCGUUGAGAAUCUGUGUA	217	ACACAGAUUCUACACGACCCA	479
RD4788	1583	1605	UAUGGGUCGUUGAGAAUCUGUGU	218	CACAGAUUCUACACGACCCAUA	480
RD4789	1584	1606	AUAUGGGUCGUUGAGAAUCUGUG	219	ACAGAUUCUACACGACCCAUAU	481
RD4790	1585	1607	UAUAUGGGUCGUUGAGAAUCUGU	220	CAGAUUCUACACGACCCAUAUA	482
RD4791	1586	1608	UCAUAUGGGUCGUUGAGAAUCUG	221	AGAUUCUACACGACCCAUAUGA	483

RD4792	1587	1609	UGCAUAUGGGUCGUUGAGAAUCU	222	GAUUCUCAACGACCCAUUAUGCA	484
RD4793	1588	1610	AGGCAUAUGGGUCGUUGAGAAUC	223	AUUCUCAACGACCCAUUAUGCCU	485
RD4794	1589	1611	UAGGCAUAUGGGUCGUUGAGAAU	224	UUCUCAACGACCCAUUAUGCCUA	486
RD4795	1590	1612	UCAGGCAUAUGGGUCGUUGAGAA	225	UCUCAACGACCCAUUAUGCCUGA	487
RD4796	1591	1613	UGCAGGCAUAUGGGUCGUUGAGA	226	CUCAACGACCCAUUAUGCCUGCA	488
RD4797	1592	1614	AGGCAGGCAUAUGGGUCGUUGAG	227	UCAACGACCCAUUAUGCCUGCCU	489
RD4798	1593	1615	AAGGCAGGCAUAUGGGUCGUUGA	228	CAACGACCCAUUAUGCCUGCCUU	490
RD4799	1594	1616	UAAGGCAGGCAUAUGGGUCGUUG	229	AACGACCCAUUAUGCCUGCCUUA	491
RD4800	1653	1675	UUCUGUACCCCCAUCCAGUCACC	230	GUGACUGGAUGGGGGUACAGAA	492
RD4801	1654	1676	UUUCUGUACCCCCAUCCAGUCAC	231	UGACUGGAUGGGGGUACAGAAA	493
RD4802	1655	1677	UUUUCUGUACCCCCAUCCAGUCA	232	GACUGGAUGGGGGUACAGAAAA	494
RD4803	1696	1718	AUCUUGGCUUUCUGGAGAGUAUU	233	AUACUCCAGAAAGCCAAGAU	495
RD4804	1697	1719	UAUCUUGGCUUUCUGGAGAGUAU	234	UACUCUCCAGAAAGCCAAGUA	496
RD4805	1698	1720	UUAUCUUGGCUUUCUGGAGAGUA	235	ACUCUCCAGAAAGCCAAGAUAA	497
RD4806	1699	1721	UGUAUCUUGGCUUUCUGGAGAGU	236	CUCUCCAGAAAGCCAAGAUACA	498
RD4807	1700	1722	UGGUAUCUUGGCUUUCUGGAGAG	237	UCUCCAGAAAGCCAAGAUACCA	499
RD4808	1701	1723	AGGGUAUCUUGGCUUUCUGGAGA	238	CUCCAGAAAGCCAAGAUACCCU	500
RD4809	1702	1724	AAGGGUAUCUUGGCUUUCUGGAG	239	UCCAGAAAGCCAAGAUACCCUU	501
RD4810	1703	1725	UAAGGGUAUCUUGGCUUUCUGGA	240	CCAGAAAGCCAAGAUACCCUUA	502
RD4811	1704	1726	UUAAGGGUAUCUUGGCUUUCUGG	241	CAGAAAGCCAAGAUACCCUUA	503
RD4812	1706	1728	UACUAAGGGUAUCUUGGCUUUCU	242	GAAAGCCAAGAUACCCUAGUA	504
RD4813	1707	1729	UCACUAAGGGUAUCUUGGCUUUC	243	AAAGCCAAGAUACCCUAGUGA	505

RD4814	1708	1730	UUCACUAAGGGUAUCUUGGCUUU	244	AAGCCAAGAUACCCUAGUGAA	506
RD4815	1709	1731	UGUCACUAAGGGUAUCUUGGCUU	245	AGCCAAGAUACCCUAGUGACA	507
RD4816	1710	1732	UGGUCACUAAGGGUAUCUUGGCU	246	GCCAAGAUACCCUAGUGACCA	508
RD4817	1711	1733	UUGGUCACUAAGGGUAUCUUGGC	247	CCAAGAUACCCUAGUGACCAA	509
RD4818	1749	1771	UUAUUUUUAUGUCCUCUGUAUCUC	248	AGAUACAGAGGACAUAAAAUAA	510
RD4819	1751	1773	UGUUAUUUUUAUGUCCUCUGUAUC	249	AUACAGAGGACAUAAAAUAACA	511
RD4820	1759	1781	AUCUUAUGGGUUAUUUUAUGUCC	250	GACAUAAAAUAACCCUAAGAU	512
RD4821	1766	1788	ACAGAUCAUCUUAUGGGUUAUUU	251	AAUAACCCUAAGAUGAUCUGU	513
RD4822	1767	1789	UACAGAUCAUCUUAUGGGUUAUU	252	AUAACCCUAAGAUGAUCUGUA	514
RD4823	1768	1790	UCACAGAUCAUCUUAUGGGUUAU	253	UAACCCUAAGAUGAUCUGUGA	515
RD4824	1769	1791	UGCACAGAUCAUCUUAUGGGUUA	254	AACCCUAAGAUGAUCUGUGCA	516
RD4825	1770	1792	UGGCACAGAUCAUCUUAUGGGUU	255	ACCCUAAGAUGAUCUGUGCCA	517
RD4826	1771	1793	UCGGCACAGAUCAUCUUAUGGGU	256	CCCAUAAGAUGAUCUGUGCCGA	518
RD4827	1772	1794	UCCGGCACAGAUCAUCUUAUGGG	257	CCAUAAGAUGAUCUGUGCCGGA	519
RD4828	1773	1795	AGCCGGCACAGAUCAUCUUAUGG	258	CAUAAGAUGAUCUGUGCCGGCU	520
RD4829	1774	1796	UAGCCGGCACAGAUCAUCUUAUG	259	AUAAGAUGAUCUGUGCCGGCUA	521
RD4830	1775	1797	UUAGCCGGCACAGAUCAUCUUAU	260	UAAGAUGAUCUGUGCCGGCUAA	522
RD4831	1776	1798	UGUAGCCGGCACAGAUCAUCUUA	261	AAGAUGAUCUGUGCCGGCUACA	523
RD4832	1777	1799	UUGUAGCCGGCACAGAUCAUCUU	262	AGAUGAUCUGUGCCGGCUACAA	524
RD4833	1778	1800	UCUGUAGCCGGCACAGAUCAUCU	263	GAUGAUCUGUGCCGGCUACAGA	525
RD4834	1779	1801	UCCUGUAGCCGGCACAGAUCAUC	264	AUGAUCUGUGCCGGCUACAGGA	526
RD4835	1780	1802	UCCCUGUAGCCGGCACAGAUCAU	265	UGAUCUGUGCCGGCUACAGGGA	527

RD4836	1781	1803	UUCCCUGUAGCCGGCACAGAUCA	266	GAUCUGUGCCGGCUACAGGGAA	528
RD4837	1782	1804	UUUCCCUGUAGCCGGCACAGAU	267	AUCUGUGCCGGCUACAGGGAAA	529
RD4838	1783	1805	UCUCCCUGUAGCCGGCACAGAU	268	UCUGUGCCGGCUACAGGGAAGA	530
RD4839	1816	1838	UCUCCCGAAUCUCCCUUGCAAGC	269	CUUGCAAGGGAGAUUCGGGAGA	531
RD4840	1817	1839	UCCUCCCGAAUCUCCCUUGCAAG	270	UUGCAAGGGAGAUUCGGGAGGA	532
RD4841	1818	1840	UGCCUCCCGAAUCUCCCUUGCAA	271	UGCAAGGGAGAUUCGGGAGGCA	533
RD5030	515	534	UAUCCGUGCAUCUUUCUUGGCGU	1058	CGCCAAGAAAGAUGCACGGAUA	1072
RD5031	592	611	UUUCAGUAGACAAUGUUACGGU	1059	CCGUAACAUUUGUCUACUGAAA	1073
RD5032	1416	1435	UGCAAAAUUUUAGGUGACUCUGC	1060	CAGAGUCACCUAAGAUUUUGCA	1074
RD5033	1699	1719	UAUCUUGGCUUUCUGGAGAGUGU	1061	CACUCUCCAGAAAGCCAAGUA	1075
RD5034	1767	1788	UACAGAUCAUCUUAUGGGUUGUU	1062	ACAACCAUAAGAUGAUCUGUA	1076
RD5059	496	515	UCAUUCUUGAGCAUUCUUGGCGA	1063	CGCCAAGAAUGCUCAGAAUGA	1077
RD5060	859	879	AAGGAGACAAAGAUUUUCUUGGG	1064	CCAAAGAAAUUUUGUCUCCUU	1078
RD5061	977	996	UGUAAAAUGAAGAAUGGCAGAGC	1065	CUCUGCCAUUCUUAUUUUACA	1079
RD5072	981	1003	UGUCAUGGUAAAAUGAAGAGUGG	1066	CACUCUUAUUUUACCAUGACA	1080
RD5094	960	980	UAGAACACUGGGAUGCUGUGC	1067	UGCACAGCAUCCAGUGUUCUA	1081
RD5095	1702	1724	AAGGGUAUCUUGGUUUUCUGGAG	1068	UCCAGAAAACCAAGAUACCCUU	1082
RD5096	584	606	UAGACAAUGUUAUGAUGCUGCA	1069	GGAGCAUCAUAACAUUUGUCUA	1083
RD5097	856	878	AGGAGACAAAGAUUUUCUUGGGA	1070	CCCAAAGAAAUUUUGUCUCCU	1084
RD5098	994	1013	UAAGAAAUCAUGUGUAUGGUAGA	1071	CUACCAUGACACUGAUUUUCUUA	1085
RD5321	591	612	UUUCAGUAGACAAUGUUACGG	1121	UCCGUAACAUUUGUCUACUGAAA	1126
RD5383	992	1014	UAAGAAAUCAUGUGUAUGGUGGA	1122	CCACCAUGACACUGAUUUUCUUA	1127

RD5384	592	614	UGCUUCAGUAGACAAUGUUGCG	1123	GCAACAUUUGUCUACUGAAGCA	1128
RD5398	514	535	UAUCCGUGCAUCUUUCUUGGCG	1124	UCGCCAAGAAAGAUGCACGGAUA	1129

Table 3
Compound Chemistry

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Compound Number	Antisense Strand (5'-3')	Anti-sense Ref ID No:	SEQ ID NO:	Sense Strand (5'-3')	Sense Ref ID NO:	SEQ ID NO:
RD4580	mU*fc*mU.fU.mC.fA.mU.fC.mC.fU.mC.fC.mU.fC.mU.fG.mA.fA.mU.fG.mA*mG*mC	IA1341	534	H9*mU*mC.mA.mU.mU.mC.fA.mG.fA.fG.fG.fA.mG.mG.mA.mU.mG.mA.mA.mG*mA*dQ	IS1732	796
RD4581	mA*fg*mA.fA.mA.fA.mU.fC.mA.fU.mC.fC.mU.fG.mA.fA.mA.fA.mG.fA.mC*mC*mU	IA1342	535	HI*mG*mU.mC.mU.mU.mU.fU.mC.fA.fG.fG.fA.mU.mG.mA.mU.mU.mU.mU.mC*mU*dQ	IS1733	797
RD4582	mU*fc*mU.fU.mG.fG.mC.fA.mG.fU.mG.fU.mU.fU.mC.fU.mG.fU.mA.fA.mC*mA*mC	IA1343	536	H4*mG*mU.mU.mA.mC.mA.fG.mA.fA.fA.fC.fA.mC.mU.mG.mC.mC.mA.mA.mG*mA*dQ	IS1734	798
RD4583	mU*fU*mC.fU.mU.fG.mG.fC.mA.fG.mU.fG.mU.fU.mU.fC.mU.fG.mU.fA.mA*mC*mA	IA1344	537	HI*mU*mU.mA.mC.mA.mG.fA.mA.fA.fC.fA.fC.mU.mG.mC.mC.mA.mA.mG.mA*mA*dQ	IS1735	799
RD4584	mA*fc*mU.fC.mU.fU.mG.fG.mC.fA.mG.fU.mG.fU.mU.fU.mC.fU.mG.fU.mA*mA*mC	IA1345	538	H4*mU*mA.mC.mA.mG.mA.fA.mA.fC.fA.fC.fU.mG.mC.mC.mA.mA.mG.mA.mG*mU*dQ	IS1736	800
RD4585	mU*fA*mC.fU.mC.fU.mU.fG.mG.fC.mA.fG.mU.fG.mU.fU.mU.fC.mU.fG.mU*mA*mA	IA1346	539	H4*mA*mC.mA.mG.mA.mA.fA.mC.fA.fC.fU.fG.mC.mC.mA.mA.mG.mA.mG.mU*mA*dQ	IS1737	801
RD4586	mU*fc*mA.fC.mU.fC.mU.fU.mG.fG.mC.fA.mG.fU.mG.fU.mU.fU.mC.fU.mG*mU*mA	IA1347	540	Hd*mC*mA.mG.mA.mA.mA.fC.mA.fC.fU.fG.fC.mC.mA.mA.mG.mA.mG.mU.mG*mA*dQ	IS1738	802
RD4587	mU*fU*mC.fA.mC.fU.mC.fU.mU.fG.mG.fC.mA.fG.mU.fG.mU.fU.mU.fC.mU*mG*mU	IA1348	541	H9*mA*mG.mA.mA.mA.mC.fA.mC.fU.fG.fC.fC.mA.mA.mG.mA.mG.mU.mG.mA*mA*dQ	IS1739	803
RD4588	mU*fU*mG.fA.mG.fC.mA.fU.mU.fG.mC.fU.mU.fG.mA.fA.mA.fG.mA.fA.mU*mA*mC	IA1349	542	H4*mA*mU.mU.mC.mU.mU.fU.mC.fA.fA.fG.fC.mA.mA.mU.mG.mC.mU.mC.mA*mA*dQ	IS1740	804
RD4589	mU*fA*mU.fU.mU.fG.mG.fU.mG.fU.mG.fA.mG.fC.mA.fU.mU.fG.mC.fU.mU*mG*mA	IA1350	543	H9*mA*mA.mG.mC.mA.mA.fU.mG.fC.fU.fC.fA.mC.mA.mC.mC.mA.mA.mA.mU*mA*dQ	IS1741	805

RD4590	mU*fU*mA.fU.mU.fU.mG.fG. mU.fG.mU.fG.mA.fG.mC.fA.m U.fU.mG.fC.mU*mU*mG	IA1351	544	Hd*mA*mG.mC.mA.mA.mU.fG. mC.fU.fC.fA.fC.mA.mC.mA.m A.mA.mU.mA*mA*dQ	IS1742	806
RD4591	mU*fG*mC.fA.mA.fG.mC.fG.m C.fU.mU.fA.mU.fU.mU.fG.mG.f U.mG.fU.mG*mA*mG	IA1352	545	H4*mC*mA.mC.mA.mC.mC.fA.m A.fA.fU.fA.fA.mG.mC.mG.mC.mU .mU.mG.mC*mA*dQ	IS1743	807
RD4592	mU*fU*mG.fC.mA.fA.mG.fC.m G.fC.mU.fU.mA.fU.mU.fU.mG.f G.mU.fG.mU*mG*mA	IA1353	546	H9*mA*mC.mA.mC.mC.mA.fA.m A.fU.fA.fA.fG.mC.mG.mC.mU.mU .mG.mC.mA*mA*dQ	IS1744	808
RD4593	mU*fU*mU.fG.mC.fA.mA.fG.m C.fG.mC.fU.mU.fA.mU.fU.mU.f G.mG.fU.mG*mU*mG	IA1354	547	Hd*mC*mA.mC.mC.mA.mA.fA.m U.fA.fA.fG.fC.mG.mC.mU.mU.mG .mC.mA.mA*mA*dQ	IS1745	809
RD4594	mU*fG*mU.fU.mG.fC.mA.fA.m G.fC.mG.fC.mU.fU.mA.fU.mU.f U.mG.fG.mU*mG*mU	IA1355	548	H9*mA*mC.mC.mA.mA.mA.fU. mA.fA.fG.fC.fG.mC.mU.mU.mG. mC.mA.mA.mC*mA*dQ	IS1746	810
RD4595	mU*fU*mG.fU.mU.fG.mC.fA.m A.fG.mC.fG.mC.fU.mU.fA.mU.f U.mU.fG.mG*mU*mG	IA1356	549	Hd*mC*mC.mA.mA.mA.mU.fA. mA.fG.fC.fG.fC.mU.mU.mG.mC. mA.mA.mC.mA*mA*dQ	IS1747	811
RD4596	mU*fU*mU.fG.mU.fU.mG.fC. mA.fA.mG.fC.mG.fC.mU.fU.mA .fU.mU.fU.mG*mG*mU	IA1357	550	H9*mC*mA.mA.mA.mU.mA.fA. mG.fC.fG.fC.fU.mU.mG.mC.mA. mA.mC.mA.mA*mA*dQ	IS1748	812
RD4597	mU*fU*mU.fU.mG.fU.mU.fG. mC.fA.mA.fG.mC.fG.mC.fU.mU .fA.mU.fU.mU*mG*mG	IA1358	551	H9*mA*mA.mA.mU.mA.mA.fG. mC.fG.fC.fU.fU.mG.mC.mA.mA. mC.mA.mA.mA*mA*dQ	IS1749	813
RD4598	mU*fC*mU.fU.mU.fG.mU.fU. mG.fC.mA.fA.mG.fC.mG.fC.mU .fU.mA.fU.mU*mU*mG	IA1359	552	Hd*mA*mA.mU.mA.mA.mG.fC. mG.fC.fU.fU.fG.mC.mA.mA.mC. mA.mA.mA.mG*mA*dQ	IS1750	814
RD4599	mU*fU*mC.fU.mU.fU.mG.fU. mU.fG.mC.fA.mA.fG.mC.fG.mC .fU.mU.fA.mU*mU*mU	IA1360	553	Hd*mA*mU.mA.mA.mG.mC.fG. mC.fU.fU.fG.fC.mA.mA.mC.mA.m A.mA.mG.mA*mA*dQ	IS1751	815
RD4600	mU*fG*mU.fC.mU.fU.mU.fG. mU.fU.mG.fC.mA.fA.mG.fC.mG .fC.mU.fU.mA*mU*mU	IA1361	554	Hd*mU*mA.mA.mG.mC.mG.fC. mU.fU.fG.fC.fA.mA.mC.mA.mA. mA.mG.mA.mC*mA*dQ	IS1752	816
RD4601	mA*fU*mG.fU.mC.fU.mU.fU.m G.fU.mU.fG.mC.fA.mA.fG.mC.f G.mC.fU.mU*mA*mU	IA1362	555	H4*mA*mA.mG.mC.mG.mC.fU. mU.fG.fC.fA.fA.mC.mA.mA.mA.m G.mA.mC.mA*mU*dQ	IS1753	817
RD4602	mA*fA*mU.fG.mU.fC.mU.fU.m U.fG.mU.fU.mG.fC.mA.fA.mG.f C.mG.fC.mU*mU*mA	IA1363	556	Hd*mA*mG.mC.mG.mC.mU.fU. mG.fC.fA.fA.fC.mA.mA.mA.mG.m A.mC.mA.mU*mU*dQ	IS1754	818
RD4603	mA*fA*mA.fU.mG.fU.mC.fU.m U.fU.mG.fU.mU.fG.mC.fA.mA.f G.mC.fG.mC*mU*mU	IA1364	557	Hd*mG*mC.mG.mC.mU.mU.fG. mC.fA.fA.fC.fA.mA.mA.mG.mA.m C.mA.mU.mU*mU*dQ	IS1755	819
RD4604	mU*fC*mC.fA.mC.fA.mU.fA.m A.fA.mU.fG.mU.fC.mU.fU.mU.f G.mU.fU.mG*mC*mA	IA1365	558	HI*mC*mA.mA.mC.mA.mA.fA.m G.fA.fC.fA.fU.mU.mU.mA.mU.m G.mU.mG.mG*mA*dQ	IS1756	820

