

COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF COAGULATION FACTOR XI (FXI)

Field of the Invention

The invention relates, in part, to compositions and methods that can be used to inhibit coagulation factor XI (FXI) gene expression.

Background

The dynamic balance of the circulatory system requires mechanisms that prevent blood loss, as well as those that counteract inappropriate intravascular obstructions. Plasma Coagulation Factor XI (hereinafter referred to as "FXI") synthesized in the liver, is a member of the coagulation cascade "intrinsic pathway", an essential component of the contact activation pathway, is conducive to the production of thrombin, which in turn is an important component that is engaged in the fibrin formation and offers protection from fibrinolysis. High levels of FXI are one of the risk factors for venous thrombosis. Thromboembolism may cause conditions such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Factor XI deficiency (also known as plasma thromboplastin antecedent (PTA) deficiency, Rosenthal syndrome and hemophilia C) is an autosomal recessive disease associated with a tendency to bleed. Most patients with Factor XI deficiency do not bleed spontaneously but can bleed seriously after trauma. Low levels of Factor XI can also occur in other disease states, including Noonan syndrome.

The most commonly used anticoagulants, warfarin, heparin, low molecular weight heparin (LMWH), and newer direct oral anticoagulants (DOAC) for the treatment of thrombotic disease, all possess significant drawbacks. For example, direct oral anticoagulants (DOAC) Rivaroxaban, Dabigatran, and Edoxaban all exhibit increased bleeding, especially increased GI bleeding risk. Currently, there remains a need for therapies to treat thromboembolic conditions without the risk of increased bleeding.

Accordingly, there is a need to find alternative treatments for thrombotic diseases with more attractive clinical profiles. One of the crucial technologies for developing RNAi drugs targeting FXI

represents a novel approach to reducing FXI levels and treating FXI-related diseases, such as thromboembolic conditions without increasing bleeding risk (thromboembolic conditions such as vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition). Also provided herein RNAi drugs targeting FXI to an animal at risk for inflammatory disease.

Summary of the Invention

In general, the present disclosure features novel FXI gene-specific RNAi agents, compositions that include FXI RNAi agents, and methods for inhibiting expression of a FXI gene in vitro and/or in vivo using the FXI RNAi agents and compositions that include FXI RNAi agents described herein. The FXI RNAi agents described herein can selectively and efficiently decrease, inhibit, or silence expression of a FXI gene in a subject, e.g., a human or animal subject.

According to an aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent includes a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a FXI RNA transcript, wherein the region of complementarity includes at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand.

Another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 143-173, 150-180, 380-410, 384-414, 389-419, 402-432, 419-449, 536-566, 1141-1171, 1488-1518, 1561-1591, 2111-2141, 2112-2142, 2113-2143, 2115-2145, 2111-2145 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 145-171, 152-178, 386-412, 382-408, 404-430, 1490-1516, 1563-1589, 2113-2139, 2114-2140, 2115-2141, 2117-2143, 2113-2143 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 148-168, 155-175, 385-405, 389-409, 394-414, 407-427, 424-444, 541-561, 1146-1166, 1493-1513, 1566-1586, 2116-2136, 2117-2137, 2118-2138, 2120-2140, 2116-2140 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In some embodiments, the FXI RNA transcript is SEQ ID NO: 1.

In some embodiments, the sense strand and the antisense strand may be the same length or different lengths. In some embodiments, each strand is no more than 40 nucleotides in length. In some embodiments, each strand is no more than 30 nucleotides in length. In some embodiments, each strand is no more than 25 nucleotides in length. In some embodiments, each strand is no more than 23 nucleotides in length. In some embodiments, each strand is no more than 21 nucleotides in length. In some embodiments, the sense and antisense strands of the RNAi agents can each be 15 to 49 nucleotides in length. In some embodiments, the antisense strand is independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the length of the sense strand is independently 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, or 49 nucleotides. In some embodiments, the sense strand and the antisense strand are both 21 nucleotides in length.

In some embodiments, the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 15 and 23 nucleotides in length. In some embodiments, the region of complementarity is 19-21 nucleotides in length. In some

embodiments, the region of complementarity is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to part of a FXI RNA transcript, which comprises at least 15, 16, 17, 18 or 19 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.

In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to part of a FXI RNA transcript which comprises at least 15, 16, 17, 18 or 19 contiguous nucleotides with 0, 1, 2, 3, 4 or 5 mismatches. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to a target region of a FXI RNA transcript which comprises at least 15, 16, 17, 18 or 19 contiguous nucleotides with 0, 1, 2, 3, 4 or 5 mismatches.

In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the antisense strand of the dsRNA agent is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In certain embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some embodiments, the dsRNA agent includes an antisense strand sequence set forth in any one of Tables 1-3. In some embodiments, the dsRNA agent includes the sequences set forth as a duplex sequence in any of Tables 1-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide. In certain embodiments, all or substantially all of the nucleotides of the antisense strand are modified nucleotides. In some embodiments, at least one of the modified nucleotides comprises: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, isomannide

nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide including a 5'-phosphorothioate group, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidite, or a non-natural base including nucleotide.

In some embodiments, the dsRNA agent includes an E-vinylphosphonate nucleotide at the 5' end of the antisense strand.

In certain embodiments, the dsRNA agent includes at least one phosphorothioate internucleoside linkage. In certain embodiments, the sense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the antisense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the sense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, the sense strand and the antisense strand each independently comprise two phosphorothioate linkages at the 5'-terminus. In some embodiments, the sense strand and the antisense strand each independently comprise two phosphorothioate linkages at the 3'-terminus.