RD4605	mU*fU*mC.fC.mA.fC.mA.fU.m A.fA.mA.fU.mG.fU.mC.fU.mU.f U.mG.fU.mU*mG*mC	IA1366	559	H9*mA*mA.mC.mA.mA.mA.fG. mA.fC.fA.fU.fU.mU.mA.mU.mG. mU.mG.mG.mA*mA*dQ	IS1757	821
RD4606	mU*fU*mA.fG.mG.fU.mC.fC.m A.fC.mA.fU.mA.fA.mA.fU.mG.f U.mC.fU.mU*mU*mG	IA1367	560	Hd*mA*mA.mG.mA.mC.mA.fU. mU.fU.fA.fU.fG.mU.mG.mG.mA. mC.mC.mU.mA*mA*dQ	IS1758	822
RD4607	mU*fc*mU.fA.mG.fG.mU.fC.m C.fA.mC.fA.mU.fA.mA.fA.mU.f G.mU.fC.mU*mU*mU	IA1368	561	Hd*mA*mG.mA.mC.mA.mU.fU. mU.fA.fU.fG.fU.mG.mG.mA.mC. mC.mU.mA.mG*mA*dQ	IS1759	823
RD4608	mU*fA*mU.fG.mU.fC.mU.fA.m G.fG.mU.fC.mC.fA.mC.fA.mU.f A.mA.fA.mU*mG*mU	IA1369	562	H9*mA*mU.mU.mU.mA.mU.fG. mU.fG.fG.fA.fC.mC.mU.mA.mG. mA.mC.mA.mU*mA*dQ	IS1760	824
RD4609	mU*fc*mA.fU.mG.fU.mC.fU.m A.fG.mG.fU.mC.fC.mA.fC.mA.f U.mA.fA.mA*mU*mG	IA1370	563	Hd*mU*mU.mU.mA.mU.mG.fU. mG.fG.fA.fC.fC.mU.mA.mG.mA. mC.mA.mU.mG*mA*dQ	IS1761	825
RD4610	mU*fU*mC.fA.mU.fG.mU.fC.m U.fA.mG.fG.mU.fC.mC.fA.mC.f A.mU.fA.mA*mA*mU	IA1371	564	H4*mU*mU.mA.mU.mG.mU.fG. mG.fA.fC.fC.fU.mA.mG.mA.mC.m A.mU.mG.mA*mA*dQ	IS1762	826
RD4611	mU*fG*mC.fC.mC.fU.mU.fC.m A.fU.mG.fU.mC.fU.mA.fG.mG.f U.mC.fC.mA*mC*mA	IA1372	565	HI*mU*mG.mG.mA.mC.mC.fU.m A.fG.fA.fC.fA.mU.mG.mA.mA.mG .mG.mG.mC*mA*dQ	IS1763	827
RD4612	mU*fU*mU.fU.mA.fU.mG.fC.m C.fC.mU.fU.mC.fA.mU.fG.mU.f C.mU.fA.mG*mG*mU	IA1373	566	H9*mC*mU.mA.mG.mA.mC.fA. mU.fG.fA.fA.fG.mG.mG.mC.mA. mU.mA.mA.mA*mA*dQ	IS1764	828
RD4613	mU*fc*mA.fU.mU.fC.mU.fU.m G.fA.mG.fC.mA.fC.mU.fC.mU.f U.mG.fG.mC*mA*mA	IA1374	567	H4*mG*mC.mC.mA.mA.mG.fA. mG.fU.fG.fC.fU.mC.mA.mA.mG. mA.mA.mU.mG*mA*dQ	IS1765	829
RD4614	mU*fA*mU.fC.mU.fU.mU.fC.m U.fU.mG.fG.mC.fA.mU.fU.mC.f U.mU.fG.mA*mG*mC	IA1375	568	H9*mU*mC.mA.mA.mG.mA.fA. mU.fG.fC.fC.fA.mA.mG.mA.mA. mA.mG.mA.mU*mA*dQ	IS1766	830
RD4615	mU*fG*mC.fA.mU.fC.mU.fU.m U.fC.mU.fU.mG.fG.mC.fA.mU.f U.mC.fU.mU*mG*mA	IA1376	569	H9*mA*mA.mG.mA.mA.mU.fG. mC.fC.fA.fA.fG.mA.mA.mA.mG.m A.mU.mG.mC*mA*dQ	IS1767	831
RD4616	mU*fc*mG.fU.mG.fC.mA.fU.m C.fU.mU.fU.mC.fU.mU.fG.mG.f C.mA.fU.mU*mC*mU	IA1377	570	HI*mA*mA.mU.mG.mC.mC.fA.m A.fG.fA.fA.fA.mG.mA.mU.mG.mC .mA.mC.mG*mA*dQ	IS1768	832
RD4617	mU*fc*mC.fG.mU.fG.mC.fA.m U.fC.mU.fU.mU.fC.mU.fU.mG.f G.mC.fA.mU*mU*mC	IA1378	571	Hd*mA*mU.mG.mC.mC.mA.fA. mG.fA.fA.fA.fG.mA.mU.mG.mC. mA.mC.mG.mG*mA*dQ	IS1769	833
RD4618	mA*fU*mC.fC.mG.fU.mG.fC.m A.fU.mC.fU.mU.fU.mC.fU.mU.f G.mG.fC.mA*mU*mU	IA1379	572	Hd*mU*mG.mC.mC.mA.mA.fG. mA.fA.fA.fG.fA.mU.mG.mC.mA. mC.mG.mG.mA*mU*dQ	IS1770	834
RD4619	mU*fA*mU.fC.mC.fG.mU.fG.m C.fA.mU.fC.mU.fU.mU.fC.mU.f U.mG.fG.mC*mA*mU	IA1380	573	H4*mG*mC.mC.mA.mA.mG.fA. mA.fA.fG.fA.fU.mG.mC.mA.mC. mG.mG.mA.mU*mA*dQ	IS1771	835

RD4620	mU*FC*mA.fU.mC.fC.mG.fU.m G.fC.mA.fU.mC.fU.mU.fU.mC.f U.mU.fG.mG*mC*mA	IA1381	574	HI*mc*mc.mA.mA.mG.mA.fA.m A.fG.fA.fU.fG.mC.mA.mC.mG.mG .mA.mU.mG*mA*dQ	IS1772	836
RD4621	mU*FA*mc.fG.mU.fG.mA.fA.m A.fA.mA.fG.mU.fG.mG.fC.mA.f G.mU.fG.mG*mA*mc	IA1382	575	H4*mc*mc.mA.mC.mU.mG.fC.m C.fA.fC.fU.fU.mU.mU.mC.mA .mC.mG.mU*mA*dQ	IS1773	837
RD4622	mA*FG*mA.fC.mA.fA.mA.fU.m G.fU.mU.fA.mC.fG.mA.fU.mG.f C.mU.fC.mC*mA*mG	IA1383	576	H4*mg*mg.mA.mG.mC.mA.fU. mC.fG.fU.fA.fA.mC.mA.mU.mU. mU.mG.mU.mC*mU*dQ	IS1774	838
RD4623	mU*FA*mg.fA.mC.fA.mA.fA.m U.fG.mU.fU.mA.fC.mG.fA.mU.f G.mC.fU.mC*mC*mA	IA1384	577	HI*mg*mg.mA.mG.mC.mA.mU.fC.m G.fU.fA.fA.fC.mA.mU.mU.mU.m G.mU.mC.mU*mA*dQ	IS1775	839
RD4624	mU*fU*mA.fG.mA.fC.mA.fA.m A.fU.mG.fU.mU.fA.mC.fG.mA.f U.mG.fC.mU*mc*mc	IA1385	578	HI*mA*mg.mC.mA.mU.mC.fG.m U.fA.fA.fC.fA.mU.mU.mU.mG.m U.mC.mU.mA*mA*dQ	IS1776	840
RD4625	mA*FG*mU.fA.mG.fA.mC.fA.m A.fA.mU.fG.mU.fU.mA.fC.mG.f A.mU.fG.mC*mU*mc	IA1386	579	Hd*mg*mc.mA.mU.mC.mG.fU. mA.fA.fC.fA.fU.mU.mU.mG.mU. mC.mU.mA.mC*mU*dQ	IS1777	841
RD4626	mU*FA*mg.fU.mA.fG.mA.fC.m A.fA.mA.fU.mG.fU.mU.fA.mC.f G.mA.fU.mG*mc*mU	IA1387	580	HI*mc*mA.mU.mC.mG.mU.fA.m A.fC.fA.fU.fU.mU.mG.mU.mC.m U.mA.mC.mU*mA*dQ	IS1778	842
RD4627	mU*FC*mA.fG.mU.fA.mG.fA.m C.fA.mA.fA.mU.fG.mU.fU.mA.f C.mG.fA.mU*mg*mc	IA1388	581	H9*mA*mU.mC.mG.mU.mA.fA. mC.fA.fU.fU.fU.mG.mU.mC.mU. mA.mC.mU.mG*mA*dQ	IS1779	843
RD4628	mU*fU*mc.fA.mG.fU.mA.fG.m A.fC.mA.fA.mA.fU.mG.fU.mU.f A.mC.fG.mA*mU*mg	IA1389	582	Hd*mU*mc.mG.mU.mA.mA.fC. mA.fU.fU.fU.fG.mU.mC.mU.mA. mC.mU.mG.mA*mA*dQ	IS1780	844
RD4629	mU*fU*mU.fC.mA.fG.mU.fA.m G.fA.mC.fA.mA.fA.mU.fG.mU.f U.mA.fC.mG*mA*mU	IA1390	583	H4*mc*mg.mU.mA.mA.mC.fA. mU.fU.fU.fG.fU.mC.mU.mA.mC. mU.mG.mA.mA*mA*dQ	IS1781	845
RD4630	mU*FG*mc.fU.mU.fC.mA.fG.m U.fA.mG.fA.mC.fA.mA.fA.mU.f G.mU.fU.mA*mc*mg	IA1391	584	HI*mU*mA.mA.mC.mA.mU.fU.m U.fG.fU.fC.fU.mA.mC.mU.mG.mA .mA.mG.mC*mA*dQ	IS1782	846
RD4631	mU*fU*mg.fC.mU.fU.mC.fA.m G.fU.mA.fG.mA.fC.mA.fA.mA.f U.mG.fU.mU*mA*mc	IA1392	585	H4*mA*mA.mC.mA.mU.mU.fU. mG.fU.fC.fU.fA.mC.mU.mG.mA. mA.mG.mC.mA*mA*dQ	IS1783	847
RD4632	mU*FG*mg.fG.mU.fG.mU.fG. mC.fU.mU.fC.mA.fG.mU.fA.mG .fA.mC.fA.mA*mA*mU	IA1393	586	H4*mU*mU.mG.mU.mC.mU.fA. mC.fU.fG.fA.fA.mG.mC.mA.mC.m A.mC.mC.mC*mA*dQ	IS1784	848
RD4633	mU*fU*mg.fG.mG.fU.mG.fU. mG.fC.mU.fU.mC.fA.mG.fU.mA .fG.mA.fC.mA*mA*mA	IA1394	587	H4*mU*mg.mU.mC.mU.mA.fC. mU.fG.fA.fA.fG.mC.mA.mC.mA. mC.mC.mC.mA*mA*dQ	IS1785	849
RD4634	mU*fU*mU.fG.mG.fG.mU.fG. mU.fG.mC.fU.mU.fC.mA.fG.m U.fA.mG.fA.mC*mA*mA	IA1395	588	H4*mg*mU.mC.mU.mA.mC.fU. mG.fA.fA.fG.fC.mA.mC.mA.mC.m C.mC.mA.mA*mA*dQ	IS1786	850

RD4635	mU*fU*mU.fU.mG.fG.mG.fU. mG.fU.mG.fC.mU.fU.mC.fA.m G.fU.mA.fG.mA*mC*mA	IA1396	589	HI*mU*mC.mU.mA.mC.mU.fG.m A.fA.fG.fC.fA.mC.mA.mC.mC. mA.mA.mA*mA*dQ	IS1787	851
RD4636	mU*fc*mA.fC.mA.fG.mG.fA.m U.fU.mU.fC.mA.fG.mU.fG.mA.f A.mA.fA.mU*mC*mC	IA1397	590	HI*mA*mU.mU.mU.mU.mC.fA.m C.fU.fG.fA.fA.mA.mU.mC.mC.mU .mG.mU.mG*mA*dQ	IS1788	852
RD4637	mU*fg*mC.fA.mC.fA.mG.fG.m A.fU.mU.fU.mC.fA.mG.fU.mG.f A.mA.fA.mA*mU*mC	IA1398	591	Hd*mU*mU.mU.mU.mC.mA.fC. mU.fG.fA.fA.mU.mC.mC.mU. mG.mU.mG.mC*mA*dQ	IS1789	853
RD4638	mU*fU*mG.fC.mA.fC.mA.fG.m G.fA.mU.fU.mU.fC.mA.fG.mU.f G.mA.fA.mA*mA*mU	IA1399	592	H4*mU*mU.mU.mC.mA.mC.fU. mG.fA.fA.fA.fU.mC.mC.mU.mG. mU.mG.mC.mA*mA*dQ	IS1790	854
RD4639	mA*fg*mU.fG.mC.fA.mC.fA.m G.fG.mA.fU.mU.fU.mC.fA.mG.f U.mG.fA.mA*mA*mA	IA1400	593	H4*mU*mU.mC.mA.mC.mU.fG. mA.fA.fA.fU.fC.mC.mU.mG.mU. mG.mC.mA.mC*mU*dQ	IS1791	855
RD4640	mA*fa*mG.fU.mG.fC.mA.fC.m A.fG.mG.fA.mU.fU.mU.fC.mA.f G.mU.fG.mA*mA*mA	IA1401	594	H4*mU*mC.mA.mC.mU.mG.fA. mA.fA.fU.fC.fC.mU.mG.mU.mG. mC.mA.mC.mU*mU*dQ	IS1792	856
RD4641	mA*fa*mA.fG.mU.fG.mC.fA.m C.fA.mG.fG.mA.fU.mU.fU.mC.f A.mG.fU.mG*mA*mA	IA1402	595	H4*mC*mA.mC.mU.mG.mA.fA. mA.fU.fC.fC.fU.mG.mU.mG.mC. mA.mC.mU.mU*mU*dQ	IS1793	857
RD4642	mU*fa*mA.fA.mG.fU.mG.fC.m A.fC.mA.fG.mG.fA.mU.fU.mU.f C.mA.fG.mU*mG*mA	IA1403	596	H9*mA*mC.mU.mG.mA.mA.fA. mU.fC.fC.fU.fG.mU.mG.mC.mA. mC.mU.mU.mU*mA*dQ	IS1794	858
RD4643	mU*fc*mA.fG.mA.fU.mU.fA.m G.fA.mA.fA.mG.fU.mG.fC.mA.f C.mA.fG.mG*mA*mU	IA1404	597	H4*mC*mC.mU.mG.mU.mG.fC. mA.fC.fU.fU.fU.mC.mU.mA.mA. mU.mC.mU.mG*mA*dQ	IS1795	859
RD4644	mU*fc*mC.fA.mG.fA.mU.fU.m A.fG.mA.fA.mA.fG.mU.fG.mC.f A.mC.fA.mG*mG*mA	IA1405	598	H9*mC*mU.mG.mU.mG.mC.fA. mC.fU.fU.fU.fC.mU.mA.mA.mU. mC.mU.mG.mG*mA*dQ	IS1796	860
RD4645	mA*fg*mC.fC.mA.fG.mA.fU.m U.fA.mG.fA.mA.fA.mG.fU.mG.f C.mA.fC.mA*mG*mG	IA1406	599	H9*mU*mG.mU.mG.mC.mA.fC. mU.fU.fU.fC.fU.mA.mA.mU.mC. mU.mG.mG.mC*mU*dQ	IS1797	861
RD4646	mA*fc*mA.fA.mG.fC.mA.fA.m C.fC.mG.fG.mG.fA.mU.fG.mA.f U.mG.fA.mG*mU*mG	IA1407	600	Hd*mC*mU.mC.mA.mU.mC.fA. mU.fC.fC.fC.fG.mG.mU.mU.mG. mC.mU.mU.mG*mU*dQ	IS1798	862
RD4647	mA*fa*mA.fA.mA.fA.mC.fA.m A.fG.mC.fA.mA.fC.mC.fG.mG.f G.mA.fU.mG*mA*mU	IA1408	601	H4*mC*mA.mU.mC.mC.mC.fG.m G.fU.fU.fG.fC.mU.mU.mG.mU.m U.mU.mU.mU*mU*dQ	IS1799	863
RD4648	mU*fa*mA.fA.mA.fA.mA.fC.m A.fA.mG.fC.mA.fA.mC.fC.mG.f G.mG.fA.mU*mG*mA	IA1409	602	H9*mA*mU.mC.mC.mC.mG.fG. mU.fU.fG.fC.fU.mU.mG.mU.mU. mU.mU.mU.mU*mA*dQ	IS1800	864
RD4649	mU*fU*mA.fA.mA.fA.mA.fA.m C.fA.mA.fG.mC.fA.mA.fC.mC.f G.mG.fG.mA*mU*mG	IA1410	603	Hd*mU*mC.mC.mC.mG.mG.fU. mU.fG.fC.fU.fU.mG.mU.mU.mU. mU.mU.mU.mA*mA*dQ	IS1801	865

RD4650	mU*FG*mU.fA.mA.fA.mA.fA.mA.fC.mA.fA.mG.fC.mA.fA.mC.fC.mG.fG.mG*mA*mU	IA1411	604	H4*mC*mC.mC.mG.mG.mU.fU.mG.fC.fU.fU.fG.mU.mU.mU.mU.mU.mU.mA.mC*mA*dQ	IS1802	866
RD4651	mA*FG*mG.fU.mA.fA.mA.fA.mA.fA.mC.fA.mA.fG.mC.fA.mA.fC.mC.fG.mG*mG*mA	IA1412	605	H9*mC*mC.mG.mG.mU.mU.fG.mC.fU.fU.fG.fU.mU.mU.mU.mU.mU.mA.mC.mC*mU*dQ	IS1803	867
RD4652	mA*FA*mG.fG.mU.fA.mA.fA.mA.fA.mA.fC.mA.fA.mG.fC.mA.fA.mC.fC.mG*mG*mG	IA1413	606	H9*mC*mG.mG.mU.mU.mG.fC.mU.fU.fG.fU.mU.mU.mU.mU.mU.mA.mC.mC*mU*dQ	IS1804	868
RD4653	mU*FA*mA.fG.mG.fU.mA.fA.mA.fA.mA.fA.mC.fA.mA.fG.mC.fA.mA.fC.mC*mG*mG	IA1414	607	H9*mG*mG.mU.mU.mG.mC.fU.mU.fG.fU.fU.fU.mU.mU.mU.mA.mC.mC.mU.mU*mA*dQ	IS1805	869
RD4654	mA*FG*mA.fA.mG.fG.mU.fA.mA.fA.mA.fA.mA.fC.mA.fA.mG.fC.mA.fA.mC*mC*mG	IA1415	608	HI*mG*mU.mU.mG.mC.mU.fU.mG.fU.fU.fU.fU.mU.mU.mA.mC.mC.mU.mU.mC*mU*dQ	IS1806	870
RD4655	mA*FA*mG.fA.mA.fG.mG.fU.mA.fA.mA.fA.mA.fA.mC.fA.mA.fG.mC.fA.mA*mC*mC	IA1416	609	HI*mU*mU.mG.mC.mU.mU.fG.mU.fU.fU.fU.fU.mU.mA.mC.mC.mU.mU.mC.mU*mU*dQ	IS1807	871
RD4656	mA*FA*mA.fG.mA.fA.mG.fG.mU.fA.mA.fA.mA.fA.mA.fC.mA.fA.mG.fC.mA*mA*mC	IA1417	610	H4*mU*mG.mC.mU.mU.mG.fU.mU.fU.fU.fU.fU.mA.mC.mC.mU.mU.mC.mU.mU*mU*dQ	IS1808	872
RD4657	mU*FG*mA.fA.mA.fA.mG.fA.mA.fG.mG.fU.mA.fA.mA.fA.mA.fA.mC.fA.mA*mG*mC	IA1418	611	H9*mU*mU.mG.mU.mU.mU.fU.mU.fU.fA.fC.fC.mU.mU.mC.mU.mU.mU.mU.mC*mA*dQ	IS1809	873
RD4658	mU*FG*mG.fA.mA.fA.mA.fG.mA.fA.mG.fG.mU.fA.mA.fA.mA.fA.mA.fC.mA*mA*mG	IA1419	612	H4*mU*mG.mU.mU.mU.mU.fU.mU.fA.fC.fC.fU.mU.mC.mU.mU.mU.mU.mC.mC*mA*dQ	IS1810	874
RD4659	mU*FG*mG.fG.mA.fA.mA.fA.mG.fA.mA.fG.mG.fU.mA.fA.mA.fA.mA.fA.mC*mA*mA	IA1420	613	H4*mG*mU.mU.mU.mU.mU.fU.mA.fC.fC.fU.fU.mC.mU.mU.mU.mU.mU.mC.mC*mA*dQ	IS1811	875
RD4660	mU*FU*mG.fG.mG.fA.mA.fA.mA.fG.mA.fA.mG.fG.mU.fA.mA.fA.mA.fA.mA*mC*mA	IA1421	614	HI*mU*mU.mU.mU.mU.mU.fA.mC.fC.fU.fU.fC.mU.mU.mU.mU.mU.mC.mC.mC.mA*mA*dQ	IS1812	876
RD4661	mU*FC*mU.fG.mG.fG.mA.fA.mA.fA.mG.fA.mA.fG.mG.fU.mA.fA.mA.fA.mA*fA.mA.fA.mA*mA*mC	IA1422	615	H4*mU*mU.mU.mU.mU.mA.fC.mC.fU.fU.fC.fU.mU.mU.mU.mC.mC.mC.mA.mG*mA*dQ	IS1813	877
RD4662	mU*FC*mC.fA.mU.fU.mC.fC.mU.fG.mG.fG.mA.fA.mA.fA.mG.fA.mA.fG.mG*mU*mA	IA1423	616	Hd*mC*mC.mU.mU.mC.mU.fU.mU.fU.fC.fC.fC.mA.mG.mG.mA.mA.mU.mG.mG*mA*dQ	IS1814	878
RD4663	mU*FU*mG.fA.mG.fA.mU.fU.mC.fU.mU.fU.mG.fG.mG.fC.mC.fA.mU.fU.mC*mC*mU	IA1424	617	HI*mG*mA.mA.mU.mG.mG.fC.mC.fC.fA.fA.fA.mG.mA.mA.mU.mC.mU.mC.mA*mA*dQ	IS1815	879
RD4664	mU*FU*mU.fU.mG.fA.mG.fA.mU.fU.mC.fU.mU.fU.mU.fU.mG.fG.mG.fC.mC.fA.mU*mU*mC	IA1425	618	Hd*mA*mU.mG.mG.mC.mC.fC.mA.fA.fA.fG.fA.mA.mU.mC.mU.mC.mA.mA.mA*mA*dQ	IS1816	880

RD4665	mU*fc*mU.fU.mU.fG.mA.fG.m A.fU.mU.fc.mU.fU.mU.fG.mG.f G.mC.fc.mA*mU*mU	IA1426	619	Hd*mU*mG.mG.mC.mC.mC.fA. mA.fA.fG.fA.fA.mU.mC.mU.mC. mA.mA.mA.mG*mA*dQ	IS1817	881
RD4666	mU*fU*mU.fc.mU.fU.mU.fG. mA.fG.mA.fU.mU.fc.mU.fU.m U.fG.mG.fG.mC*mC*mA	IA1427	620	HI*mG*mC.mC.mC.mA.mA.fA.m G.fA.fA.fU.fc.mU.mC.mA.mA.mA .mG.mA.mA*mA*dQ	IS1818	882
RD4667	mA*fg*mA.fc.mA.fA.mA.fG.m A.fU.mU.fU.mC.fU.mU.fU.mG.f A.mG.fA.mU*mU*mC	IA1428	621	Hd*mA*mU.mC.mU.mC.mA.fA. mA.fG.fA.fA.fA.mU.mC.mU.mU. mU.mG.mU.mC*mU*dQ	IS1819	883
RD4668	mU*fg*mA.fG.mA.fc.mA.fA.m A.fG.mA.fU.mU.fU.mC.fU.mU.f U.mG.fA.mG*mA*mU	IA1429	622	H4*mC*mU.mC.mA.mA.mA.fG. mA.fA.fA.fU.fc.mU.mU.mU.mG. mU.mC.mU.mC*mA*dQ	IS1820	884
RD4669	mA*fg*mG.fA.mG.fA.mC.fA.m A.fA.mG.fA.mU.fU.mU.fc.mU.f U.mU.fG.mA*mG*mA	IA1430	623	H9*mU*mC.mA.mA.mA.mG.fA. mA.fA.fU.fc.fU.mU.mU.mG.mU. mC.mU.mC.mC*mU*dQ	IS1821	885
RD4670	mA*fa*mG.fG.mA.fG.mA.fc.m A.fA.mA.fG.mA.fU.mU.fU.mC.f U.mU.fU.mG*mA*mG	IA1431	624	H4*mC*mA.mA.mA.mG.mA.fA. mA.fU.fc.fU.fU.mU.mG.mU.mC. mU.mC.mC.mU*mU*dQ	IS1822	886
RD4671	mU*fa*mA.fG.mG.fA.mG.fA.m C.fA.mA.fA.mG.fA.mU.fU.mU.f C.mU.fU.mU*mG*mA	IA1432	625	H9*mA*mA.mA.mG.mA.mA.fA. mU.fc.fU.fU.fU.mG.mU.mC.mU. mC.mC.mU.mU*mA*dQ	IS1823	887
RD4672	mA*fU*mC.fc.mA.fc.mU.fc.m U.fc.mA.fG.mA.fU.mG.fU.mU.f U.mU.fA.mA*mG*mG	IA1433	626	H9*mU*mU.mA.mA.mA.mA.fc. mA.fU.fc.fU.fG.mA.mG.mA.mG. mU.mG.mG.mA*mU*dQ	IS1824	888
RD4673	mA*fa*mU.fc.mC.fA.mC.fU.m C.fU.mC.fA.mG.fA.mU.fG.mU.f U.mU.fU.mA*mA*mG	IA1434	627	H4*mU*mA.mA.mA.mA.mC.fA. mU.fc.fU.fG.fA.mG.mA.mG.mU. mG.mG.mA.mU*mU*dQ	IS1825	889
RD4674	mA*fa*mC.fA.mC.fU.mG.fG.m G.fA.mU.fG.mC.fU.mG.fU.mG.f C.mC.fU.mG*mC*mA	IA1435	628	HI*mC*mA.mG.mG.mC.mA.fc.m A.fG.fc.fA.fU.mC.mC.mC.mA.mG. mU.mG.mU*mU*dQ	IS1826	890
RD4675	mU*fa*mA.fc.mA.fc.mU.fG.m G.fG.mA.fU.mG.fc.mU.fG.mU.f G.mC.fc.mU*mG*mC	IA1436	629	H9*mA*mG.mG.mC.mA.mC.fA. mG.fc.fA.fU.fc.mC.mC.mA.mG.m U.mG.mU.mU*mA*dQ	IS1827	891
RD4676	mA*fg*mA.fA.mC.fA.mC.fU.m G.fG.mG.fA.mU.fG.mC.fU.mG.f U.mG.fc.mC*mU*mG	IA1437	630	Hd*mG*mG.mC.mA.mC.mA.fG. mC.fA.fU.fc.fc.mC.mA.mG.mU.m G.mU.mU.mC*mU*dQ	IS1828	892
RD4677	mU*fa*mG.fA.mA.fc.mA.fc.m U.fG.mG.fG.mA.fU.mG.fc.mU.f G.mU.fG.mC*mC*mU	IA1438	631	HI*mG*mC.mA.mC.mA.mG.fc.m A.fU.fc.fc.fc.mA.mG.mU.mG.mU .mU.mC.mU*mA*dQ	IS1829	893
RD4678	mU*fc*mA.fG.mA.fA.mC.fA.m C.fU.mG.fG.mG.fA.mU.fG.mC.f U.mG.fU.mG*mC*mC	IA1439	632	HI*mC*mA.mC.mA.mG.mC.fA.m U.fc.fc.fc.fA.mG.mU.mG.mU.mU .mC.mU.mG*mA*dQ	IS1830	894
RD4679	mU*fg*mC.fA.mG.fA.mA.fc.m A.fc.mU.fG.mG.fG.mA.fU.mG.f C.mU.fG.mU*mG*mC	IA1440	633	H9*mA*mC.mA.mG.mC.mA.fU. mC.fc.fc.fA.fG.mU.mG.mU.mU. mC.mU.mG.mC*mA*dQ	IS1831	895

RD4680	mU*fA*mA.fU.mG.fG.mC.fA.m G.fA.mA.fC.mA.fC.mU.fG.mG.f G.mA.fU.mG*mC*mU	IA1441	634	HI*mC*mA.mU.mC.mC.mC.fA.m G.fU.fG.fU.fU.mC.mU.mG.mC.m C.mA.mU.mU*mA*dQ	IS1832	896
RD4681	mA*fG*mA.fA.mU.fG.mG.fC.m A.fG.mA.fA.mC.fA.mC.fU.mG.f G.mG.fA.mU*mG*mC	IA1442	635	H9*mA*mU.mC.mC.mC.mA.fG. mU.fG.fU.fU.fC.mU.mG.mC.mC. mA.mU.mU.mC*mU*dQ	IS1833	897
RD4682	mA*fA*mG.fA.mA.fU.mG.fG.m C.fA.mG.fA.mA.fC.mA.fC.mU.f G.mG.fG.mA*mU*mG	IA1443	636	Hd*mU*mC.mC.mC.mA.mG.fU. mG.fU.fU.fC.fU.mG.mC.mC.mA. mU.mU.mC.mU*mU*dQ	IS1834	898
RD4683	mU*fG*mU.fA.mA.fA.mA.fU.m G.fA.mA.fG.mA.fA.mU.fG.mG.f C.mA.fG.mA*mA*mC	IA1444	637	H4*mU*mC.mU.mG.mC.mC.fA. mU.fU.fC.fU.fU.mC.mA.mU.mU. mU.mU.mA.mC*mA*dQ	IS1835	899
RD4684	mU*fG*mG.fU.mA.fA.mA.fA.m U.fG.mA.fA.mG.fA.mA.fU.mG.f G.mC.fA.mG*mA*mA	IA1445	638	H4*mC*mU.mG.mC.mC.mA.fU. mU.fC.fU.fU.fC.mA.mU.mU.mU. mU.mA.mC.mC*mA*dQ	IS1836	900
RD4685	mU*fG*mU.fC.mA.fU.mG.fG.m U.fA.mA.fA.mA.fU.mG.fA.mA.f G.mA.fA.mU*mG*mG	IA1446	639	H9*mA*mU.mU.mC.mU.mU.fC. mA.fU.fU.fU.fU.mA.mC.mC.mA. mU.mG.mA.mC*mA*dQ	IS1837	901
RD4686	mU*fU*mG.fU.mC.fA.mU.fG.m G.fU.mA.fA.mA.fA.mU.fG.mA.f A.mG.fA.mA*mU*mG	IA1447	640	Hd*mU*mU.mC.mU.mU.mC.fA. mU.fU.fU.fU.fA.mC.mC.mA.mU. mG.mA.mC.mA*mA*dQ	IS1838	902
RD4687	mA*fG*mU.fG.mU.fC.mA.fU.m G.fG.mU.fA.mA.fA.mA.fU.mG.f A.mA.fG.mA*mA*mU	IA1448	641	H4*mU*mC.mU.mU.mC.mA.fU. mU.fU.fU.fA.fC.mC.mA.mU.mG. mA.mC.mA.mC*mU*dQ	IS1839	903
RD4688	mU*fA*mA.fA.mU.fC.mA.fG.m U.fG.mU.fC.mA.fU.mG.fG.mU.f A.mA.fA.mA*mU*mG	IA1449	642	Hd*mU*mU.mU.mU.mA.mC.fC. mA.fU.fG.fA.fC.mA.mC.mU.mG. mA.mU.mU.mU*mA*dQ	IS1840	904
RD4689	mA*fG*mA.fA.mA.fU.mC.fA.m G.fU.mG.fU.mC.fA.mU.fG.mG.f U.mA.fA.mA*mA*mU	IA1450	643	H4*mU*mU.mU.mA.mC.mC.fA. mU.fG.fA.fC.fA.mC.mU.mG.mA. mU.mU.mU.mC*mU*dQ	IS1841	905
RD4690	mA*fA*mG.fA.mA.fA.mU.fC.m A.fG.mU.fG.mU.fC.mA.fU.mG.f G.mU.fA.mA*mA*mA	IA1451	644	H4*mU*mU.mA.mC.mC.mA.fU. mG.fA.fC.fA.fC.mU.mG.mA.mU. mU.mU.mC.mU*mU*dQ	IS1842	906
RD4691	mU*fA*mA.fG.mA.fA.mA.fU.m C.fA.mG.fU.mG.fU.mC.fA.mU.f G.mG.fU.mA*mA*mA	IA1452	645	H4*mU*mA.mC.mC.mA.mU.fG. mA.fC.fA.fC.fU.mG.mA.mU.mU. mU.mC.mU.mU*mA*dQ	IS1843	907
RD4692	mA*fG*mC.fA.mA.fC.mA.fA.m U.fA.mU.fC.mC.fA.mG.fU.mU.f C.mU.fU.mC*mU*mC	IA1453	646	Hd*mG*mA.mA.mG.mA.mA.fC. mU.fG.fG.fA.fU.mA.mU.mU.mG. mU.mU.mG.mC*mU*dQ	IS1844	908
RD4693	mU*fA*mG.fC.mA.fA.mC.fA.m A.fU.mA.fU.mC.fC.mA.fG.mU.f U.mC.fU.mU*mC*mU	IA1454	647	HI*mA*mA.mG.mA.mA.mC.fU.m G.fG.fA.fU.fA.mU.mU.mG.mU.m U.mG.mC.mU*mA*dQ	IS1845	909
RD4694	mA*fA*mA.fA.mA.fC.mU.fG.m G.fC.mA.fG.mC.fG.mG.fA.mC.f G.mG.fC.mA*mU*mU	IA1455	648	Hd*mU*mG.mC.mC.mG.mU.fC. mC.fG.fC.fU.fG.mC.mC.mA.mG.m U.mU.mU.mU*mU*dQ	IS1846	910

RD4695	mA*fA*mA.fA.mA.fA.mC.fU.m G.fG.mC.fA.mG.fC.mG.fG.mA.f C.mG.fG.mC*mA*mU	IA1456	649	H4*mG*mC.mC.mG.mU.mC.fC. mG.fC.fU.fG.fC.mC.mA.mG.mU. mU.mU.mU.mU*mU*dQ	IS1847	911
RD4696	mU*fA*mA.fA.mA.fA.mA.fC.m U.fG.mG.fC.mA.fG.mC.fG.mG.f A.mC.fG.mG*mC*mA	IA1457	650	HI*mC*mC.mG.mU.mC.mC.fG.m C.fU.fG.fC.fC.mA.mG.mU.mU.mU .mU.mU.mU*mA*dQ	IS1848	912
RD4697	mU*fU*mA.fA.mA.fA.mA.fA.m C.fU.mG.fG.mC.fA.mG.fC.mG.f G.mA.fC.mG*mG*mC	IA1458	651	H9*mC*mG.mU.mC.mC.mG.fC. mU.fG.fC.fC.fA.mG.mU.mU.mU. mU.mU.mU.mA*mA*dQ	IS1849	913
RD4698	mU*fG*mU.fA.mA.fA.mA.fA.m A.fC.mU.fG.mG.fC.mA.fG.mC.f G.mG.fA.mC*mG*mG	IA1459	652	H9*mG*mU.mC.mC.mG.mC.fU. mG.fC.fC.fA.fG.mU.mU.mU.mU. mU.mU.mA.mC*mA*dQ	IS1850	914
RD4699	mA*fG*mG.fU.mA.fA.mA.fA.m A.fA.mC.fU.mG.fG.mC.fA.mG.f C.mG.fG.mA*mC*mG	IA1460	653	HI*mU*mC.mC.mG.mC.mU.fG.m C.fC.fA.fG.fU.mU.mU.mU.mU.m U.mA.mC.mC*mU*dQ	IS1851	915
RD4700	mU*fA*mG.fG.mU.fA.mA.fA.m A.fA.mA.fC.mU.fG.mG.fC.mA.f G.mC.fG.mG*mA*mC	IA1461	654	H4*mC*mC.mG.mC.mU.mG.fC. mC.fA.fG.fU.fU.mU.mU.mU.mU. mA.mC.mC.mU*mA*dQ	IS1852	916
RD4701	mA*fU*mA.fG.mG.fU.mA.fA.m A.fA.mA.fA.mC.fU.mG.fG.mC.f A.mG.fC.mG*mG*mA	IA1462	655	H9*mC*mG.mC.mU.mG.mC.fC. mA.fG.fU.fU.fU.mU.mU.mU.mA. mC.mC.mU.mA*mU*dQ	IS1853	917
RD4702	mA*fU*mG.fU.mG.fU.mA.fU. mC.fC.mA.fG.mA.fG.mA.fU.mG .fC.mC.fU.mC*mC*mU	IA1463	656	HI*mG*mA.mG.mG.mC.mA.fU.m C.fU.fC.fU.fG.mG.mA.mU.mA.mC .mA.mC.mA*mU*dQ	IS1854	918
RD4703	mU*fU*mU.fU.mG.fG.mU.fG. mG.fU.mA.fC.mA.fC.mU.fC.mA .fU.mU.fA.mU*mC*mC	IA1464	657	HI*mA*mU.mA.mA.mU.mG.fA.m G.fU.fG.fU.fA.mC.mC.mA.mC.mC .mA.mA.mA*mA*dQ	IS1855	919
RD4704	mU*fG*mA.fU.mU.fU.mU.fG. mG.fU.mG.fG.mU.fA.mC.fA.mC .fU.mC.fA.mU*mU*mA	IA1465	658	Hd*mA*mU.mG.mA.mG.mU.fG. mU.fA.fC.fC.fA.mC.mC.mA.mA.m A.mA.mU.mC*mA*dQ	IS1856	920
RD4705	mU*fU*mG.fA.mU.fU.mU.fU. mG.fG.mU.fG.mG.fU.mA.fC.m A.fC.mU.fC.mA*mU*mU	IA1466	659	Hd*mU*mG.mA.mG.mU.mG.fU. mA.fC.fC.fA.fC.mC.mA.mA.mA.m A.mU.mC.mA*mA*dQ	IS1857	921
RD4706	mU*fU*mU.fG.mA.fU.mU.fU. mU.fG.mG.fU.mG.fG.mU.fA.m C.fA.mC.fU.mC*mA*mU	IA1467	660	H4*mG*mA.mG.mU.mG.mU.fA. mC.fC.fA.fC.fC.mA.mA.mA.mA.m U.mC.mA.mA*mA*dQ	IS1858	922
RD4707	mU*fC*mU.fU.mG.fA.mU.fU.m U.fU.mG.fG.mU.fG.mG.fU.mA.f C.mA.fC.mU*mC*mA	IA1468	661	HI*mA*mG.mU.mG.mU.mA.fC.m C.fA.fC.fC.fA.mA.mA.mA.mU.mC. mA.mA.mG*mA*dQ	IS1859	923
RD4708	mU*fG*mC.fU.mU.fG.mA.fU.m U.fU.mU.fG.mG.fU.mG.fG.mU. fA.mC.fA.mC*mU*mC	IA1469	662	Hd*mG*mU.mG.mU.mA.mC.fC. mA.fC.fC.fA.fA.mA.mA.mU.mC.m A.mA.mG.mC*mA*dQ	IS1860	924
RD4709	mU*fG*mG.fC.mU.fU.mG.fA.m U.fU.mU.fU.mG.fG.mU.fG.mG. fU.mA.fC.mA*mC*mU	IA1470	663	HI*mU*mG.mU.mA.mC.mC.fA.m C.fC.fA.fA.fA.mA.mU.mC.mA.mA. mG.mC.mC*mA*dQ	IS1861	925