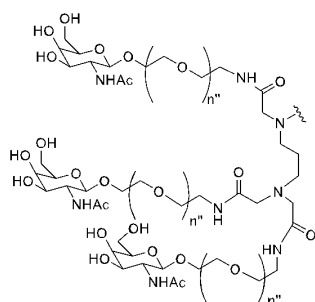
In some embodiments, all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides.

In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide, a 2'-fluoro nucleotide and an UNA modified nucleotide, wherein less than 6 modified nucleotides are 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 3 or 5 2'-fluoro nucleotides, preferably, the antisense strand comprises 5 2'-fluoro nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein less than 4 modified nucleotides are 2'-fluoro nucleotides. In certain embodiments, the sense strand comprises 3 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises at least one UNA modified nucleotide and 5 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 18 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 7, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at

position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 18 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 7, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the sense strand comprises 3 2'-fluoro nucleotides at positions 8, 11 and 13 counting from the first matching position of the 3' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the sense strand comprises 3 2'-fluoro nucleotides at positions 9, 11 and 13 counting from the first matching position of the 3' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3. In some embodiments, the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide and further includes one or more targeting groups or linking groups. In some embodiments, the one or more targeting groups or linking groups are conjugated to the sense strand. In some embodiments, the targeting group or linking group includes N-acetyl-galactosamine (GalNAc).

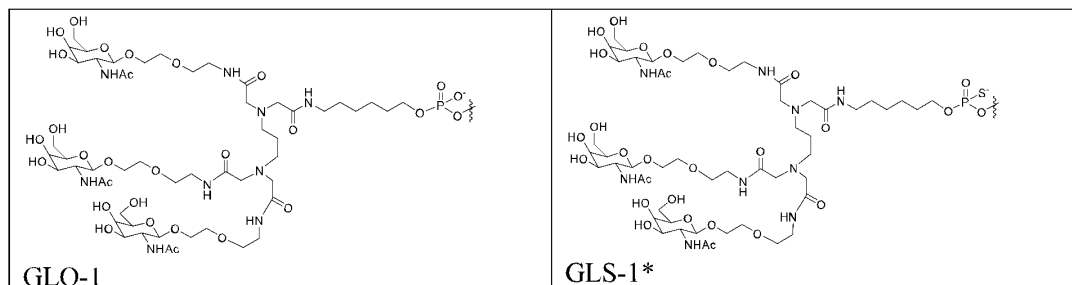
In some embodiments, the targeting group has a structure:

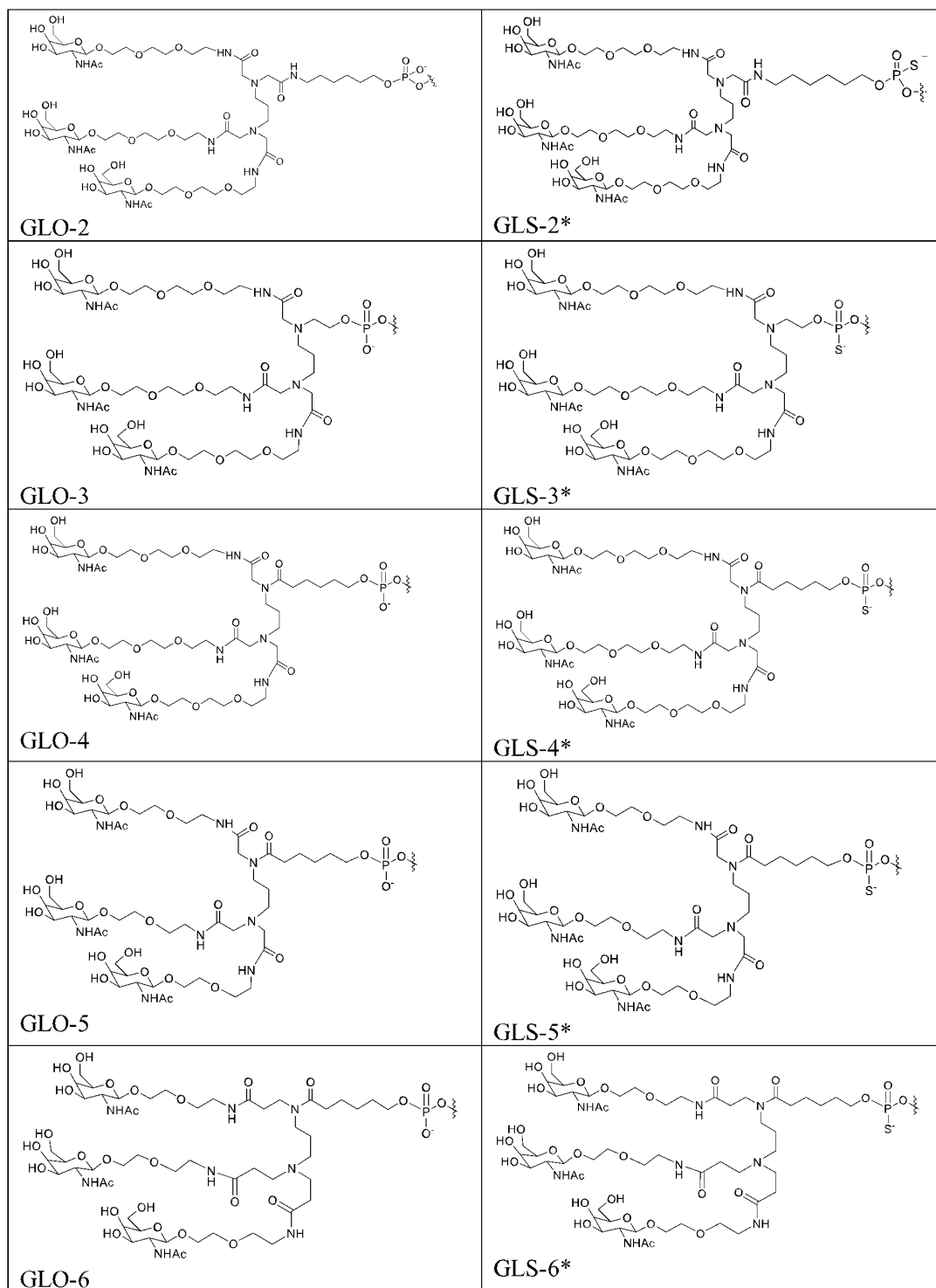


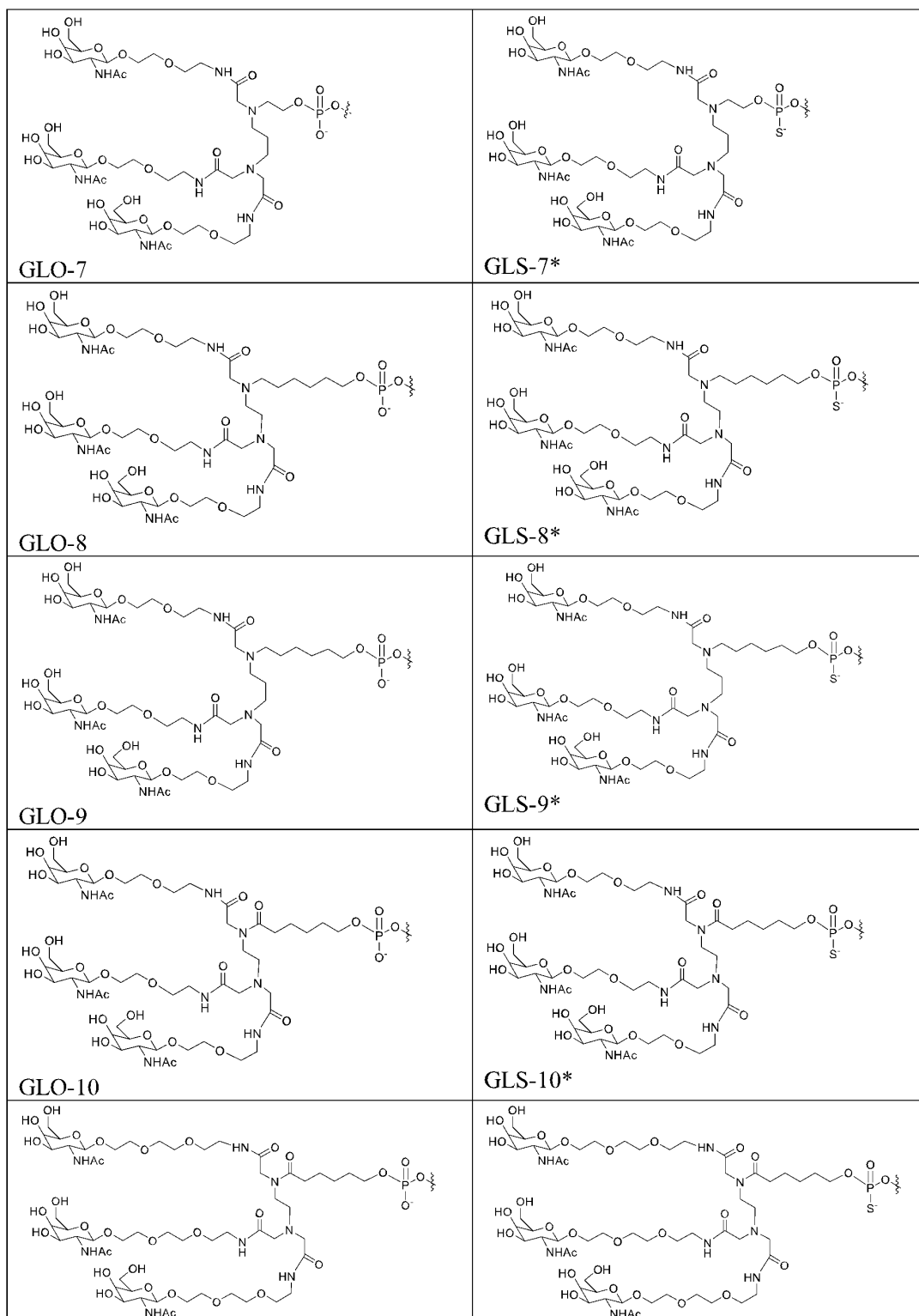
Formula I

n'' are independently selected from 1 or 2.

In some embodiments, the targeting group has a structure:







GLO-11 	GLS-11*
GLO-12 	GLS-12*
GLO-13 	GLS-13*
GLO-14 	GLS-14*
GLO-15 	GLS-15*

GLO-16	GLS-16*.
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In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 3'-terminal end of the sense strand.

In some embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each end of the sense strand includes one inverted abasic residue. In certain embodiments, each end of the sense strand includes one imann residue.

In some embodiments, the dsRNA agent has two blunt ends. In some embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In some embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides.