RD4710	mU*fG*mG.fG.mC.fU.mU.fG. mA.fU.mU.fU.mU.fG.mG.fU.m G.fG.mU.fA.mC*mA*mC	IA1471	664	H4*mG*mU.mA.mC.mC.mA.fC. mC.fA.fA.fA.fA.mU.mC.mA.mA.m G.mC.mC.mC*mA*dQ	IS1862	926
RD4711	mU*fU*mG.fG.mG.fC.mU.fU. mG.fA.mU.fU.mU.fU.mG.fG.m U.fG.mG.fU.mA*mC*mA	IA1472	665	HI*mU*mA.mC.mC.mA.mC.fC.m A.fA.fA.fA.fU.mC.mA.mA.mG.mC .mC.mC.mA*mA*dQ	IS1863	927
RD4712	mU*fc*mU.fG.mG.fG.mC.fU.m U.fG.mA.fU.mU.fU.mU.fG.mG.f U.mG.fG.mU*mA*mC	IA1473	666	H4*mA*mC.mC.mA.mC.mC.fA.m A.fA.fA.fU.fC.mA.mA.mG.mC.mC. mC.mA.mG*mA*dQ	IS1864	928
RD4713	mU*fc*mC.fU.mG.fG.mG.fC.m U.fU.mG.fA.mU.fU.mU.fU.mG.f G.mU.fG.mG*mU*mA	IA1474	667	Hd*mC*mC.mA.mC.mC.mA.fA.m A.fA.fU.fC.fA.mA.mG.mC.mC.mC. mA.mG.mG*mA*dQ	IS1865	929
RD4714	mA*fU*mC.fC.mU.fG.mG.fG.m C.fU.mU.fG.mA.fU.mU.fU.mU.f G.mG.fU.mG*mG*mU	IA1475	668	H9*mC*mA.mC.mC.mA.mA.fA.m A.fU.fC.fA.fA.mG.mC.mC.mC.mA. mG.mG.mA*mU*dQ	IS1866	930
RD4715	mU*FA*mU.fC.mC.fU.mG.fG.m G.fC.mU.fU.mG.fA.mU.fU.mU.f U.mG.fG.mU*mG*mG	IA1476	669	H9*mA*mC.mC.mA.mA.mA.fA.m U.fC.fA.fA.fG.mC.mC.mA.mG. mG.mA.mU*mA*dQ	IS1867	931
RD4716	mU*fG*mA.fU.mC.fC.mU.fG.m G.fG.mC.fU.mU.fG.mA.fU.mU.f U.mU.fG.mG*mU*mG	IA1477	670	Hd*mC*mC.mA.mA.mA.mA.fU. mC.fA.fA.fG.fC.mC.mC.mA.mG.m G.mA.mU.mC*mA*dQ	IS1868	932
RD4717	mA*fc*mG.fA.mU.fC.mC.fU.m G.fG.mG.fC.mU.fU.mG.fA.mU.f U.mU.fU.mG*mG*mU	IA1478	671	H9*mC*mA.mA.mA.mA.mU.fC. mA.fA.fG.fC.fC.mC.mA.mG.mG.m A.mU.mC.mG*mU*dQ	IS1869	933
RD4718	mA*FA*mC.fG.mA.fU.mC.fC.m U.fG.mG.fG.mC.fU.mU.fG.mA.f U.mU.fU.mU*mG*mG	IA1479	672	H9*mA*mA.mA.mA.mU.mC.fA. mA.fG.fC.fC.fC.mA.mG.mG.mA.m U.mC.mG.mU*mU*dQ	IS1870	934
RD4719	mU*FA*mA.fC.mG.fA.mU.fC.m C.fU.mG.fG.mG.fC.mU.fU.mG.f A.mU.fU.mU*mU*mG	IA1480	673	Hd*mA*mA.mA.mU.mC.mA.fA. mG.fC.fC.fC.fA.mG.mG.mA.mU. mC.mG.mU.mU*mA*dQ	IS1871	935
RD4720	mU*fc*mA.fA.mC.fG.mA.fU.m C.fC.mU.fG.mG.fG.mC.fU.mU.f G.mA.fU.mU*mU*mU	IA1481	674	Hd*mA*mA.mU.mC.mA.mA.fG. mC.fC.fC.fA.fG.mG.mA.mU.mC.m G.mU.mU.mG*mA*dQ	IS1872	936
RD4721	mU*fc*mC.fA.mA.fC.mG.fA.m U.fC.mC.fU.mG.fG.mG.fC.mU.f U.mG.fA.mU*mU*mU	IA1482	675	Hd*mA*mU.mC.mA.mA.mG.fC. mC.fC.fA.fG.fG.mA.mU.mC.mG. mU.mU.mG.mG*mA*dQ	IS1873	937
RD4722	mU*fU*mC.fC.mA.fA.mC.fG.m A.fU.mC.fC.mU.fG.mG.fG.mC.f U.mU.fG.mA*mU*mU	IA1483	676	Hd*mU*mC.mA.mA.mG.mC.fC. mC.fA.fG.fG.fA.mU.mC.mG.mU. mU.mG.mG.mA*mA*dQ	IS1874	938
RD4723	mU*fc*mU.fC.mC.fA.mA.fC.m G.fA.mU.fC.mC.fU.mG.fG.mG.f C.mU.fU.mG*mA*mU	IA1484	677	H4*mC*mA.mA.mG.mC.mC.fC.m A.fG.fG.fA.fU.mC.mG.mU.mU.m G.mG.mA.mG*mA*dQ	IS1875	939
RD4724	mU*fc*mC.fU.mC.fC.mA.fA.m C.fG.mA.fU.mC.fC.mU.fG.mG.f G.mC.fU.mU*mG*mA	IA1485	678	H9*mA*mA.mG.mC.mC.mC.fA.m G.fG.fA.fU.fC.mG.mU.mU.mG.m G.mA.mG.mG*mA*dQ	IS1876	940

RD4725	mU*fA*mG.fU.mU.fC.mC.fU.m C.fC.mA.fA.mC.fG.mA.fU.mC.fC .mU.fG.mG*mG*mC	IA1486	679	H9*mC*mC.mA.mG.mG.mA.fU. mC.fG.fU.fU.fG.mG.mA.mG.mG. mA.mA.mC.mU*mA*dQ	IS1877	941
RD4726	mU*fc*mA.fG.mU.fU.mC.fC.m U.fC.mC.fA.mA.fC.mG.fA.mU.f C.mC.fU.mG*mG*mG	IA1487	680	H9*mC*mA.mG.mG.mA.mU.fC. mG.fU.fU.fG.fG.mA.mG.mG.mA. mA.mC.mU.mG*mA*dQ	IS1878	942
RD4727	mA*fg*mG.fU.mG.fU.mC.fU.m C.fU.mG.fA.mG.fU.mG.fG.mG.f U.mG.fA.mG*mG*mU	IA1488	681	H9*mC*mU.mC.mA.mC.mC.fC.m A.fC.fU.fC.fA.mG.mA.mG.mA.mC .mA.mC.mC*mU*dQ	IS1879	943
RD4728	mU*fA*mG.fG.mU.fG.mU.fC.m U.fC.mU.fG.mA.fG.mU.fG.mG.f G.mU.fG.mA*mG*mG	IA1489	682	H9*mU*mC.mA.mC.mC.mC.fA.m C.fU.fC.fA.fG.mA.mG.mA.mC.mA .mC.mC.mU*mA*dQ	IS1880	944
RD4729	mA*fc*mA.fG.mG.fU.mG.fU.m C.fU.mC.fU.mG.fA.mG.fU.mG.f G.mG.fU.mG*mA*mG	IA1490	683	H4*mC*mA.mC.mC.mC.mA.fC.m U.fC.fA.fG.fA.mG.mA.mC.mA.mC .mC.mU.mG*mU*dQ	IS1881	945
RD4730	mU*fU*mU.fC.mC.fA.mA.fU.m G.fA.mU.fG.mG.fA.mG.fC.mC.f U.mC.fC.mA*mC*mA	IA1491	684	HI*mU*mG.mG.mA.mG.mG.fC.m U.fC.fC.fA.fU.mC.mA.mU.mU.mG .mG.mA.mA*mA*dQ	IS1882	946
RD4731	mU*fU*mU.fU.mC.fC.mA.fA.m U.fG.mA.fU.mG.fG.mA.fG.mC.f C.mU.fC.mC*mA*mC	IA1492	685	H4*mG*mG.mA.mG.mG.mC.fU. mC.fC.fA.fU.fC.mA.mU.mU.mG. mG.mA.mA.mA*mA*dQ	IS1883	947
RD4732	mA*fU*mC.fC.mA.fC.mU.fG.m G.fU.mU.fU.mC.fC.mA.fA.mU.f G.mA.fU.mG*mG*mA	IA1493	686	H9*mC*mA.mU.mC.mA.mU.fU. mG.fG.fA.fA.fA.mC.mC.mA.mG. mU.mG.mG.mA*mU*dQ	IS1884	948
RD4733	mA*fU*mA.fU.mC.fC.mA.fC.m U.fG.mG.fU.mU.fU.mC.fC.mA.f A.mU.fG.mA*mU*mG	IA1494	687	Hd*mU*mC.mA.mU.mU.mG.fG. mA.fA.fA.fC.fC.mA.mG.mU.mG. mG.mA.mU.mA*mU*dQ	IS1885	949
RD4734	mU*fA*mA.fU.mA.fU.mC.fC.m A.fC.mU.fG.mG.fU.mU.fU.mC.f C.mA.fA.mU*mG*mA	IA1495	688	H9*mA*mU.mU.mG.mG.mA.fA. mA.fC.fC.fA.fG.mU.mG.mG.mA. mU.mA.mU.mU*mA*dQ	IS1886	950
RD4735	mA*fc*mC.fC.mC.fA.mU.fA.m G.fA.mA.fA.mC.fA.mG.fU.mG.f A.mG.fC.mG*mG*mC	IA1496	689	H9*mC*mG.mC.mU.mC.mA.fC.m U.fG.fU.fU.fU.mC.mU.mA.mU.m G.mG.mG.mG*mU*dQ	IS1887	951
RD4736	mU*fA*mC.fC.mC.fC.mA.fU.m A.fG.mA.fA.mA.fC.mA.fG.mU.f G.mA.fG.mC*mG*mG	IA1497	690	H9*mG*mC.mU.mC.mA.mC.fU. mG.fU.fU.fU.fC.mU.mA.mU.mG. mG.mG.mG.mU*mA*dQ	IS1888	952
RD4737	mU*fU*mA.fC.mC.fC.mC.fA.m U.fA.mG.fA.mA.fA.mC.fA.mG.f U.mG.fA.mG*mC*mG	IA1498	691	HI*mC*mU.mC.mA.mC.mU.fG.m U.fU.fU.fC.fU.mA.mU.mG.mG.m G.mG.mU.mA*mA*dQ	IS1889	953
RD4738	mU*fc*mU.fA.mC.fC.mC.fC.m A.fU.mA.fG.mA.fA.mA.fC.mA.f G.mU.fG.mA*mG*mC	IA1499	692	H9*mU*mC.mA.mC.mU.mG.fU. mU.fU.fC.fU.fA.mU.mG.mG.mG. mG.mU.mA.mG*mA*dQ	IS1890	954
RD4739	mU*fU*mC.fU.mA.fC.mC.fC.m C.fA.mU.fA.mG.fA.mA.fA.mC.f A.mG.fU.mG*mA*mG	IA1500	693	H4*mC*mA.mC.mU.mG.mU.fU. mU.fC.fU.fA.fU.mG.mG.mG.mG. mU.mA.mG.mA*mA*dQ	IS1891	955

RD4740	mA*fC*mU.fC.mU.fA.mC.fC.m C.fC.mA.fU.mA.fG.mA.fA.mA.f C.mA.fG.mU*mG*mA	IA1501	694	H9*mA*mC.mU.mG.mU.mU.fU. mC.fU.fA.fU.fG.mG.mG.mG.mU. mA.mG.mA.mG*mU*dQ	IS1892	956
RD4741	mU*fA*mC.fU.mC.fU.mA.fC.m C.fC.mC.fA.mU.fA.mG.fA.mA.f A.mC.fA.mG*mU*mG	IA1502	695	Hd*mC*mU.mG.mU.mU.mU.fC. mU.fA.fU.fG.fG.mG.mG.mU.mA. mG.mA.mG.mU*mA*dQ	IS1893	957
RD4742	mU*fG*mA.fC.mU.fC.mU.fA.m C.fC.mC.fC.mA.fU.mA.fG.mA.f A.mA.fC.mA*mG*mU	IA1503	696	H9*mU*mG.mU.mU.mU.mC.fU. mA.fU.fG.fG.mG.mU.mA.mG. mA.mG.mU.mC*mA*dQ	IS1894	958
RD4743	mU*fU*mG.fA.mC.fU.mC.fU.m A.fC.mC.fC.mC.fA.mU.fA.mG.f A.mA.fA.mC*mA*mG	IA1504	697	H4*mG*mU.mU.mU.mC.mU.fA. mU.fG.fG.fG.fG.mU.mA.mG.mA. mG.mU.mC.mA*mA*dQ	IS1895	959
RD4744	mU*fG*mU.fG.mA.fC.mU.fC.m U.fA.mC.fC.mC.fC.mA.fU.mA.f G.mA.fA.mA*mC*mA	IA1505	698	HI*mU*mU.mU.mC.mU.mA.fU. mG.fG.fG.fG.fU.mA.mG.mA.mG. mU.mC.mA.mC*mA*dQ	IS1896	960
RD4745	mA*fG*mG.fU.mG.fA.mC.fU.m C.fU.mA.fC.mC.fC.mC.fA.mU.fA .mG.fA.mA*mA*mC	IA1506	699	H4*mU*mU.mC.mU.mA.mU.fG. mG.fG.fG.fU.fA.mG.mA.mG.mU. mC.mA.mC.mC*mU*dQ	IS1897	961
RD4746	mU*fA*mG.fG.mU.fG.mA.fC.m U.fC.mU.fA.mC.fC.mC.fC.mA.f U.mA.fG.mA*mA*mA	IA1507	700	H4*mU*mC.mU.mA.mU.mG.fG. mG.fG.fU.fA.fG.mA.mG.mU.mC. mA.mC.mC.mU*mA*dQ	IS1898	962
RD4747	mU*fU*mA.fG.mG.fU.mG.fA. mC.fU.mC.fU.mA.fC.mC.fC.mC. fA.mU.fA.mG*mA*mA	IA1508	701	H4*mC*mU.mA.mU.mG.mG.fG. mG.fU.fA.fG.fA.mG.mU.mC.mA. mC.mC.mU.mA*mA*dQ	IS1899	963
RD4748	mU*fU*mU.fA.mG.fG.mU.fG. mA.fC.mU.fC.mU.fA.mC.fC.mC. fC.mA.fU.mA*mG*mA	IA1509	702	H9*mU*mA.mU.mG.mG.mG.fG. mU.fA.fG.fA.fG.mU.mC.mA.mC. mC.mU.mA.mA*mA*dQ	IS1900	964
RD4749	mU*fC*mU.fU.mA.fG.mG.fU.m G.fA.mC.fU.mC.fU.mA.fC.mC.f C.mC.fA.mU*mA*mG	IA1510	703	H4*mA*mU.mG.mG.mG.mG.fU. mA.fG.fA.fG.fU.mC.mA.mC.mC.m U.mA.mA.mG*mA*dQ	IS1901	965
RD4750	mA*fU*mC.fU.mU.fA.mG.fG.m U.fG.mA.fC.mU.fC.mU.fA.mC.f C.mC.fC.mA*mU*mA	IA1511	704	Hd*mU*mG.mG.mG.mG.mU.fA. mG.fA.fG.fU.fC.mA.mC.mC.mU. mA.mA.mG.mA*mU*dQ	IS1902	966
RD4751	mA*fA*mU.fC.mU.fU.mA.fG.m G.fU.mG.fA.mC.fU.mC.fU.mA.f C.mC.fC.mC*mA*mU	IA1512	705	H4*mG*mG.mG.mG.mU.mA.fG. mA.fG.fU.fC.fA.mC.mC.mU.mA.m A.mG.mA.mU*mU*dQ	IS1903	967
RD4752	mA*fA*mA.fA.mU.fC.mU.fU.m A.fG.mG.fU.mG.fA.mC.fU.mC.f U.mA.fC.mC*mC*mC	IA1513	706	HI*mG*mG.mU.mA.mG.mA.fG. mU.fC.fA.fC.fC.mU.mA.mA.mG.m A.mU.mU.mU*mU*dQ	IS1904	968
RD4753	mU*fA*mA.fA.mA.fU.mC.fU.m U.fA.mG.fG.mU.fG.mA.fC.mU.f C.mU.fA.mC*mC*mC	IA1514	707	HI*mG*mU.mA.mG.mA.mG.fU. mC.fA.fC.fC.fU.mA.mA.mG.mA.m U.mU.mU.mU*mA*dQ	IS1905	969
RD4754	mU*fC*mA.fA.mA.fA.mU.fC.m U.fU.mA.fG.mG.fU.mG.fA.mC.f U.mC.fU.mA*mC*mC	IA1515	708	HI*mU*mA.mG.mA.mG.mU.fC.m A.fC.fC.fU.fA.mA.mG.mA.mU.mU .mU.mU.mG*mA*dQ	IS1906	970