In certain embodiments, the dsRNA comprises a duplex selected from the group consisting of AV01124.um, AV01126.um, AV01138.um, AV01141.um, AV01152.um, AV01180.um, AV01204.um, AV01124 -19-1.um, AV01126 -19-1.um, AV01138-19-1.um, AV01141-19-1.um, AV01152-19-1.um, AV01180-19-1.um, AV01204-19-1.um. In certain embodiments, the dsRNA comprises a duplex selected from the group consisting of AV01124, AV01126, AV01138, AV01141, AV01152, AV01180, AV01204. In certain embodiments, the dsRNA comprises a duplex selected from the group consisting of AD00990, AD00991, AD00997, AD00768, AD00999, AD01002, AD00773, AD00998, AD00776, AD01018, AD00990-1, AD00991-1, AD00997-1, AD00998-1, AD00999-1, AD01002-1, AD01016-1, AD00990-2, AD00997-2, AD02352, AD02362, AD02375-1, AD02399, AD02444, AD02445, AD02446, AD02447.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to a FXI RNA transcript, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand sequence may be represented by formula (II):



wherein:

each N'_F represents a 2'-fluoro-modified nucleotide; each N'_{N1} and N'_{N2} independently represents a modified or unmodified nucleotide, N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides; each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' and n' are each independently an integer of 0 to 7.

In some embodiments, N'_{N1} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N'_{N2} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, m' is 2 and n' is 4, or m' is 2 and n' is 2. In some embodiments, m' is 1 and n' is 4, or m' is 1 and n' is 2. In some embodiments, m' is 0 and n' is 4, or m' is 0 and n' is 2.

In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 3'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, the sense strand includes two inverted abasic residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the sense strand includes two imann residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to a FXI RNA transcript, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand sequence may be represented by formula (III):



formula (III)

wherein:

each N_F represents a 2'-fluoro-modified nucleotide; each N_{M1} , N_{M2} , N_{M3} , N_{M4} , and N_{M5} independently represents a modified or unmodified nucleotide; each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7.

In some embodiments, N_{M2} , N_{M3} and N_{M4} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M2} , N_{M3} , N_{M4} , and N_{M5} have only three 2'-fluoro-modified nucleotides.

In some embodiments, N_{M1} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide and N_{M4} represents an UNA modified nucleotide.

In some embodiments, n is 1, or n is 2, or n is 3.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand is complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to a FXI RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA duplex represented by formula (IV):

sense: 5'-(N'_L)_n N'_L N'_L N'_L N'_L N'_F N'_L N'_F N'_L N'_{N1} N'_{N2} N'_L N'_L N'_L N'_L N'_L (N'_L)_m-3'

antisense: 3'-(N_L)_n N_{M1} N_L N_{M2} N_L N_F N_L N_{M3} N_L N_L N_L N_L N_{M4} N_L N_{M5} N_L N_L N_F N_L -5'

formula (IV)

wherein:

each strand is about 18 to about 30 nucleotides in length;

each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N'_{N1} , and N'_{N2} each independently represents a modified or unmodified nucleotide; N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides; each N_L and N'_L independently represents a

modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' , n' and n are each independently an integer of 0 to 7.

In some embodiments, N'_{N1} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N'_{N2} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, m' is 2 and n' is 4, or m' is 2 and n' is 2. In some embodiments, m' is 1 and n' is 4, or m' is 1 and n' is 2.

In some embodiments, N_{M2} , N_{M3} and N_{M4} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M2} , N_{M3} , N_{M4} , and N_{M5} have only three 2'-fluoro-modified nucleotides.

In some embodiments, N_{M1} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide and N_{M4} represents an UNA modified nucleotide.

In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, the sense strand includes two inverted abasic residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15. In certain embodiments, the sense strand includes two imann residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the dsRNA agent has two blunt ends. In certain embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In certain embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides.

According to an aspect of the invention, a composition is provided that includes any embodiment of the aforementioned dsRNA agent aspect of the invention. In certain embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In some embodiments, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

According to another aspect of the invention a cell is provided that includes any embodiment of an aforementioned dsRNA agent aspect of the invention. In some embodiments, the cell is a mammalian cell, optionally a human cell.

According to another aspect of the invention, a method of inhibiting the expression of a FXI gene in a cell, is provided, the method including: (i) preparing a cell including an effective amount of any embodiment of the aforementioned dsRNA agent aspect of the invention or any embodiment of an aforementioned composition of the invention. In certain embodiments, the method also includes: (ii) maintaining the prepared cell for a time sufficient to obtain degradation of the mRNA transcript of a FXI gene, thereby inhibiting expression of the FXI gene in the cell. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject by IV administration. In certain embodiments, the method also includes assessing inhibition of the FXI gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of a FXI-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the FXI-associated disease or condition and/or to a control physiological characteristic of the FXI-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the FXI gene in the subject. In some embodiments, the physiological characteristic is one or more of: the FXI mRNA level and the FXI protein level. A reduction in the expression of FXI may also be assessed indirectly by measuring a decrease in biological activity of FXI, e.g., In some embodiments, the FXI protein may be an active form (FXIa). The active form of FXI may promote converting FIX from its inactive form (FIX) to its active form (FIXa). FXI activity may be assessed with a blood test that characterizes coagulation of blood. Non-limiting examples of such

blood tests are a partial thromboplastin time (PTT) test or activated partial thromboplastin time test (aPTT or APTT). FXI activity in a test plasma sample may be assayed by adding the test plasma sample to a plasma sample that is immunodepleted of FXI and comparing clotting of the resulting combined sample to a reference sample with a reference amount of FXI.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of FXI protein is provided, the method including: administering to a subject an effective amount of an embodiment of any aforementioned dsRNA agent aspect of the invention or an embodiment of any aforementioned composition of the invention, to inhibit FXI gene expression. In some embodiments, the disease, disorder or condition associated with FXI is thromboembolic condition. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. Also provided are methods useful treating, preventing, or ameliorating a thromboembolic condition without increasing bleeding risk in an individual. In certain embodiments, the individual is at risk for a thromboembolic condition, including, but not limited to infarct, thrombosis, embolism, thromboembolism such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a thromboembolic condition include immobility, surgery (particularly orthopedic surgery), dialysis, malignancy, pregnancy, older age, use of oral contraceptives, atrial fibrillation, previous thromboembolic condition, chronic inflammatory disease, inherited or acquired prothrombotic clotting disorders and thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD). Certain outcomes associated with development of a thromboembolic condition include decreased blood flow through an affected vessel, death of tissue, and death.

In some embodiments, the method also includes: administering an additional therapeutic regimen to the subject. In some embodiments, the additional therapeutic regimen includes a treatment for the FXI-associated disease or condition. In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other pharmaceutical agents at the same time. In certain embodiments, methods comprise co-administering one or more pharmaceutical compositions described herein with one or more other

pharmaceutical agents at different times. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared separately. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include anticoagulant or antiplatelet agents. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include NSAID/Cyclooxygenase inhibitors, such as, aspirin. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include adenosine diphosphate (ADP) receptor inhibitors, such as, clopidogrel (PLAVIX) and ticlopidine (TICLID). In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include phosphodiesterase inhibitors, such as, cilostazol (PLETAL). In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include, glycoprotein IIB/IIIA inhibitors, such as, abciximab (REOPRO), eptifibatide (INTEGRILIN), tirofiban (AGGRASTAT), and defibrotide. In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include, adenosine reuptake inhibitors, such as, dipyridamole (PERSANTINE). In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include, but are not limited to, warfarin (and related coumarins), heparin, direct thrombin inhibitors (such as lepirudin, bivalirudin), apixaban, LOVENOX (enoxaparin), and small molecular compounds that interfere directly with the enzymatic action of particular coagulation factors (e.g. rivaroxaban, which interferes with Factor Xa). In certain embodiments, the anticoagulant or antiplatelet agent is administered prior to administration of a pharmaceutical composition described herein. In certain embodiments, the anticoagulant or antiplatelet agent is administered following administration of a pharmaceutical composition described herein. In certain embodiments the anticoagulant or antiplatelet agent is administered at the same time as a pharmaceutical composition described herein. In certain embodiments, the dosage unit of a co-administered anticoagulant or antiplatelet agent is the same as the dosage unit that would be administered if the anticoagulant or antiplatelet agent was administered alone. In certain embodiments the dosage unit of a co-administered anticoagulant or antiplatelet agent is lower than the dosage unit that would be administered if the anticoagulant or

antiplatelet agent was administered alone. In certain embodiments the dosage unit of a co-administered anticoagulant or antiplatelet agent is greater than the dosage unit that would be administered if the anticoagulant or antiplatelet agent was administered alone. In certain embodiments, methods may comprise co-administering a pharmaceutical composition described herein with an anti-inflammatory agent. In certain embodiments, the anti-inflammatory agent modifies a symptom of the inflammatory disease or condition. In certain embodiments, the anti-inflammatory agent modifies progression of the inflammatory disease or condition. Non-limiting examples of inflammatory diseases and conditions are autoimmune diseases (e.g. arthritis, colitis or diabetes), trauma, surgery, sepsis, allergic inflammation, and asthma. Non-limiting examples of anti-inflammatory agents include, but are not limited to, methotrexate, abatacept, infliximab, cyclophosphamide, azathioprine, corticosteroids, cyclosporin A, aminosalicylates, sulfasalazine, hydroxychloroquine, leflunomide, etanercept, efalizumab, 6-mercapto- purine (6-MP), and tumor necrosis factor-alpha (TNFalpha), and other cytokine blockers or antagonists. In certain embodiments, the anti-inflammatory agent comprises a non-steroidal anti-inflammatory drug (NSAID). In certain embodiments, NSAIDs reduce inflammatory reactions in an animal. NSAIDs include, but are not limited to, acetyl salicylic acid, choline magnesium salicylate, diflunisal, magnesium salicylate, salsalate, sodium salicylate, diclofenac, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, naproxen, nabumetone, phenylbutazone, piroxicam, sulindac, tolmetin, acetaminophen, ibuprofen, Cox-2 inhibitors, meloxicam and tramadol. In certain embodiments, methods comprise administering a pharmaceutical composition disclosed herein and an anti-inflammatory agent concomitantly or sequentially. In certain embodiments, methods comprise administering the anti inflammatory agent prior to administering the pharmaceutical composition described herein. In certain embodiments, methods comprise administering the anti-inflammatory agent after administering a pharmaceutical composition described herein. In certain embodiments, methods comprise administering the anti-inflammatory agent and a pharmaceutical composition described herein at the same time. In certain embodiments, the dosage unit of a co-administered anti-inflammatory agent is the same as the dosage unit that would be administered if the anti-inflammatory agent was administered alone. In certain embodiments the dosage unit of a co-administered anti-inflammatory agent is lower than the dosage unit that would be administered if the anti-inflammatory agent was administered alone. In certain embodiments the dosage unit of a co-administered anti-inflammatory agent is greater than the