RD4755	mU*fG*mC.fA.mA.fA.mA.fU.m C.fU.mU.fA.mG.fG.mU.fG.mA.f C.mU.fc.mU*mA*mC	IA1516	709	H4*mA*mG.mA.mG.mU.mC.fA. mC.fc.fU.fA.fA.mG.mA.mU.mU. mU.mU.mG.mC*mA*dQ	IS1907	971
RD4756	mA*fG*mA.fc.mA.fc.mG.fc.m A.fA.mA.fA.mU.fc.mU.fU.mA.f G.mG.fU.mG*mA*mC	IA1517	710	H4*mC*mA.mC.mC.mU.mA.fA.m G.fA.fU.fU.fU.mU.mG.mC.mG.m U.mG.mU.mC*mU*dQ	IS1908	972
RD4757	mU*fc*mU.fU.mG.fA.mA.fc.m C.fc.mC.fA.mA.fA.mG.fA.mA.f A.mG.fA.mU*mG*mU	IA1518	711	H9*mA*mU.mC.mU.mU.mU.fc. mU.fU.fU.fG.fG.mG.mU.mU. mC.mA.mA.mG*mA*dQ	IS1909	973
RD4758	mU*fU*mC.fU.mU.fG.mA.fA.m C.fc.mC.fc.mA.fA.mA.fG.mA.fA .mA.fG.mA*mU*mG	IA1519	712	Hd*mU*mC.mU.mU.mU.mC.fU. mU.fU.fG.fG.fG.mG.mU.mU.mC. mA.mA.mG.mA*mA*dQ	IS1910	974
RD4759	mU*fU*mU.fC.mU.fU.mG.fA.m A.fc.mC.fc.mC.fA.mA.fA.mG.fA .mA.fA.mG*mA*mU	IA1520	713	H4*mC*mU.mU.mU.mC.mU.fU. mU.fG.fG.fG.fG.mU.mU.mC.mA. mA.mG.mA.mA*mA*dQ	IS1911	975
RD4760	mA*fU*mU.fU.mC.fU.mU.fG.m A.fA.mC.fc.mC.fc.mA.fA.mA.fG .mA.fA.mA*mG*mA	IA1521	714	H9*mU*mU.mU.mC.mU.mU.fU. mG.fG.fG.fG.fU.mU.mC.mA.mA. mG.mA.mA.mA*mU*dQ	IS1912	976
RD4761	mU*fA*mU.fU.mU.fc.mU.fU. mG.fA.mA.fc.mC.fc.mC.fA.mA. fA.mG.fA.mA*mA*mG	IA1522	715	H4*mU*mU.mC.mU.mU.mU.fG. mG.fG.fG.fU.fU.mC.mA.mA.mG. mA.mA.mA.mU*mA*dQ	IS1913	977
RD4762	mU*fU*mA.fU.mU.fU.mC.fU. mU.fG.mA.fA.mC.fc.mC.fc.mA. fA.mA.fG.mA*mA*mA	IA1523	716	H4*mU*mC.mU.mU.mU.mG.fG. mG.fG.fU.fU.fc.mA.mA.mG.mA. mA.mA.mU.mA*mA*dQ	IS1914	978
RD4763	mA*fU*mU.fA.mU.fU.mU.fc.m U.fU.mG.fA.mA.fc.mC.fc.mC.f A.mA.fA.mG*mA*mA	IA1524	717	H4*mC*mU.mU.mU.mG.mG.fG. mG.fU.fU.fc.fA.mA.mG.mA.mA. mA.mU.mA.mA*mU*dQ	IS1915	979
RD4764	mU*fU*mA.fU.mU.fA.mU.fU. mU.fc.mU.fU.mG.fA.mA.fc.mC .fc.mC.fA.mA*mA*mG	IA1525	718	H4*mU*mU.mG.mG.mG.mG.fU. mU.fc.fA.fA.fG.mA.mA.mA.mU. mA.mA.mU.mA*mA*dQ	IS1916	980
RD4765	mU*fG*mA.fU.mU.fA.mU.fU. mA.fU.mU.fU.mC.fU.mU.fG.m A.fA.mC.fc.mC*mC*mA	IA1526	719	HI*mG*mG.mG.mU.mU.mC.fA. mA.fG.fA.fA.fA.mU.mA.mA.mU. mA.mA.mU.mC*mA*dQ	IS1917	981
RD4766	mU*fG*mG.fA.mU.fU.mA.fU. mU.fA.mU.fU.mU.fc.mU.fU.m G.fA.mA.fc.mC*mC*mC	IA1527	720	HI*mG*mG.mU.mU.mC.mA.fA.m G.fA.fA.fA.fU.mA.mA.mU.mA.mA .mU.mC.mC*mA*dQ	IS1918	982
RD4767	mA*fU*mG.fG.mA.fU.mU.fA.m U.fU.mA.fU.mU.fU.mC.fU.mU.f G.mA.fA.mC*mC*mC	IA1528	721	HI*mG*mU.mU.mC.mA.mA.fG.m A.fA.fA.fU.fA.mA.mU.mA.mA.mU .mC.mC.mA*mU*dQ	IS1919	983
RD4768	mU*fU*mU.fU.mC.fA.mA.fc.m A.fA.mG.fG.mC.fA.mA.fU.mA.f U.mC.fA.mU*mA*mC	IA1529	722	H4*mA*mU.mG.mA.mU.mA.fU. mU.fG.fc.fc.fU.mU.mG.mU.mU. mG.mA.mA.mA*mA*dQ	IS1920	984
RD4769	mU*fA*mG.fU.mU.fU.mC.fA.m A.fc.mA.fA.mG.fG.mC.fA.mA.f U.mA.fU.mC*mA*mU	IA1530	723	H4*mG*mA.mU.mA.mU.mU.fG. mC.fc.fU.fU.fG.mU.mU.mG.mA. mA.mA.mC.mU*mA*dQ	IS1921	985

RD4770	mU*FC*mA.fG.mU.fU.mU.fC.m A.fA.mC.fA.mA.fG.mG.fC.mA.f A.mU.fA.mU*mC*mA	IA1531	724	HI*mA*mU.mA.mU.mU.mG.fC.m C.fU.fU.fG.fU.mU.mG.mA.mA.m A.mC.mU.mG*mA*dQ	IS1922	986
RD4771	mU*FC*mC.fA.mG.fU.mU.fU.m C.fA.mA.fC.mA.fA.mG.fG.mC.f A.mA.fU.mA*mU*mC	IA1532	725	Hd*mU*mA.mU.mU.mG.mC.fC. mU.fU.fG.fU.fU.mG.mA.mA.mA. mC.mU.mG.mG*mA*dQ	IS1923	987
RD4772	mU*fU*mC.fC.mA.fG.mU.fU.m U.fC.mA.fA.mC.fA.mA.fG.mG.f C.mA.fA.mU*mA*mU	IA1533	726	H4*mA*mU.mU.mG.mC.mC.fU. mU.fG.fU.fU.fG.mA.mA.mA.mC. mU.mG.mG.mA*mA*dQ	IS1924	988
RD4773	mU*fU*mU.fC.mC.fA.mG.fU.m U.fU.mC.fA.mA.fC.mA.fA.mG.f G.mC.fA.mA*mU*mA	IA1534	727	Hd*mU*mU.mG.mC.mC.mU.fU. mG.fU.fU.fG.fA.mA.mA.mC.mU. mG.mG.mA.mA*mA*dQ	IS1925	989
RD4774	mU*FG*mU.fU.mU.fC.mC.fA.m G.fU.mU.fU.mC.fA.mA.fC.mA.f A.mG.fG.mC*mA*mA	IA1535	728	H4*mG*mC.mC.mU.mU.mG.fU. mU.fG.fA.fA.fA.mC.mU.mG.mG. mA.mA.mA.mC*mA*dQ	IS1926	990
RD4775	mU*FG*mG.fU.mU.fU.mC.fC.m A.fG.mU.fU.mU.fC.mA.fA.mC.f A.mA.fG.mG*mC*mA	IA1536	729	HI*mC*mC.mU.mU.mG.mU.fU.m G.fA.fA.fA.fC.mU.mG.mG.mA.mA .mA.mC.mC*mA*dQ	IS1927	991
RD4776	mA*FC*mU.fG.mU.fG.mG.fU.m U.fU.mC.fC.mA.fG.mU.fU.mU.f C.mA.fA.mC*mA*mA	IA1537	730	H4*mG*mU.mU.mG.mA.mA.fA. mC.fU.fG.fG.fA.mA.mA.mC.mC.m A.mC.mA.mG*mU*dQ	IS1928	992
RD4777	mU*FA*mC.fU.mG.fU.mG.fG.m U.fU.mU.fC.mC.fA.mG.fU.mU.f U.mC.fA.mA*mC*mA	IA1538	731	HI*mU*mU.mG.mA.mA.mA.fC.m U.fG.fG.fA.fA.mA.mC.mC.mA.mC .mA.mG.mU*mA*dQ	IS1929	993
RD4778	mU*FC*mA.fC.mU.fG.mU.fG.m G.fU.mU.fU.mC.fC.mA.fG.mU.f U.mU.fC.mA*mA*mC	IA1539	732	H4*mU*mG.mA.mA.mA.mC.fU. mG.fG.fA.fA.fA.mC.mC.mA.mC.m A.mG.mU.mG*mA*dQ	IS1930	994
RD4779	mU*fU*mC.fA.mC.fU.mG.fU.m G.fG.mU.fU.mU.fC.mC.fA.mG.f U.mU.fU.mC*mA*mA	IA1540	733	H4*mG*mA.mA.mA.mC.mU.fG. mG.fA.fA.fA.fC.mC.mA.mC.mA.m G.mU.mG.mA*mA*dQ	IS1931	995
RD4780	mA*FA*mU.fU.mC.fA.mC.fU.m G.fU.mG.fG.mU.fU.mU.fC.mC.f A.mG.fU.mU*mU*mC	IA1541	734	Hd*mA*mA.mC.mU.mG.mG.fA. mA.fA.fC.fC.fA.mC.mA.mG.mU.m G.mA.mA.mU*mU*dQ	IS1932	996
RD4781	mU*FA*mA.fU.mU.fC.mA.fC.m U.fG.mU.fG.mG.fU.mU.fU.mC.f C.mA.fG.mU*mU*mU	IA1542	735	Hd*mA*mC.mU.mG.mG.mA.fA. mA.fC.fC.fA.fC.mA.mG.mU.mG.m A.mA.mU.mU*mA*dQ	IS1933	997
RD4782	mU*fU*mA.fA.mU.fU.mC.fA.m C.fU.mG.fU.mG.fG.mU.fU.mU.f C.mC.fA.mG*mU*mU	IA1543	736	Hd*mC*mU.mG.mG.mA.mA.fA. mC.fC.fA.fC.fA.mG.mU.mG.mA.m A.mU.mU.mA*mA*dQ	IS1934	998
RD4783	mU*fU*mG.fU.mG.fU.mA.fA. mU.fU.mC.fA.mC.fU.mG.fU.m G.fG.mU.fU.mU*mC*mC	IA1544	737	HI*mA*mA.mA.mC.mC.mA.fC.m A.fG.fU.fG.fA.mA.mU.mU.mA.mC .mA.mC.mA*mA*dQ	IS1935	999
RD4784	mU*FC*mU.fG.mU.fG.mU.fA.m A.fU.mU.fC.mA.fC.mU.fG.mU.f G.mG.fU.mU*mU*mC	IA1545	738	Hd*mA*mA.mC.mC.mA.mC.fA.m G.fU.fG.fA.fA.mU.mU.mA.mC.mA .mC.mA.mG*mA*dQ	IS1936	1000

RD4785	mA*fU*mC.fU.mG.fU.mG.fU.m A.fA.mU.fU.mC.fA.mC.fU.mG.f U.mG.fG.mU*mU*mU	IA1546	739	Hd*mA*mC.mC.mA.mC.mA.fG.m U.fG.fA.fA.fU.mU.mA.mC.mA.mC .mA.mG.mA*mU*dQ	IS1937	1001
RD4786	mU*fG*mG.fG.mU.fC.mG.fU. mU.fG.mA.fG.mA.fA.mU.fC.m U.fG.mU.fG.mU*mA*mA	IA1547	740	H4*mA*mC.mA.mC.mA.mG.fA. mU.fU.fC.fU.fC.mA.mA.mC.mG. mA.mC.mC.mC*mA*dQ	IS1938	1002
RD4787	mA*fU*mG.fG.mG.fU.mC.fG.m U.fU.mG.fA.mG.fA.mA.fU.mC.f U.mG.fU.mG*mU*mA	IA1548	741	Hd*mC*mA.mC.mA.mG.mA.fU. mU.fC.fU.fC.fA.mA.mC.mG.mA.m C.mC.mC.mA*mU*dQ	IS1939	1003
RD4788	mU*fA*mU.fG.mG.fG.mU.fC.m G.fU.mU.fG.mA.fG.mA.fA.mU.f C.mU.fG.mU*mG*mU	IA1549	742	H9*mA*mC.mA.mG.mA.mU.fU. mC.fU.fC.fA.fA.mC.mG.mA.mC.m C.mC.mA.mU*mA*dQ	IS1940	1004
RD4789	mA*fU*mA.fU.mG.fG.mG.fU. mC.fG.mU.fU.mG.fA.mG.fA.mA .fU.mC.fU.mG*mU*mG	IA1550	743	Hd*mC*mA.mG.mA.mU.mU.fC. mU.fC.fA.fA.fC.mG.mA.mC.mC.m C.mA.mU.mA*mU*dQ	IS1941	1005
RD4790	mU*fA*mU.fA.mU.fG.mG.fG. mU.fC.mG.fU.mU.fG.mA.fG.m A.fA.mU.fC.mU*mG*mU	IA1551	744	H9*mA*mG.mA.mU.mU.mC.fU. mC.fA.fA.fC.fG.mA.mC.mC.mC.m A.mU.mA.mU*mA*dQ	IS1942	1006
RD4791	mU*fC*mA.fU.mA.fU.mG.fG.m G.fU.mC.fG.mU.fU.mG.fA.mG.f A.mA.fU.mC*mU*mG	IA1552	745	Hd*mG*mA.mU.mU.mC.mU.fC. mA.fA.fC.fG.fA.mC.mC.mC.mA.m U.mA.mU.mG*mA*dQ	IS1943	1007
RD4792	mU*fG*mC.fA.mU.fA.mU.fG.m G.fG.mU.fC.mG.fU.mU.fG.mA.f G.mA.fA.mU*mC*mU	IA1553	746	H1*mA*mU.mU.mC.mU.mC.fA.m A.fC.fG.fA.fC.mC.mC.mA.mU.mA. mU.mG.mC*mA*dQ	IS1944	1008
RD4793	mA*fG*mG.fC.mA.fU.mA.fU.m G.fG.mG.fU.mC.fG.mU.fU.mG.f A.mG.fA.mA*mU*mC	IA1554	747	Hd*mU*mU.mC.mU.mC.mA.fA. mC.fG.fA.fC.fC.mC.mA.mU.mA.m U.mG.mC.mC*mU*dQ	IS1945	1009
RD4794	mU*fA*mG.fG.mC.fA.mU.fA.m U.fG.mG.fG.mU.fC.mG.fU.mU.f G.mA.fG.mA*mA*mU	IA1555	748	H4*mU*mC.mU.mC.mA.mA.fC. mG.fA.fC.fC.fC.mA.mU.mA.mU.m G.mC.mC.mU*mA*dQ	IS1946	1010
RD4795	mU*fC*mA.fG.mG.fC.mA.fU.m A.fU.mG.fG.mG.fU.mC.fG.mU.f U.mG.fA.mG*mA*mA	IA1556	749	H4*mC*mU.mC.mA.mA.mC.fG. mA.fC.fC.fC.fA.mU.mA.mU.mG.m C.mC.mU.mG*mA*dQ	IS1947	1011
RD4796	mU*fG*mC.fA.mG.fG.mC.fA.m U.fA.mU.fG.mG.fG.mU.fC.mG.f U.mU.fG.mA*mG*mA	IA1557	750	H9*mU*mC.mA.mA.mC.mG.fA. mC.fC.fC.fA.fU.mA.mU.mG.mC.m C.mU.mG.mC*mA*dQ	IS1948	1012
RD4797	mA*fG*mG.fC.mA.fG.mG.fC.m A.fU.mA.fU.mG.fG.mG.fU.mC.f G.mU.fU.mG*mA*mG	IA1558	751	H4*mC*mA.mA.mC.mG.mA.fC.m C.fC.fA.fU.fA.mU.mG.mC.mC.mU .mG.mC.mC*mU*dQ	IS1949	1013
RD4798	mA*fA*mG.fG.mC.fA.mG.fG.m C.fA.mU.fA.mU.fG.mG.fG.mU.f C.mG.fU.mU*mG*mA	IA1559	752	H9*mA*mA.mC.mG.mA.mC.fC.m C.fA.fU.fA.fU.mG.mC.mC.mU.mG .mC.mC.mU*mU*dQ	IS1950	1014
RD4799	mU*fA*mA.fG.mG.fC.mA.fG.m G.fC.mA.fU.mA.fU.mG.fG.mG.f U.mC.fG.mU*mU*mG	IA1560	753	Hd*mA*mC.mG.mA.mC.mC.fC.m A.fU.fA.fU.fG.mC.mC.mU.mG.mC .mC.mU.mU*mA*dQ	IS1951	1015

RD4800	mU*fU*mC.fU.mG.fU.mA.fC.m C.fC.mC.fC.mA.fU.mC.fC.mA.fG .mU.fC.mA*mC*mC	IA1561	754	HI*mU*mG.mA.mC.mU.mG.fG. mA.fU.fG.fG.fG.mG.mG.mU.mA. mC.mA.mG.mA*mA*dQ	IS1952	1016
RD4801	mU*fU*mU.fC.mU.fG.mU.fA.m C.fC.mC.fC.mC.fA.mU.fC.mC.fA .mG.fU.mC*mA*mC	IA1562	755	H4*mG*mA.mC.mU.mG.mG.fA. mU.fG.fG.fG.fG.mG.mU.mA.mC. mA.mG.mA.mA*mA*dQ	IS1953	1017
RD4802	mU*fU*mU.fU.mC.fU.mG.fU. mA.fC.mC.fC.mC.fC.mA.fU.mC. fC.mA.fG.mU*mC*mA	IA1563	756	HI*mA*mC.mU.mG.mG.mA.fU.m G.fG.fG.fG.fG.mU.mA.mC.mA.m G.mA.mA.mA*mA*dQ	IS1954	1018
RD4803	mA*fU*mC.fU.mU.fG.mG.fC.m U.fU.mU.fC.mU.fG.mG.fA.mG.f A.mG.fU.mA*mU*mU	IA1564	757	Hd*mU*mA.mC.mU.mC.mU.fC. mC.fA.fG.fA.fA.mA.mG.mC.mC.m A.mA.mG.mA*mU*dQ	IS1955	1019
RD4804	mU*fA*mU.fC.mU.fU.mG.fG.m C.fU.mU.fU.mC.fU.mG.fG.mA.f G.mA.fG.mU*mA*mU	IA1565	758	H4*mA*mC.mU.mC.mU.mC.fC.m A.fG.fA.fA.fA.mG.mC.mC.mA.mA. mG.mA.mU*mA*dQ	IS1956	1020
RD4805	mU*fU*mA.fU.mC.fU.mU.fG.m G.fC.mU.fU.mU.fC.mU.fG.mG.f A.mG.fA.mG*mU*mA	IA1566	759	Hd*mC*mU.mC.mU.mC.mC.fA. mG.fA.fA.fA.fG.mC.mC.mA.mA.m G.mA.mU.mA*mA*dQ	IS1957	1021
RD4806	mU*fG*mU.fA.mU.fC.mU.fU.m G.fG.mC.fU.mU.fU.mC.fU.mG.f G.mA.fG.mA*mG*mU	IA1567	760	H9*mU*mC.mU.mC.mC.mA.fG. mA.fA.fA.fG.fC.mC.mA.mA.mG.m A.mU.mA.mC*mA*dQ	IS1958	1022
RD4807	mU*fG*mG.fU.mA.fU.mC.fU.m U.fG.mG.fC.mU.fU.mU.fC.mU.f G.mG.fA.mG*mA*mG	IA1568	761	H4*mC*mU.mC.mC.mA.mG.fA. mA.fA.fG.fC.fC.mA.mA.mG.mA.m U.mA.mC.mC*mA*dQ	IS1959	1023
RD4808	mA*fG*mG.fG.mU.fA.mU.fC.m U.fU.mG.fG.mC.fU.mU.fU.mC.f U.mG.fG.mA*mG*mA	IA1569	762	H9*mU*mC.mC.mA.mG.mA.fA. mA.fG.fC.fC.fA.mA.mG.mA.mU. mA.mC.mC.mC*mU*dQ	IS1960	1024
RD4809	mA*fA*mG.fG.mG.fU.mA.fU.m C.fU.mU.fG.mG.fC.mU.fU.mU.f C.mU.fG.mG*mA*mG	IA1570	763	H4*mC*mC.mA.mG.mA.mA.fA. mG.fC.fC.fA.fA.mG.mA.mU.mA. mC.mC.mC.mU*mU*dQ	IS1961	1025
RD4810	mU*fA*mA.fG.mG.fG.mU.fA.m U.fC.mU.fU.mG.fG.mC.fU.mU.f U.mC.fU.mG*mG*mA	IA1571	764	H9*mC*mA.mG.mA.mA.mA.fG. mC.fC.fA.fA.fG.mA.mU.mA.mC.m C.mC.mU.mU*mA*dQ	IS1962	1026
RD4811	mU*fU*mA.fA.mG.fG.mG.fU. mA.fU.mC.fU.mU.fG.mG.fC.m U.fU.mU.fC.mU*mG*mG	IA1572	765	H9*mA*mG.mA.mA.mA.mG.fC. mC.fA.fA.fG.fA.mU.mA.mC.mC.m C.mU.mU.mA*mA*dQ	IS1963	1027
RD4812	mU*fA*mC.fU.mA.fA.mG.fG.m G.fU.mA.fU.mC.fU.mU.fG.mG.f C.mU.fU.mU*mC*mU	IA1573	766	HI*mA*mA.mA.mG.mC.mC.fA.m A.fG.fA.fU.fA.mC.mC.mC.mU.mU .mA.mG.mU*mA*dQ	IS1964	1028
RD4813	mU*fC*mA.fC.mU.fA.mA.fG.m G.fG.mU.fA.mU.fC.mU.fU.mG.f G.mC.fU.mU*mU*mC	IA1574	767	Hd*mA*mA.mG.mC.mC.mA.fA. mG.fA.fU.fA.fC.mC.mC.mU.mU. mA.mG.mU.mG*mA*dQ	IS1965	1029
RD4814	mU*fU*mC.fA.mC.fU.mA.fA.m G.fG.mG.fU.mA.fU.mC.fU.mU.f G.mG.fC.mU*mU*mU	IA1575	768	Hd*mA*mG.mC.mC.mA.mA.fG. mA.fU.fA.fC.fC.mC.mU.mU.mA. mG.mU.mG.mA*mA*dQ	IS1966	1030