dosage unit that would be administered if the anticoagulant or antiplatelet agent was administered alone. In certain embodiments, the co-administration of a second pharmaceutical agent enhances the anticoagulant or anti-inflammatory effect of a pharmaceutical composition described herein, such that co administration of the two results in an anticoagulant or anti-inflammatory effect that is greater than the effect of administering the pharmaceutical composition described herein. In certain embodiments, the co-administration results in anticoagulant or anti-inflammatory effects that are additive of the effects of the two when administered alone. In certain embodiments, the co-administration results in anticoagulant or anti-inflammatory effects that are supra-additive of the effects of the two when administered alone. In certain embodiments, co-administration of a second pharmaceutical agent increases an antithrombotic activity or anti-inflammatory activity of the pharmaceutical composition relative to that provided by the pharmaceutical composition alone, without increased bleeding risk. In certain embodiments, methods comprise co-administering a pharmaceutical composition described herein and an antiplatelet therapy to an animal in need thereof. In certain embodiments, the animal in need thereof may be an animal having a condition selected from thromboembolism, atrial fibrillation, a heart valve disorder, valvular heart disease, stroke, coronary artery disease (CAD), and a mechanical heart valve, and a combination thereof. In certain embodiments, administering a pharmaceutical composition described herein in combination with an antiplatelet therapy results in little to no detectable increase in risk of bleeding as compared to antiplatelet therapy alone. In certain embodiments, the risk profile or risk indications are unchanged over antiplatelet therapy alone. In certain embodiments, methods comprise administering a pharmaceutical composition described herein to a dialysis patient, including but not limited to an animal with end stage renal disease (ESRD) or chronic kidney disease (CKD), wherein the animal is co-administered at least one pharmaceutical agent selected from heparin, erythropoietin, darbopoetin, iron, Vitamin D or analogues thereof, phosphate binders, and a combination thereof. In certain embodiments, the animal receives dialysis. In certain embodiments, the pharmaceutical agent is administered at a dose that does not differ from a comparative dose that would be prescribed in the absence of administering the pharmaceutical composition.

In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the method also includes determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject. In some embodiments, a means of

determining an efficacy of the treatment in the subject comprises: (i) determining one or more physiological characteristics of the FXI-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the FXI-associated disease or condition wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject. In some embodiments, expression of the FXI gene can be assessed based on the level or change in level of any variable associated with FXI gene expression, such as FXI mRNA level, FXI protein level in the subject, or the FXI protein may be an active form (FXIa). FXI activity may be assessed with a blood test that characterizes coagulation of blood. blood tests are a partial thromboplastin time (PTT) test or activated partial thromboplastin time test (aPTT or APTT).

According to another aspect of the invention, a method of decreasing a level of FXI protein in a subject compared to a baseline pre-treatment level of FXI protein in the subject, is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any aforementioned composition of the invention, to decrease the level of FXI gene expression. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

According to another aspect of the invention, a method of altering a physiological characteristic of a FXI-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the FXI-associated disease or condition in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any aforementioned composition of the invention, to alter the physiological characteristic of the FXI-associated disease or condition in the subject. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration. In certain embodiments, the physiological characteristic is one or more of: FXI mRNA level, FXI protein level in the subject, or FXI activity. The FXI activity may cause a reduction in blood clotting activity in the animal. Blood clotting may be measured by a standard test, for example, but not limited to, activated partial thromboplastin time (aPTT) test, prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a blood sample of the animal.

According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of FXI protein is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and wherein the nucleotide sequence of the agent is about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1. In some embodiments, the equivalent region is any one of the target regions of SEQ ID NO: 1 and the complementary sequence is one provided in one of Tables 1-3. In certain embodiments, the antisense polynucleotide agent includes one of the antisense sequences provided in one of Tables 1-3.

According to another aspect of the invention, a composition including an embodiment of any aforementioned antisense polynucleotide agents is provided. In some embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents for treatment of a FXI-associated disease or condition. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In certain embodiments, the composition is formulated for subcutaneous or IV administration.

According to another aspect of the invention a cell that includes an embodiment of any of the aforementioned antisense polynucleotide agents is provided. In some embodiments, the cell is a mammalian cell, optionally a human cell.

According to another aspect of the invention, a method of inhibiting the expression of a FXI gene in a cell is provided, the method including: (i) preparing a cell including an effective amount of an embodiment of any aforementioned antisense polynucleotide agents. In some embodiments, the method also includes (ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of a FXI gene, thereby inhibiting expression of the FXI gene in the cell.

According to another aspect of the invention, a method of inhibiting expression of a FXI gene in a subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agent.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of FXI protein, the method including administering to a subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to inhibit FXI gene

expression. In certain embodiments, the disease or condition is thromboembolic condition. In certain embodiments, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. Also provided are methods useful treating, preventing, or ameliorating a thromboembolic condition without increasing bleeding risk in an individual. In certain embodiments, the individual is at risk for a thromboembolic condition, including, but not limited to infarct, thrombosis, embolism, thromboembolism such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a thromboembolic condition include immobility, surgery (particularly orthopedic surgery), dialysis, malignancy, pregnancy, older age, use of oral contraceptives, atrial fibrillation, previous thromboembolic condition, chronic inflammatory disease, inherited or acquired prothrombotic clotting disorders and thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD). Certain outcomes associated with development of a thromboembolic condition include decreased blood flow through an affected vessel, death of tissue, and death.

According to another aspect of the invention, a method of decreasing a level of FXI protein in a subject compared to a baseline pre-treatment level of FXI protein in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to decrease the level of FXI gene expression. In certain embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration.

Brief Description of the Sequences

SEQ ID NO: 1 and SEQ ID NO: 2 (reverse complement) are Homo sapiens coagulation factor XI mRNA [NCBI Reference Sequence: NM_000128.4].

SEQ ID NO: 3 and SEQ ID NO: 4 (reverse complement) are Mus musculus (house mouse) coagulation factor XI mRNA [NCBI Reference Sequence: NM_001411665.1].

SEQ ID NOs: 5-198,715-1000 are shown in Table 1 and are sense strand sequences.

SEQ ID NOs: 199-392,1001- 1286 are shown in Table 1 and are antisense strand sequences.

SEQ ID NOs: 393-586, 1287-1568 are shown in Table 2 with chemical modifications.

SEQ ID NOs: 587-714, 1567-1728 are shown in Table 3. A delivery molecule is indicated as "GLX-__" at the 3' end or 5' end of each sense strand.

Detailed Description

The invention in part, includes RNAi agents, for example, though not limited to double stranded (ds) RNAi agents, which are capable of inhibiting coagulation factor XI (FXI) gene expression. The invention, in part also includes compositions comprising FXI RNAi agents and methods of use of the compositions. FXI RNAi agents disclosed herein may be attached to delivery compounds for delivery to cells, including to hepatocytes. Pharmaceutical compositions of the invention may include at least one dsRNA FXI agent and a delivery compound. In some embodiments of compositions and methods of the invention, the delivery compound is a GalNAc-containing delivery compound. FXI RNAi agents delivered to cells are capable of inhibiting FXI gene expression, thereby reducing activity in the cell of the FXI protein product of the gene. dsRNAi agents of the invention can be used to treat FXI -associated diseases and conditions.

In some embodiments of the invention reducing FXI expression in a cell or subject treats a disease or condition associated with FXI expression in the cell or subject, respectively. Non-limiting examples of diseases and conditions that may be treated by reducing FXI activity are: thromboembolic condition, such as deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition, or other diseases for which reducing a level and activity of FXI protein is medically beneficial.

As used herein, "G," "C," "A" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, and uracil as a base, respectively. However, it will be understood that the term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person understands that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine,

or adenine may be replaced in the nucleotide sequences of the invention by a nucleotide containing, for example, inosine. Sequences comprising such replacement moieties are embodiments of the invention.

As used herein, "coagulation factor XI gene expression" used interchangeably with the term "FXI" refers to the naturally occurring gene that encodes a cell inducing coagulation factor XI protein from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise. The term also refers to fragments and variants of native FXI that maintain at least one in vivo or in vitro activity of a native FXI. As used herein, the term "inhibiting coagulation factor XI gene expression" includes inhibiting the expression of the FXI gene as well as variants (e. g., naturally occurring variants) or mutants of the factor XI gene, inhibiting the expression of FXI mRNA, inhibiting the expression of FXI RNA transcript, and/or inhibiting the expression of FXI protein. The FXI gene may be a wild-type human FXI gene, a mutant human FXI gene, or a transgenic human FXI gene in the case of genetically manipulated cells, cell groups, or organisms. The amino acid and complete coding sequences of the reference sequence of the human FXI gene may be found in, for example, GenBank Ref Seq Accession No. NM_000128.4 (SEQ ID NO: 1 and SEQ ID NO:2). Mus musculus (house mouse) coagulation FXI mRNA GenBank Ref Seq Accession No. NM_001411665.1 (SEQ ID NO:3 and SEQ ID NO:4); Additional examples of FXI mRNA sequences are readily available using publicly available databases, e.g., GenBank, UniProt, Ensembl and OMIM, for example, NM_001354804.2 (coagulation factor XI isoform 3 precursor).

"Factor XI", "FXI", "Factor 11" and "F11" is used interchangeably herein. "Factor XI nucleic acid" or "Factor XI nucleic acid" means any nucleic acid encoding FXI. For example, in certain embodiments, a Factor XI nucleic acid includes a DNA sequence encoding Factor XI, an RNA sequence transcribed from DNA encoding Factor XI (including genomic DNA comprising introns and exons), and an mRNA sequence encoding Factor XI. "Factor XI mRNA" means an mRNA encoding a Factor XI protein.

"FXI specific inhibitor" refers to any agent capable of specifically inhibiting the expression of FXI mRNA and/or FXI protein at the molecular level. For example, FXI specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of FXI mRNA and/or FXI protein. In certain embodiments, by specifically modulating FXI mRNA level and/or FXI protein expression, FXI

specific inhibitors may affect components of the inflammatory pathway. Similarly, in certain embodiments, FXI specific inhibitors may affect other molecular processes in an animal.

The following describes how to make and use compositions comprising FXI single-stranded (ssRNA) and dsRNA agents to inhibit FXI gene expression, as well as compositions and methods for treating diseases and conditions caused by or modulated by FXI gene expression. The term “RNAi” is also known in the art, and may be referred to as “siRNA”.