RD4815	mU*FG*mU.fC.mA.fC.mU.fA.m A.fG.mG.fG.mU.fA.mU.fC.mU.f U.mG.fG.mC*mU*mU	IA1576	769	Hd*mG*mC.mC.mA.mA.mG.fA. mU.fA.fC.fC.fC.mU.mU.mA.mG. mU.mG.mA.mC*mA*dQ	IS1967	1031
RD4816	mU*FG*mG.fU.mC.fA.mC.fU.m A.fA.mG.fG.mG.fU.mA.fU.mC.f U.mU.fG.mG*mC*mU	IA1577	770	HI*mC*mC.mA.mA.mG.mA.fU.m A.fC.fC.fC.fU.mU.mA.mG.mU.mG .mA.mC.mC*mA*dQ	IS1968	1032
RD4817	mU*fU*mG.fG.mU.fC.mA.fC.m U.fA.mA.fG.mG.fG.mU.fA.mU.f C.mU.fU.mG*mG*mC	IA1578	771	H9*mC*mA.mA.mG.mA.mU.fA. mC.fC.fC.fU.fU.mA.mG.mU.mG. mA.mC.mC.mA*mA*dQ	IS1969	1033
RD4818	mU*fU*mA.fU.mU.fU.mU.fA. mU.fG.mU.fC.mC.fU.mC.fU.mG .fU.mA.fU.mC*mU*mC	IA1579	772	Hd*mG*mA.mU.mA.mC.mA.fG. mA.fG.fG.fA.fC.mA.mU.mA.mA. mA.mA.mU.mA*mA*dQ	IS1970	1034
RD4819	mU*FG*mU.fU.mA.fU.mU.fU. mU.fA.mU.fG.mU.fC.mC.fU.mC .fU.mG.fU.mA*mU*mC	IA1580	773	Hd*mU*mA.mC.mA.mG.mA.fG. mG.fA.fC.fA.fU.mA.mA.mA.mA. mU.mA.mA.mC*mA*dQ	IS1971	1035
RD4820	mA*fU*mC.fU.mU.fA.mU.fG.m G.fG.mU.fU.mA.fU.mU.fU.mU.f A.mU.fG.mU*mC*mC	IA1581	774	HI*mA*mC.mA.mU.mA.mA.fA.m A.fU.fA.fA.fC.mC.mA.mU.mA. mA.mG.mA*mU*dQ	IS1972	1036
RD4821	mA*FC*mA.fG.mA.fU.mC.fA.m U.fC.mU.fU.mA.fU.mG.fG.mG.f U.mU.fA.mU*mU*mU	IA1582	775	Hd*mA*mU.mA.mA.mC.mC.fC.m A.fU.fA.fA.fG.mA.mU.mG.mA.m U.mC.mU.mG*mU*dQ	IS1973	1037
RD4822	mU*FA*mC.fA.mG.fA.mU.fC.m A.fU.mC.fU.mU.fA.mU.fG.mG.f G.mU.fU.mA*mU*mU	IA1583	776	Hd*mU*mA.mA.mC.mC.mC.fA.m U.fA.fA.fG.fA.mU.mG.mA.mU.mC .mU.mG.mU*mA*dQ	IS1974	1038
RD4823	mU*FC*mA.fC.mA.fG.mA.fU.m C.fA.mU.fC.mA.fU.mA.fU.mG.f G.mG.fU.mU*mA*mU	IA1584	777	H4*mA*mA.mC.mC.mC.mA.fU.m A.fA.fG.fA.fU.mG.mA.mU.mC.mU .mG.mU.mG*mA*dQ	IS1975	1039
RD4824	mU*FG*mC.fA.mC.fA.mG.fA.m U.fC.mA.fU.mC.fU.mU.fA.mU.f G.mG.fG.mU*mU*mA	IA1585	778	Hd*mA*mC.mC.mC.mA.mU.fA.m A.fG.fA.fU.fG.mA.mU.mC.mU.m G.mU.mG.mC*mA*dQ	IS1976	1040
RD4825	mU*FG*mG.fC.mA.fC.mA.fG.m A.fU.mC.fA.mU.fC.mU.fU.mA.f U.mG.fG.mG*mU*mU	IA1586	779	Hd*mC*mC.mC.mA.mU.mA.fA.m G.fA.fU.fG.fA.mU.mC.mU.mG.m U.mG.mC.mC*mA*dQ	IS1977	1041
RD4826	mU*FC*mG.fG.mC.fA.mC.fA.m G.fA.mU.fC.mA.fU.mC.fU.mU.f A.mU.fG.mG*mG*mU	IA1587	780	H9*mC*mC.mA.mU.mA.mA.fG. mA.fU.fG.fA.fU.mC.mU.mG.mU. mG.mC.mC.mG*mA*dQ	IS1978	1042
RD4827	mU*FC*mC.fG.mG.fC.mA.fC.m A.fG.mA.fU.mC.fA.mU.fC.mU.f U.mA.fU.mG*mG*mG	IA1588	781	H9*mC*mA.mU.mA.mA.mG.fA. mU.fG.fA.fU.fC.mU.mG.mU.mG. mC.mC.mG.mG*mA*dQ	IS1979	1043
RD4828	mA*FG*mC.fC.mG.fG.mC.fA.m C.fA.mG.fA.mU.fC.mA.fU.mC.f U.mU.fA.mU*mG*mG	IA1589	782	H9*mA*mU.mA.mA.mG.mA.fU. mG.fA.fU.fC.fU.mG.mU.mG.mC. mC.mG.mG.mC*mU*dQ	IS1980	1044
RD4829	mU*FA*mG.fC.mC.fG.mG.fC.m A.fC.mA.fG.mA.fU.mC.fA.mU.f C.mU.fU.mA*mU*mG	IA1590	783	Hd*mU*mA.mA.mG.mA.mU.fG. mA.fU.fC.fU.fG.mU.mG.mC.mC. mG.mG.mC.mU*mA*dQ	IS1981	1045

RD4830	mU*fU*mA.fG.mC.fC.mG.fG.m C.fA.mC.fA.mG.fA.mU.fC.mA.f U.mC.fU.mU*mA*mU	IA1591	784	H4*mA*mA.mG.mA.mU.mG.fA. mU.fC.fU.fG.fU.mG.mC.mC.mG. mG.mC.mU.mA*mA*dQ	IS1982	1046
RD4831	mU*fG*mU.fA.mG.fC.mC.fG.m G.fC.mA.fC.mA.fG.mA.fU.mC.f A.mU.fC.mU*mU*mA	IA1592	785	Hd*mA*mG.mA.mU.mG.mA.fU. mC.fU.fG.fU.fG.mC.mC.mG.mG. mC.mU.mA.mC*mA*dQ	IS1983	1047
RD4832	mU*fU*mG.fU.mA.fG.mC.fC.m G.fG.mC.fA.mC.fA.mG.fA.mU.f C.mA.fU.mC*mU*mU	IA1593	786	Hd*mG*mA.mU.mG.mA.mU.fC. mU.fG.fU.fG.fC.mC.mG.mG.mC. mU.mA.mC.mA*mA*dQ	IS1984	1048
RD4833	mU*fC*mU.fG.mU.fA.mG.fC.m C.fG.mG.fC.mA.fC.mA.fG.mA.f U.mC.fA.mU*mC*mU	IA1594	787	HI*mA*mU.mG.mA.mU.mC.fU.m G.fU.fG.fC.fC.mG.mG.mC.mU.mA .mC.mA.mG*mA*dQ	IS1985	1049
RD4834	mU*fC*mC.fU.mG.fU.mA.fG.m C.fC.mG.fG.mC.fA.mC.fA.mG.f A.mU.fC.mA*mU*mC	IA1595	788	Hd*mU*mG.mA.mU.mC.mU.fG. mU.fG.fC.fC.fG.mG.mC.mU.mA. mC.mA.mG.mG*mA*dQ	IS1986	1050
RD4835	mU*fC*mC.fC.mU.fG.mU.fA.m G.fC.mC.fG.mG.fC.mA.fC.mA.f G.mA.fU.mC*mA*mU	IA1596	789	H4*mG*mA.mU.mC.mU.mG.fU. mG.fC.fC.fG.fG.mC.mU.mA.mC.m A.mG.mG.mG*mA*dQ	IS1987	1051
RD4836	mU*fU*mC.fC.mC.fU.mG.fU.m A.fG.mC.fC.mG.fG.mC.fA.mC.f A.mG.fA.mU*mC*mA	IA1597	790	HI*mA*mU.mC.mU.mG.mU.fG. mC.fC.fG.fG.fC.mU.mA.mC.mA.m G.mG.mG.mA*mA*dQ	IS1988	1052
RD4837	mU*fU*mU.fC.mC.fC.mU.fG.m U.fA.mG.fC.mC.fG.mG.fC.mA.f C.mA.fG.mA*mU*mC	IA1598	791	Hd*mU*mC.mU.mG.mU.mG.fC. mC.fG.fG.fC.fU.mA.mC.mA.mG. mG.mG.mA.mA*mA*dQ	IS1989	1053
RD4838	mU*fC*mU.fU.mC.fC.mC.fU.m G.fU.mA.fG.mC.fC.mG.fG.mC.f A.mC.fA.mG*mA*mU	IA1599	792	H4*mC*mU.mG.mU.mG.mC.fC. mG.fG.fC.fU.fA.mC.mA.mG.mG. mG.mA.mA.mG*mA*dQ	IS1990	1054
RD4839	mU*fC*mU.fC.mC.fC.mG.fA.m A.fU.mC.fU.mC.fC.mC.fU.mU.f G.mC.fA.mA*mG*mC	IA1600	793	H9*mU*mU.mG.mC.mA.mA.fG. mG.fG.fA.fG.fA.mU.mU.mC.mG. mG.mG.mA.mG*mA*dQ	IS1991	1055
RD4840	mU*fC*mC.fU.mC.fC.mC.fG.m A.fA.mU.fC.mU.fC.mC.fC.mU.f U.mG.fC.mA*mA*mG	IA1601	794	H4*mU*mG.mC.mA.mA.mG.fG. mG.fA.fG.fA.fU.mU.mC.mG.mG. mG.mA.mG.mG*mA*dQ	IS1992	1056
RD4841	mU*fG*mC.fC.mU.fC.mC.fC.m G.fA.mA.fU.mC.fU.mC.fC.mC.f U.mU.fG.mC*mA*mA	IA1602	795	H4*mG*mC.mA.mA.mG.mG.fG. mA.fG.fA.fU.fU.mC.mG.mG.mG. mA.mG.mG.mC*mA*dQ	IS1993	1057
RD5030	mU*fA*mU.fC.mC.fG.mU.fG.m C.fA.mU.fC.mU.fU.mU.fC.mU.f U.mG.fG.mC*mG*mU	IA1635	1086	H9*mG*mC.mC.mA.mA.mG.fA. mA.fA.fG.fA.fU.mG.mC.mA.mC. mG.mG.mA.mU*mA*dQ	IS2026	1100
RD5031	mU*fU*mU.fC.mA.fG.mU.fA.m G.fA.mC.fA.mA.fA.mU.fG.mU.f U.mA.fC.mG*mG*mU	IA1636	1087	H9*mC*mG.mU.mA.mA.mC.fA. mU.fU.fU.fG.fU.mC.mU.mA.mC. mU.mG.mA.mA*mA*dQ	IS2027	1101
RD5032	mU*fG*mC.fA.mA.fA.mA.fU.m C.fU.mU.fA.mG.fG.mU.fG.mA.f C.mU.fC.mU*mG*mC	IA1637	1088	H9*mA*mG.mA.mG.mU.mC.fA. mC.fC.fU.fA.fA.mG.mA.mU.mU. mU.mU.mG.mC*mA*dQ	IS2028	1102

RD5033	mU*fA*mU.fC.mU.fU.mG.fG.m C.fU.mU.fU.mC.fU.mG.fG.mA.f G.mA.fG.mU*mG*mU	IA1638	1089	H9*mA*mC.mU.mC.mU.mC.fC.m A.fG.fA.fA.fA.mG.mC.mC.mA.mA. mG.mA.mU*mA*dQ	IS2029	1103
RD5034	mU*fA*mC.fA.mG.fA.mU.fC.m A.fU.mC.fU.mU.fA.mU.fG.mG.f G.mU.fU.mG*mU*mU	IA1639	1090	Hd*mC*mA.mA.mC.mC.mC.fA.m U.fA.fA.fG.fA.mU.mG.mA.mU.mC .mU.mG.mU*mA*dQ	IS2030	1104
RD5059	mU*fC*mA.fU.mU.fC.mU.fU.m G.fA.mG.fC.mA.fU.mU.fC.mU.f U.mG.fG.mC*mG*mA	IA1641	1091	H9*mG*mC.mC.mA.mA.mG.fA. mA.fU.fG.fC.fU.mC.mA.mA.mG. mA.mA.mU.mG*mA*dQ	IS2043	1105
RD5060	mA*fA*mG.fG.mA.fG.mA.fC.m A.fA.mA.fG.mA.fU.mU.fU.mC.f U.mU.fU.mG*mG*mG	IA1642	1092	H9*mC*mA.mA.mA.mG.mA.fA. mA.fU.fC.fU.fU.mU.mG.mU.mC. mU.mC.mC.mU*mU*dQ	IS2044	1106
RD5061	mU*fG*mU.fA.mA.fA.mA.fU.m G.fA.mA.fG.mA.fA.mU.fG.mG.f C.mA.fG.mA*mG*mC	IA1643	1093	H9*mU*mC.mU.mG.mC.mC.fA. mU.fU.fC.fU.fU.mC.mA.mU.mU. mU.mU.mA.mC*mA*dQ	IS2045	1107
RD5072	mU*fG*mU.fC.mA.fU.mG.fG.m U.fA.mA.fA.mA.fU.mG.fA.mA.f G.mA.fG.mU*mG*mG	IA1645	1094	H9*mA*mC.mU.mC.mU.mU.fC. mA.fU.fU.fU.fU.mA.mC.mC.mA. mU.mG.mA.mC*mA*dQ	IS2047	1108
RD5094	mU*fA*mG.fA.mA.fC.mA.fC.m U.fG.mG.fG.mA.fU.mG.fC.mU.f G.mU*fG*mC	IA1649	1095	H4*mG*mC.mA.mC.mA.mG.fC. mA.fU.fC.fC.fC.mA.mG.mU.mG. mU.mU.mC.mU*mA*dQ	IS2052	1109
RD5095	mA*fA*mG.fG.mG.fU.mA.fU.m C.fU.mU.fG.mG.fU.mU.fU.mU.f C.mU.fG.mG*mA*mG	IA1650	1096	H4*mC*mC.mA.mG.mA.mA.fA. mA.fC.fC.fA.fA.mG.mA.mU.mA.m C.mC.mC.mU*mU*dQ	IS2053	1110
RD5096	mU*fA*mG.fA.mC.fA.mA.fA.m U.fG.mU.fU.mA.fU.mG.fA.mU.f G.mC.fU.mC*mC*mA	IA1651	1097	H1*mG*mA.mG.mC.mA.mU.fC.m A.fU.fA.fA.fC.mA.mU.mU.mU.mG .mU.mC.mU*mA*dQ	IS2054	1111
RD5097	mA*fG*mG.fA.mG.fA.mC.fA.m A.fA.mG.fA.mU.fU.mU.fC.mU.f U.mU.fG.mG*mG*mA	IA1652	1098	H9*mC*mC.mA.mA.mA.mG.fA. mA.fA.fU.fC.fU.mU.mU.mG.mU. mC.mU.mC.mC*mU*dQ	IS2055	1112
RD5098	mU*fA*mA.fG.mA.fA.mA.fU.m C.fA.mG.fU.mG.fU.mC.fA.mU.f G.mG.fU.mA*mG*mA	IA1653	1099	H9*mU*mA.mC.mC.mA.mU.fG. mA.fC.fA.fC.fU.mG.mA.mU.mU. mU.mC.mU.mU*mA*dQ	IS2056	1113
RD5321	mU*fU*mU.fC.mA.fG.mU.fA.m G.fA.mC.fA.mA.fA.mU.fG.mU.f U.mA.fC*mG*mG	IA1724	1131	H4*mC*mC.mG.mU.mA.mA.mC. fA.mU.fU.fU.fG.fU.mC.mU.mA.m C.mU.mG.mA.mA*mA*dQ	IS2142	1136
RD5383	mU*fA*mA.fG.mA.fA.mA.fU.m C.fA.mG.fU.mG.fU.mC.fA.mU.f G.mG.fU.mG*mG*mA	IA1729	1132	H9*mC*mA.mC.mC.mA.mU.fG. mA.fC.fA.fC.fU.mG.mA.mU.mU. mU.mC.mU.mU*mA*dQ	IS2148	1137
RD5384	mU*fG*mC.fU.mU.fC.mA.fG.m U.fA.mG.fA.mC.fA.mA.fA.mU.f G.mU.fU.mG*mC*mG	IA1730	1133	H1*mC*mA.mA.mC.mA.mU.fU.m U.fG.fU.fC.fU.mA.mC.mU.mG.mA .mA.mG.mC*mA*dQ	IS2149	1138
RD5398	mU*fA*mU.fC.mC.fG.mU.fG.m C.fA.mU.fC.mU.fU.mU.fC.mU.f U.mG.fG*mC*mG	IA1731	1134	H4*mC*mG.mC.mC.mA.mA.mG. fA.mA.fA.fG.fA.fU.mG.mC.mA.m C.mG.mG.mA.mU*mA*dQ	IS2150	1139

The structure of compound RD4581 is shown in **FIG. 1**. The structure of compound RD4595 is shown in **FIG. 2**. The structure of compound RD4622 is shown in **FIG. 3**. The structure of compound RD4626 is shown in **FIG. 4**. The structure of compound RD4627 is shown in **FIG. 5**. The structure of compound RD4630 is shown in **FIG. 6**. The structure of compound RD4636 is shown in **FIG. 7**. The structure of compound RD4663 is shown in **FIG. 8**. The structure of compound RD4692 is shown in **FIG. 9**. The structure of compound RD4707 is shown in **FIG. 10**. The structure of compound RD4708 is shown in **FIG. 11**. The structure of compound RD4730 is shown in **FIG. 12**. The structure of compound RD4740 is shown in **FIG. 13**. The structure of compound RD4749 is shown in **FIG. 14**. The structure of compound RD4751 is shown in **FIG. 15**. The structure of compound RD4754 is shown in **FIG. 16**. The structure of compound RD4783 is shown in **FIG. 17**. The structure of compound RD4791 is shown in **FIG. 18**. The structure of compound RD4811 is shown in **FIG. 19**. The structure of compound RD4812 is shown in **FIG. 20**. The structure of compound RD5030 is shown in **FIG. 21**. The structure of compound RD5031 is shown in **FIG. 22**. The structure of compound RD5032 is shown in **FIG. 23**. The structure of compound RD5033 is shown in **FIG. 24**. The structure of compound RD5034 is shown in **FIG. 25**.

Example 1: Effect of modified oligonucleotides targeting human Factor XI in human hepatocytes

Plateable cryopreserved human hepatocytes were thawed at 37°C and poured into 50 mL of Cryopreserved Hepatocyte Recovery Medium (Gibco Catalog #CM7000) medium at 37°C. The cell suspension was centrifuged at 100×g for 10min. The supernatant was removed and the cell pellet was resuspended in 3 mL of Plating Medium (William's E Medium, no phenol red + Primary Hepatocyte Thawing and Plating Supplements (Gibco Catalog #CM3000)). The hepatocyte suspension was counted for viability and cell concentration using Trypan blue exclusion. Cell density was further diluted with Plating Medium to a final concentration of 1×10^6 viable cells per mL to provide hepatocyte suspensions. Wells of collagen I-coated 96-well microtiter plates were pre-wet with 50 µL of Plating Medium and the hepatocyte suspensions were dispensed at 50,000 cells/well using wide-bore pipet tips. The assay plates were incubated in a 37°C, 5% CO₂ humidified incubator for 5 hours to allow for cell attachment. Medium was then replaced with 100 µL of pre-warmed Incubation Medium (William's E Medium, no phenol red + Primary Hepatocyte Maintenance Supplements (Gibco Catalog #CM4000)).

The following day, compounds were diluted to a final concentration of 1 μ M in pre-warmed Incubation Medium. Medium was removed from the wells and the diluted compounds were added in triplicate. The cells were incubated in a 37°C, 5% CO₂ humidified incubator for 72 hours. Medium was removed, cells were washed with PBS and then lysed in 130 μ L of RA-1 buffer + 1% β -mercaptoethanol. RNA isolation was then performed using the NucleoSpin 96 RNA Core kit (Macherey-Nagel Catalog #740466.4). 50 ng of total RNA from each well was used for quantitative PCR (qPCR) to determine Factor XI gene expression. The following TaqMan probes were used for qPCR: human Factor XI (Hs01038035_m1) and human 18S (Hs99999901_s1). For some compound sequences that were found to overlap with the previously mentioned Factor XI probe, an alternate one was used instead: human Factor XI (Hs01030009_m1). Δ Ct values were determined by subtracting the 18S Ct value from the Factor XI Ct value. $\Delta\Delta$ Ct values were then determined by subtracting the average Δ Ct value of the untreated cells from the Δ Ct value of each test sample. Using the equation, $2^{(-\Delta\Delta Ct)}$, provided the relative amount of gene expression compared to the untreated cells. The average Factor XI inhibition for each compound is provided in the table below. Some of the compounds were tested in multiple replicates.

Table 4
Average Factor XI Inhibition

Compound	% Factor XI Inhibition at 1uM				
	Replicate 1	Replicate 2	Replicate 3	Replicate 4	Average
RD4580	ND				ND
RD4581	52	72			62
RD4582	9				9
RD4583	13				13
RD4584	ND				ND
RD4585	ND				ND
RD4586	ND				ND
RD4587	ND				ND
RD4588	ND				ND
RD4589	ND				ND
RD4590	42				42
RD4591	43				43
RD4592	51				51
RD4593	24				24
RD4594	49				49
RD4595	79				79
RD4596	49				49
RD4597	60	64			62

RD4598	ND				ND
RD4599	13				13
RD4600	4				4
RD4601	48	48			48
RD4602	5				5
RD4603	ND				ND
RD4604	ND				ND
RD4605	58	41	48		49
RD4606	ND				ND
RD4607	26				26
RD4608	48	39			44
RD4609	ND				ND
RD4610	25	63			44
RD4611	26				26
RD4612	72				72
RD4613	50	41			45
RD4614	45				45
RD4615	38				38
RD4616	58	53			56
RD4617	8				8
RD4618	ND				ND
RD4619	65	22	24	43	38
RD4620	46				46
RD4621	33				33
RD4622	52	ND	49		51
RD4623	56	27	19		34
RD4624	40				40
RD4625	40				40
RD4626	23				23
RD4627	38				38
RD4628	21				21
RD4629	74	3	41	56	43
RD4630	23				23
RD4631	29				29
RD4632	34				34
RD4633	28				28
RD4634	ND				ND
RD4635	53	ND	ND		53
RD4636	58	6	ND		32
RD4637	20				20
RD4638	51	22	20		31
RD4639	ND				ND
RD4640	37				37
RD4641	12				12

RD4642	52	24	52		43
RD4643	9				9
RD4644	27				27
RD4645	11				11
RD4646	32				32
RD4647	ND				ND
RD4648	ND				ND
RD4649	30				30
RD4650	25				25
RD4651	54	39	65		53
RD4652	43				43
RD4653	46				46
RD4654	49	ND	ND		49
RD4655	69	43			56
RD4656	58	61	28	60	60
RD4657	41				41
RD4658	38				38
RD4659	9				9
RD4660	51		1		26
RD4661	7				7
RD4662	27				27
RD4663	65	3	ND		34
RD4664	21				21
RD4665	12				12
RD4666	7				7
RD4667	ND				ND
RD4668	49	28	37		38
RD4669	61	56	50	67	58
RD4670	70	42	62	77	63
RD4671	51	26			38
RD4672	73	30			52
RD4673	64	6	18		29
RD4674	ND				ND
RD4675	ND				ND
RD4676	ND				ND
RD4677	72	36			54
RD4678	ND				ND
RD4679	ND				ND
RD4680	ND				ND
RD4681	39				39
RD4682	ND				ND
RD4683	73	52	6	64	49
RD4684	37				37
RD4685	52	60	71		61
RD4686	ND				ND

RD4687	31				31
RD4688	84	47	1	60	48
RD4689	22				22
RD4690	6				6
RD4691	76	47	40	71	59
RD4692	72	42	56		57
RD4693	54	36			45
RD4694	54	ND	ND		54
RD4695	15				15
RD4696	37				37
RD4697	27				27
RD4698	26				26
RD4699	25				25
RD4700	26				26
RD4701	38				38
RD4702	15				15
RD4703	58				58
RD4704	38				38
RD4705	82	22	31		45
RD4706	61	51	75		62
RD4707	37				37
RD4708	47	34			41
RD4709	28				28
RD4710	37				37
RD4711	56	31			43
RD4712	50	38			44
RD4713	45	ND	12		28
RD4714	ND				ND
RD4715	58	16			37
RD4716	61	20	ND	21	34
RD4717	31				31
RD4718	ND				ND
RD4719	60	48	54	73	59
RD4720	32				32
RD4721	ND				ND
RD4722	17				17
RD4723	62	39	17	52	42
RD4724	ND				ND
RD4725	52	34	87		58
RD4726	14				14
RD4727	ND				ND
RD4728	ND				ND
RD4729	43	ND			43
RD4730	39				39
RD4731	56	32	13		34

RD4732	25				25
RD4733	27				27
RD4734	ND				ND
RD4735	ND				ND
RD4736	ND				ND
RD4737	17				17
RD4738	45				45
RD4739	74	37	7	13	33
RD4740	62				62
RD4741	29				29
RD4742	ND				ND
RD4743	46	ND	33		40
RD4744	27				27
RD4745	75	37	4	34	38
RD4746	ND				ND
RD4747	ND	ND			ND
RD4748	53	55			54
RD4749	ND				ND
RD4750	41				41
RD4751	ND				ND
RD4752	54				54
RD4753	14				14
RD4754	64				64
RD4755	ND	25			25
RD4756	ND				ND
RD4757	45	41			43
RD4758	35				35
RD4759	ND				ND
RD4760	5				5
RD4761	ND				ND
RD4762	ND				ND
RD4763	ND	32			32
RD4764	ND				ND
RD4765	71				71
RD4766	37				37
RD4767	47				47
RD4768	18				18
RD4769	ND				ND
RD4770	14				14
RD4771	31				31
RD4772	29				29
RD4773	ND	ND			ND
RD4774	49	12			30
RD4775	47				47
RD4776	21				21

RD4777	1				1
RD4778	15				15
RD4779	7				7
RD4780	3				3
RD4781	34				34
RD4782	ND				ND
RD4783	41				41
RD4784	ND	ND			ND
RD4785	40				40
RD4786	ND				ND
RD4787	3				3
RD4788	23				23
RD4789	7				7
RD4790	26				26
RD4791	ND				ND
RD4792	7				7
RD4793	22				22
RD4794	ND				ND
RD4795	16				16
RD4796	11				11
RD4797	ND				ND
RD4798	13				13
RD4799	30				30
RD4800	25				25
RD4801	ND				ND
RD4802	ND				ND
RD4803	11				11
RD4804	7				7
RD4805	ND				ND
RD4806	72	73	82	55	71
RD4807	35				35
RD4808	20				20
RD4809	2	67	54		41
RD4810	65	80	77	75	74
RD4811	33				33
RD4812	38				38
RD4813	24				24
RD4814	19				19
RD4815	18				18
RD4816	9				9
RD4817	13				13
RD4818	48	55	63		55
RD4819	39				39
RD4820	4				4
RD4821	29				29

RD4822	22				22
RD4823	29				29
RD4824	40				40
RD4825	30				30
RD4826	19				19
RD4827	16				16
RD4828	12				12
RD4829	37				37
RD4830	19				19
RD4831	ND				ND
RD4832	ND				ND
RD4833	49				49
RD4834	ND				ND
RD4835	45	ND			45
RD4836	ND				ND
RD4837	ND				ND
RD4838	29				29
RD4839	ND				ND
RD4840	27				27
RD4841	31				31

Example 2: Effect of modified oligonucleotides targeting human Factor XI in cynomolgus monkeys

Compounds RD4622, RD4626, RD4627, RD4630, RD4730, RD4749, RD4751, RD4811, RD5030, RD5031, RD5032, and RD5061 were evaluated in cynomolgus monkeys. Prior to the study the monkeys were kept in quarantine during which the animals were observed daily for general health. Twelve groups of 1 cynomolgus monkey each were injected with a single 6 mg/kg subcutaneous dose of oligonucleotide on Day 1 of the study. All animals were bled on day -6 and on day 1 (prior to dosing), 8, 15, 22, 29, 36, 43, 50, 57 and 64 for plasma analysis. The protocols described are approved by the Institutional Animal Care and Use Committee (IACUC). Circulating FXI levels were quantified using an ELISA specific for human FXI (and cross-reactive with cynomolgus), according to manufacturer's protocol (*VisuLize* FXI Antigen Kit, Affinity Biologicals #FXI-AG). FXI inhibition data are expressed as percent inhibition from baseline value (average of Day -6 and Day 1 prior to dosing) and presented in Table 6 below. Clinical chemistry was performed on Day -6 and Day 64.

Table 5
FXI %Inhibition

	Days								
Compound	8	15	22	29	36	43	50	57	64
RD4622	57	82	76	83	78	69	74	68	58
RD4626	75	90	93	92	92	92	92	92	90
RD4627	44	65	69	74	70	73	69	68	70
RD4630	60	87	93	93	92	93	92	93	93
RD4730	20	45	53	51	32	45	11	29	21
RD4749	52	71	80	83	79	81	80	79	78
RD4751	61	79	77	75	69	63	55	53	39
RD4811	14	37	36	49	31	24	32	26	16
RD5030	71	90	91	94	92	91	91	89	87
RD5031	70	87	89	90	89	88	87	86	86
RD5032	2	9	19	25	19	17	7	-3	22
RD5061	75	90	93	91	90	91	90	89	88

Example 3: Effect of modified oligonucleotides targeting human Factor XI in cynomolgus monkeys

Compounds RD4783, RD4791, RD5033, RD4812, RD5034, RD4624, RD4707, RD4754, RD5059, RD5060, RD5072, RD4692, and RD4708 were evaluated in cynomolgus monkeys. Prior to the study the monkeys were kept in quarantine during which the animals were observed daily for general health. Thirteen groups of 1 cynomolgus monkey each were injected with a single 6 mg/kg subcutaneous dose of oligonucleotide on Day 1 of the study. All animals were bled on day -6 and on days 1 (prior to dosing), 8, 15, 22, 29, 36, 43, 50, 57 and 64 for plasma analysis. The protocols described were approved by the Institutional Animal Care and Use Committee (IACUC). Circulating FXI levels were quantified using an ELISA specific for human FXI (and cross-reactive with cynomolgus), according to manufacturer's protocol (*VisuLize* FXI Antigen Kit, Affinity Biologicals #FXI-AG). FXI inhibition data are expressed as percent of inhibition from baseline value (average of Day -6 and Day 1 prior to dosing). Clinical chemistry was performed on Day -6 and Day 64.

Table 6
FXI %Inhibition

	Days								
Compound	8	15	22	29	36	43	50	57	64
RD4624	54	81	73	77	84	81	76	80	76
RD4692	63	80	79	80	82	74	65	66	59

RD4707	14	63	63	62	57	60	41	57	61
RD4708	22	32	60	49	53	48	37	51	54
RD4754	44	69	81	82	84	81	72	68	67
RD4783	48	65	73	76	79	73	71	71	75
RD4791	51	54	63	71	63	58	61	67	54
RD4812	28	76	60	55	63	53	68	45	40
RD5033	43	62	52	48	58	49	31	51	45
RD5034	29	47	60	54	52	51	32	46	38
RD5059	56	83	80	78	84	85	78	82	83
RD5060	70	90	95	95	92	93	80	87	86
RD5072	57	78	85	88	86	89	89	76	77

Example 4: Effect of modified oligonucleotides targeting human Factor XI in cynomolgus monkeys

- Compounds RD4595, RD5094, RD4663, RD4740, RD4581, RD5095, RD4636, RD5096, RD5097, and RD5098 were evaluated in cynomolgus monkeys. Prior to the study the monkeys were kept in quarantine during which the animals were observed daily for general health. Ten groups of 1 cynomolgus monkey each were injected with a single 6 mg/kg subcutaneous dose of oligonucleotide on Day 1 of the study. All animals were bled on day -6 and on days 1 (prior to dosing), 8, 15, 22, 29, 36, 43, 50, 57 and 64 for plasma analysis. The protocols described were approved by the Institutional Animal Care and Use Committee (IACUC). Circulating FXI levels were quantified using an ELISA specific for human FXI (and cross-reactive with cynomolgus), according to manufacturer's protocol (*VisuLize* FXI Antigen Kit, Affinity Biologicals #FXI-AG). FXI inhibition data are expressed as percent inhibition from baseline value (average of Day -6 and Day 1 prior to dosing). Clinical chemistry was performed on Day -6 and Day 64.

Table 7
FXI %Inhibition

	Days								
Compound	8	15	22	29	36	43	50	57	64
RD4581	66	86	86	87	84	86	73	79	77
RD4595	67	87	90	92	91	92	85	88	84
RD4636	1	14	2	38	15	21	12	36	26
RD4663	63	82	89	87	85	83	79	83	82
RD4740	16	50	66	67	61	57	58	59	39
RD5094	66	88	89	91	89	92	88	83	84

RD5095	24	67	76	75	57	63	52	56	53
RD5096	54	85	87	90	89	90	80	83	79
RD5097	57	85	88	88	86	87	78	80	79
RD5098	66	90	92	88	88	89	84	77	73

Example 5: Effect of modified oligonucleotides targeting human Factor XI in cynomolgus monkeys

- Compounds RD5321, RD4806, RD5383, RD5384 and RD5398 were evaluated in cynomolgus monkeys. Prior to the study the monkeys were kept in quarantine during which the animals were observed daily for general health. All animals were injected with a single 3 mg/kg subcutaneous dose of oligonucleotide on Day 1 of the study (n=2). All animals were bled on day -6 and on days 1 (prior to dosing), 8, 15, 22, 29, 36, 43, 50, 57 and 64 for plasma analysis. The protocols described were approved by the Institutional Animal Care and Use Committee (IACUC). Circulating FXI levels were quantified using an ELISA specific for human FXI (and cross-reactive with cynomolgus), according to manufacturer's protocol (*VisuLize* FXI Antigen Kit, Affinity Biologicals #FXI-AG). FXI inhibition data are expressed as percent inhibition from baseline value (average of Day -6 and Day 1 prior to dosing). Clinical chemistry was performed on Day -6 and Day 64.

Table 8
FXI %Inhibition

	Days								
Compound	8	15	22	29	36	43	50	57	64
RD4806	38	54	63	41	38	29	28	27	26
RD5030	46	78	83	72	72	72	67	61	56
RD5061	61	78	86	81	79	77	73	72	70
RD5094	47	77	85	79	74	68	66	67	59
RD5098	47	49	79	60	55	54	35	33	24
RD5383	39	37	67	58	51	56	52	37	37
RD5384	30	30	73	67	69	72	57	56	64
RD5398	53	53	80	68	72	71	57	64	66
RD5321	61	47	74	77	74	75	71	67	64

SEQ ID NO: 1

>NM_000128.4 Homo sapiens coagulation factor XI (FXI), transcript variant 1, mRNA

5 GACCATTTCTACACAAGCTCATTTCAGAGGAGGATGAAGACCATTTTGGAGGAAGAAAAGCACCCCTTATT
AAGAATTGCAGCAAGTAAGCCAACAAGGCTTTTTCAGGATGATTTTCTTATATCAAGTGGTACATTTTCAT
TTTATTTACTTCAGTTTTCTGGTGAATGTGTGACTCAGTTGTTGAAGGACACCTGCTTTGAAGGAGGGGAC
ATTACTACGGTCTTCACACCAAGCGCCAAGTACTGCCAGGTAGTCTGCACCTACCACCCAAGATGTTTAC
TCTTCACTTTTCACGGCGGAATCACCATCTGAGGATCCCACCCGATGGTTTACTTGTGTCTGAAAAGACAG
10 TGTTACAGAAACACTGCCAAGAGTGAATAGGACAGCAGCGATTTCTGGGTATTCTTTCAAGCAATGCTCA
CACCAAATAAGCGCTTGCAACAAAGACATTTATGTGGACCTAGACATGAAGGGCATAAACTATAACAGCT
CAGTTGCCAAGAGTGTCTCAAGAATGCCAAGAAAGATGCACGGATGACGTCCACTGCCACTTTTTACGTA
CGCCACAAGGCAGTTTTCCAGCCTGGAGCATCGTAACATTTGTCTACTGAAGCACACCCAAAACAGGGACA
CCAACCAGAATAACGAAGCTCGATAAAGTGGTGTCTGGATTTTCACTGAAATCCTGTGCACTTTCTAATC
TGGCTTGTATTAGGGACATTTTCCCTAATACGGTGTGTTGCAGACAGCAACATCGACAGTGTATGGCTCC
15 CGATGCTTTTTGTCTGTGGCCGAATCTGCACTCATCATCCCGGTTGCTTGTTTTTACCTTCTTTCCAG
GAATGGCCCCAAGAATCTCAAAGAAATCTTGTCTCCTTAAACATCTGAGAGTGGATTGCCCAGTACAC
GCATTAAAAAGAGCAAAGCTCTTCTGGTTTCAGTCTACAAAGCTGCAGGCACAGCATCCCAGTGTCTG
CCATTCTTCATTTTACCATGACACTGATTTCTTGGGAGAAGAAGTGGATATTGTTGCTGCAAAAAGTCAC
GAGGCCTGCCAGAACTGTGCACCAATGCCGTCCGCTGCCAGTTTTTTACCTATAACCCAGCCCAAGCAT
20 CCTGCAACGAAGGGAAGGGCAAGTGTTACTTAAAGCTTCTTCAAACGGATCTCCAATAAAATACTTCA
CGGGAGAGGAGGCATCTCTGGATACACATTAAGGTTGTGTAAGTGGATAATGAGTGTACCACCAAATC
AAGCCCAGGATCGTTGGAGGAAGTGCCTGTCTGTTGCTGGTGGTGGCCGTGGCAGGTGACCCGTGCACACAA
CCTCACCCACTCAGAGACACCTGTGTGGAGGCTCCATCATTGGAACAGTGGATATTAACAGCCGCTCA
CTGTTTTCTATGGGGTAGAGTCACCTAAGATTTTGCCTGTCTACAGTGGCATTTTAAATCAATCTGAAATA
25 AAAGAGGACACATCTTCTTGGGGTTCAAGAAATAATAATCCATGATCAGTATAAAATGGCAGAAAGCG
GGTATGATATTGCCTTGTGAAACTGGAACACAGTGAATTACACAGATTCTCAACGACCCATATGCCT
GCCTTCCAAAGGAGATAGAAATGTAATATACACTGATTGCTGGGTGACTGGATGGGGGTACAGAAAATA
AGAGACAAAATACAAAATACTCTCCAGAAAGCCAAGATACCCTTAGTGACCAACGAAGAGTGCCAGAAGA
GATACAGAGGACATAAAATAACCCATAAGATGATCTGTGCCGGCTACAGGGAAGGAGGGAAGGACGCTTG
30 CAAGGGAGATTTCGGGAGGCCCTCTGTCTGCAACACAATGAGGTCTGGCATCTGGTAGGCATCACGAGC
TGGGGCGAAGGCTGTGCTCAAAGGGAGCGGCCAGGTGTTACACCAACGTGGTTCGAGTACGTGGACTGGA
TTCTGGAGAAAACCTCAAGCAGTGTGAATGGGTTCACAGGGGCCATTGGAGTCCCTGAAGGACCCAGGATT
TGCTGGGAGAGGGTGTGAGTTCACTGTGCCAGCATGCTTCTCCACAGTAACACGCTGAAGGGGCTTGG
TGTTTGTAAGAAAATGCTAGAAGAAAACAACTGTCAAGTTGTTATGTCCAAAACCTCCCGTTCTATGA
35 TCGTTGTAGTTTGTGTTGAGCATTCACTCTCTTTGTTTTGATCAGCTTCTATGGAGTCCAAGAATTACC
ATAAGGCAATATTTCTGAAGATTACTATATAGGCAGATATAGCAGAAAAATAACCAAGTAGTGGCAGTGGG
GATCAGGCAGAAGAACTGGTAAAAGAAGCCACCATAAATAGATTTGTTGATGAAAGATGAAAACCTGGAA
GAAAGGAGAACAAAGACAGTCTTCACCATTTTGCAGGAATCTACACTCTGCCTATGTGAACACATTTCTT
TTGTAAAGAAAGAAATGATTGCAATTTAATGGCAGATTTTCAGAAATAGTCAGGAATTCTTGTCAATTTCCA
40 TTTTAAATATATATTAATAAAAAATCAGTTCGAGTAGACACGAGCTAAGAGTGAATGTGAAGATAACAGA
ATTTCTGTGTGGAAGAGGATTACAAGCAGCAATTTACCTGGAAGTGATACCTTAGGGGCAATCTTGAAGA
TACACTTTCTGAAAAATGATTTGTGATGGATTGTATATTTATTTAAATATCTTGGGAGGGGAGGCTGA
TGGAGATAGGGAGCATGCTCAAACCTCCCTAAGACAAGCTGCTGCTGTGACTATGGGCTCCCAAAGAGCT
AGATCGTATATTTATTTGACAAAAATCACCATAGACTGCATCCATACTACAGAGAAAAACAATTAGGGC
45 GCAAATGGATAGTTACAGTAAAGTCTTCAGCAAGCAGCTGCCTGTATTCTAAGCACTGGGATTTTCTGTT
TCGTGCAAAATATTTATCTCATTATTGTTGTGATCTAGTTCAATAACCTAGAATTTGAATTGTCACCAT
AGCTTTCAATCTGTGCCAACCACTATACAATTCATCAAGTG

EQUIVALENTS AND SCOPE

It is to be understood that this disclosure is not limited to any or all of the particular embodiments described expressly herein, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular
5 embodiments only and is not intended to be limiting.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and
10 materials are now described. As will be readily apparent to the skilled artisan, and should be understood from the terms used herein, where words or terms are defined herein, their applicability should not be limited to the embodiments immediately preceding or following the definition and should be used where context permits throughout the disclosure.

All publications and patents cited in this specification are cited to disclose and
15 describe the methods and/or materials in connection with which the publications are cited. All such publications and patents are herein incorporated by references as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. Such incorporation by reference is expressly limited to the methods and/or materials described in the cited publications and patents and does not extend to any
20 lexicographical definitions from the cited publications and patents (i.e., any lexicographical definition in the publications and patents cited that is not also expressly repeated in the disclosure should not be treated as such and should not be read as defining any terms appearing in the accompanying claims). If there is a conflict between any of the incorporated references and this disclosure, this disclosure shall control. In addition, any particular
25 embodiment of this disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

30 The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such

publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features
5 which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

In the claims articles such as “a,” “an,” and “the” may mean one or more than one
10 unless indicated to the contrary or otherwise evident from the context. Wherever used herein, a pronoun in a gender (e.g., masculine, feminine, neuter, other, *etc.*) the pronoun shall be construed as gender neutral (e.g., construed to refer to all genders equally) regardless of the implied gender unless the context clearly indicates or requires otherwise. Wherever used
15 herein, words used in the singular include the plural, and words used in the plural includes the singular, unless the context clearly indicates or requires otherwise. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is
20 present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from
25 one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists (e.g., in Markush group format), each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where
30 the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted

that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included in such ranges unless otherwise specified. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are
5 expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The
10 scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the disclosure, as defined in the following claims.

15

CLAIMS

What is claimed is:

1. A compound comprising a modified oligonucleotide 14 to 23 linked nucleosides in length having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least
5 17, at least 18, at least 19, at least 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139.
2. A compound comprising a modified oligonucleotide 14 to 23 linked nucleosides in
10 length having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139.
3. A compound comprising a modified oligonucleotide having a nucleobase sequence
15 selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139.
4. The compound of any one of claims 1-3, wherein the modified oligonucleotide is at
20 least 80%, at least 85%, at least 90%, or at least 95% complementary to SEQ ID NO: 1 or 3 or the complement thereof.
5. The compound of any one of claims 1-4, wherein the modified oligonucleotide
25 comprises at least one modification selected from a modified internucleoside linkage, a modified sugar, and a modified nucleobase.
6. The compound of any one of claims 1-5, wherein the compound is double-stranded.
7. A compound comprising a first modified oligonucleotide 14 to 23 linked nucleosides
30 in length having a nucleobase sequence comprising at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-

1134, or 1136-1139 and a second modified oligonucleotide 14 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

8. A compound comprising a first modified oligonucleotide 14 to 23 linked nucleosides in length having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, or 1136-1139, and a second modified oligonucleotide 14 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

10

9. A compound comprising a first modified oligonucleotide having a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs: 10-271, 272-533, 534-795, 796-1057, 1058-1071, 1072-1085, 1086-1099, 1100-1113, 1121-1124, 1126-1129, 1131-1134, and 1136-1139, and a second modified oligonucleotide 19 to 23 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide.

10. The compound of any one of claims 7-9, wherein the first modified oligonucleotide has at least 80%, at least 85%, at least 90%, or at least 95% complementarity or identity to SEQ ID NO: 1 or 3 over its length.

11. The compound of any one of claims 7-10, wherein the first modified oligonucleotide has at least 1, at least 2, at least 3 mismatches to a region of SEQ ID NO: 1 or 3 that is the same length as the first modified oligonucleotide.

25

12. The compound of any one of claims 7-11, wherein the region of complementarity between the first modified oligonucleotide and the second modified oligonucleotide is 14 to 23 linked nucleosides in length.

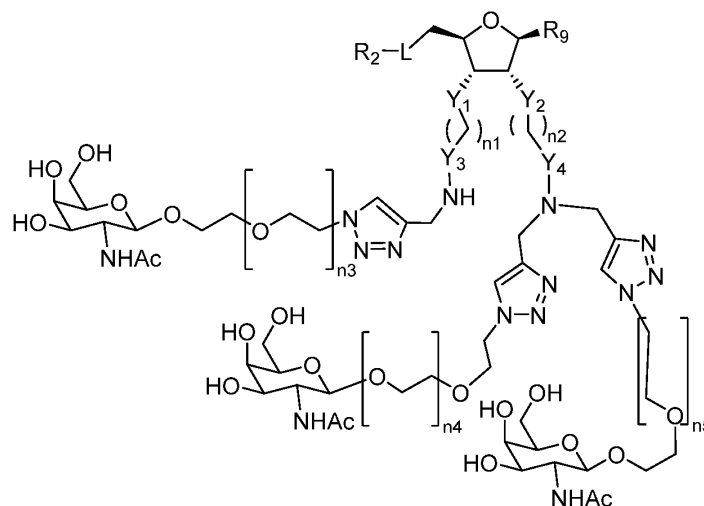
13. The compound of any one of claims 7-11, wherein the region of complementarity between the first modified oligonucleotide and the second modified oligonucleotide is 19 to 23 linked nucleosides in length.

14. The compound of any one of claims 7-11, wherein the region of complementarity between the first modified oligonucleotide and the second modified oligonucleotide is 21 to 23 linked nucleosides in length.
- 5 15. The compound of any one of claims 7-11, wherein the first modified oligonucleotide is fully complementary to the second modified oligonucleotide.
16. The compound of any one of claims 7-15, wherein the first modified oligonucleotide comprises at least one modification selected from a modified internucleoside linkage, a
10 modified sugar, and a modified nucleobase.
17. The compound of any one of claims 7-16, wherein the second modified oligonucleotide comprises at least one modification selected from the group consisting of a modified internucleoside linkage, a modified sugar, and a modified nucleobase.
15
18. The compound of any one of claims 5, 16 and 17, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage or a methylphosphonate internucleoside linkage.
- 20 19. The compound of claim 18, wherein the phosphorothioate internucleoside linkage or methylphosphonate internucleoside linkage is at the 3' terminus of the first or second modified oligonucleotide or at the 5' terminus of the first modified oligonucleotide.
20. The compound of any one of claims 5, 16 and 17, wherein the modified sugar
25 comprises a modification selected from the group consisting of a halogen, an alkoxy group and a bicyclic sugar.
21. The compound of claim 20, wherein the modified sugar comprises a 2'-F modification.
30
22. The compound of claim 20, wherein the modified sugar comprises a 2'-OMe modification.

23. The compound of any one of claims 7-15, wherein each nucleoside of the first modified oligonucleotide comprises a modified sugar.
24. The compound of any one of claims 7-15, wherein each nucleoside of the second modified oligonucleotide comprises a modified sugar.
25. The compound of claim 23 or 24, wherein the modified sugar comprises a modification selected from the group consisting of a halogen, an alkoxy group and a bicyclic sugar, or a combination thereof.
26. The compound of claim 25, wherein the modified sugar comprises a modification selected from group consisting of LNA, cEt, 2'-MOE, 2'-F, 2'-OMe, and 2'-deoxy, or a combination thereof.
27. The compound of claim 23, wherein the first modified oligonucleotide comprises no more than ten 2'-F sugar modifications.
28. The compound of claim 24, wherein the second modified oligonucleotide comprises no more than five 2'-F sugar modifications.
29. The compound of any preceding claim, comprising a conjugate group.
30. The compound of claim 29, wherein the conjugate group is attached to the 5' end of the modified oligonucleotide.
31. The compound of claim 29 or 30, wherein the conjugate group comprises a targeting moiety.
32. The compound of claim 31, wherein the targeting moiety comprises one or more GalNAc.
33. The compound of claim 32, wherein the modified oligonucleotide is the second modified oligonucleotide.

34. The compound of claim 32 or 33, wherein the one or more GalNAc are attached to the 2' or 3' position of the ribosyl ring of the 5' nucleoside of the modified oligonucleotide.

35. The compound of claim 34, wherein the 5' nucleoside is of the following formula:



5

Formula X,

wherein:

R^9 is H, adenine, guanine, thymine, cytosine, or uracil, or adenine, guanine, thymine, cytosine, or uracil, each comprising a Protecting Group (PG), a modified nucleobase, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or a nucleobase isostere;

L is a bond, a phosphodiester bond, a phosphorothioate bond, a triazole, a tetrazole, an amide, a reverse-amide, a carbamate, a carbonate, urea, alkyl, or heteroalkyl;

R^2 is the oligonucleotide sequence;

Y_1 is O, CH_2 , CH_2O , or optionally substituted NH;

Y_2 is O, CH_2 , CH_2O , or optionally substituted NH;

Y_3 is CO, SO_2 , $P(O)O$, $CH_2-O-C(O)$, $CH_2-NH-C(O)$, $CH_2-NH-SO_2$, or CH_2 ;

Y_4 is CO, SO_2 , $P(O)O$, $CH_2-O-C(O)$, $CH_2-NH-C(O)$, $CH_2-NH-SO_2$, or CH_2 ;

n_2 is 0, 1, 2, 3, 4, 5, or 6; and

each n_1 , n_3 , n_4 and n_5 is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

20

36. The compound of claim 34, wherein the 5' nucleoside is selected from any one of Formulae I-VIII and wherein R' is S and R is the portion of the modified oligonucleotide other than the 5' nucleoside.
- 5 37. The compound of claim 34, wherein the 5' nucleoside is selected from any one of Formulae I-VIII and wherein R' is O and R is the portion of the modified oligonucleotide other than the 5' nucleoside.
38. A compound comprising a first modified oligonucleotide selected from the group
10 consisting of any one of Ref ID NOs: IA1341-IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and IA1729-IA1731, and a second modified oligonucleotide 14 to 21 linked nucleosides in length fully complementary to the first modified oligonucleotide.
- 15 39. A compound comprising a first modified oligonucleotide selected from the group consisting of Ref ID NOs: IA1341-IA1602, IA1635-IA1639, IA1641-IA1643, IA1645, IA1649-IA1653, IA1724, and IA1729-IA1731, and a second modified oligonucleotide selected from the group consisting of Ref ID NOs: IS1732-IS1993, IS2026-IS2030, IS2043-IS2045, IS2047, IS2052-IS2056, IS2142, and IS2148-2150.
- 20 40. A compound comprising a first modified oligonucleotide selected from any of the Ref ID NOs listed in Table 3 and a second modified oligonucleotide selected from any of the Ref ID NOs listed in Table 3.
- 25 41. A compound of any one of claims 1-40, wherein the compound is in a pharmaceutically acceptable salt form.
42. The compound of claim 41, wherein the pharmaceutically acceptable salt is a sodium salt.
- 30 43. The compound of claim 41, wherein the pharmaceutically acceptable salt is a potassium salt.

44. A composition comprising the compound or modified oligonucleotide of any one of claims 1-43 and a pharmaceutically acceptable carrier.
45. A composition comprising a compound or modified oligonucleotide of any preceding claim, for use in therapy.
46. A method of treating, preventing or ameliorating a disease, disorder or condition associated with FXI in an individual comprising administering to the individual a compound targeted to FXI, thereby treating, preventing, or ameliorating the disease, disorder or condition.
47. A method of administering the compound or modified oligonucleotide of any one of claims 1-43 or composition of claim 45 to an individual.
48. The method of claim 46 or 47, wherein the disease, disorder or condition is FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.
49. The method of any one of claims 46-48, wherein administering the compound inhibits or reduces or improves FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g.,

Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.

5 50. A method of inhibiting expression of FXI in a cell comprising contacting the cell with a compound targeted to FXI, thereby inhibiting expression of FXI in the cell.

51. The method of claim 50, wherein the cell is in the liver of an individual.

10 52. The method of claim 51, wherein the individual has, or is at risk of having, FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an
15 autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis,
20 endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.

53. A method of reducing or inhibiting FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an
25 inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral
30 infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in an individual, comprising administering a compound targeted to FXI to the individual, thereby reducing or inhibiting FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g.,

heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis in the individual.

10

54. The method of claim 53, wherein the individual has, or is at risk of having, FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.

15

20

55. The method of any one of claims 46-54, wherein the compound is a compound targeted to FXI.

25

56. The method of any one of claims 46-55, wherein the compound or modified oligonucleotide is the compound or modified oligonucleotide of any one of claims 1-43 or composition of claim 44.

30

57. The method of claim 56, wherein the compound or composition is administered parenterally.

58. Use of a compound targeted to FXI for treating, preventing, or ameliorating a disease, disorder or condition associated with FXI.

59. The use of claim 58, wherein the disease, disorder or condition is a FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.
60. The use of claim 58 or 59, wherein the compound is a compound targeted to FXI.
61. The use of any one of claims 58-60, wherein the compound or modified oligonucleotide is the compound or modified oligonucleotide of any one of claims 1-43 or composition of claim 44.
62. Use of a compound targeted to FXI in the manufacture of a medicament for treating, preventing, or ameliorating a disease, disorder or condition associated with FXI.
63. The use of claim 62, wherein the disease is a FXI related disease, disorder or condition or a symptom thereof, a thromboembolic disease, disorder or condition (e.g., heart attack, stroke, deep vein thrombosis, pulmonary embolism, atrial fibrillation or unstable angina), an inflammatory disease, disorder or condition, an allergic disease, disorder or condition (e.g., allergic rhinitis, chronic rhinosinusitis), an autoimmune disease, disorder or condition (e.g., multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), a cardiovascular disease, disorder or condition, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type 1, 2, 3 or 4 hypersensitivity), infectious disease (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease), or pancreatitis.

64. The use of claim 62 or 63, wherein the compound is a compound targeted to FXI.
65. The use of any one of claims 62-64, wherein the compound or modified
oligonucleotide is the compound or modified oligonucleotide of any one of claims 1-43 or
5 composition of claim 44.
66. The method or use of any preceding claim, wherein the compound or composition is
administered to an individual about once every three months to about once every year.
- 10 67. The method or use of any preceding claim, wherein the compound or composition is
administered to an individual about once every three months, about once every six months, or
about once every year.