As used herein, the term “RNAi” refers to an agent that comprises RNA and mediates targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. As is known in the art, an RNAi target region refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a gene, including messenger RNA (mRNA) that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion. A target sequence may be from 8-30 nucleotides long (inclusive), from 10 - 30 nucleotides long (inclusive), from 12 - 25 nucleotides long (inclusive), from 15 - 23 nucleotides long (inclusive), from 16 -23 nucleotides long (inclusive), or from 18 – 23 nucleotides long (inclusive), including all shorter lengths within each stated range. In some embodiments of the invention, a target sequence is 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides long. In certain embodiment a target sequence is between 9 and 26 nucleotides long (inclusive), including all sub-ranges and integers there between. For example, though not intended to be limiting, in certain embodiments of the invention a target sequence is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides long, with the sequence fully or at least substantially complementary to at least part of an RNA transcript of a FXI gene. Some aspects of the invention include pharmaceutical compositions comprising one or more FXI dsRNA agents and a pharmaceutically acceptable carrier. In certain embodiments of the invention, a FXI RNAi as described herein inhibits expression of FXI protein.

As used herein, a “dsRNA agent” means a composition that contains an RNA or RNA-like (e.g., chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting translation of messenger RNA (mRNA) transcripts of a target mRNA in a sequence specific manner. Although not wishing to be limited to a particular theory, dsRNA agents of the invention may operate through the RNA interference mechanism (i.e., inducing RNA interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or

RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). Methods for silencing genes in plant, invertebrate, and vertebrate cells are well known in the art [see, for example, (Sharp et al., *Genes Dev.* 2001, 15:485; Bernstein, et al., (2001) *Nature* 409:363; Nykanen, et al., (2001) *Cell* 107:309; and Elbashir, et al., (2001) *Genes Dev.* 15:188)], the disclosure of each of which is incorporated herein by reference in its entirety.]. Art-known gene silencing procedures can be used in conjunction with the disclosure provided herein to inhibit expression of FXI.

DsRNA agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to short interfering RNAs (siRNAs), RNAi agents, micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the dsRNA agents described herein is at least partially complementary to the mRNA being targeted. It is understood in the art that different lengths of dsRNA duplex structure can be used to inhibit target gene expression. For example, dsRNAs having a duplex structure of 19, 20, 21, 22, and 23 base pairs are known to be effective to induce RNA interference (Elbashir et al., *EMBO* 2001, 20:6877-6888). It is also known in the art that shorter or longer RNA duplex structures are also effective to induce RNA interference. FXI dsRNAs in certain embodiments of the invention can include at least one strand of a length of minimally 21 nt or may have shorter duplexes based on one of the sequences set forth in any one of Tables 1-3, but minus 1, 2, 3, or 4 nucleotides on one or both ends may also be effective as compared to the dsRNAs set forth in Tables 1-3, respectively. In some embodiments of the invention, FXI dsRNA agents may have a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one or more sequences of Tables 1-3, and differ in their ability to inhibit the expression of a FXI gene by not more than 5%, 10%, 15%, 20%, 25%, or 30% from the level of inhibition resulting from a dsRNA comprising the full sequence. A sense sequence, an antisense sequence and a duplex disclosed in Tables 1-3 may be referred to herein as a “parent” sequence, meaning that the sequences disclosed in Tables 1-3 may be modified, shortened, lengthened, include substitutions, etc. as set forth herein, with the resulting sequences retaining all or at least a portion of the efficacy of their parent sequences in methods and compositions of the invention. Sense and antisense strands included in a dsRNA of the invention are independently selected. As used herein the term “independently selected” means each of two or more like elements can be selected independent of the selection of the other elements. For example, though not intended to be limiting, in preparing a dsRNA of the invention, one may select the “elements” of the two strands to include in the duplex. One selected element, the sense sequence may be SEQ ID NO: 394 (shown in Table

2) and the other selected element, the antisense sequence, may be SEQ ID NO:491, or may be SEQ ID NO: 491 that is modified, shortened, lengthened, and/or includes 1, 2, or 3 substitutions as compared to its parent sequence SEQ ID NO: 491. It will be understood that a duplex of the invention need not include both sense and antisense sequences shown as paired in duplexes in Tables 1-3. Each sense and antisense strand sequence in the tables is immediately followed by its SEQ ID NO.

Certain embodiments of compositions and methods of the invention comprise a single-strand RNA in a composition and/or administered to a subject. For example, an antisense strand such as one listed in any one of Tables 1-3 may be a composition or in a composition administered to a subject to reduce FXI polypeptide activity and/or expression of FXI gene in the subject. Tables 1-3 show certain FXI dsRNA agent antisense strand and sense strand core stretch base sequences. A single-strand antisense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand antisense agent” or an “antisense polynucleotide agent”. A single-strand sense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand sense agent” or a “sense polynucleotide agent”. The term “base sequence” is used herein in reference to a polynucleotide sequence without chemical modifications or delivery compounds. For example, the sense strand GCAAGGUCUUUCAGGAUGAA (SEQ ID NO: 6) shown in Table 1 is the base sequence for SEQ ID NO: 394 in Table 2 and for SEQ ID NO: 587 in Table 3, with SEQ ID NO: 394 and SEQ ID NO: 587 shown with their chemical modifications and a delivery compound. Sequences disclosed herein may be assigned identifiers. For example, a single-stranded sense sequence may be identified with a “Sense strand SS#”; a single stranded antisense sequence may be identified with an “Antisense strand AS#” and a duplex that includes a sense strand and an antisense strand may be identified with a “Duplex AD#/AV#”.

Table 1 includes sense and antisense strands and provides the identification number of duplexes formed from the sense and antisense strand on the same line in Table 1. In certain embodiments of the invention an antisense sequence includes nucleobase u or nucleobase a in position 1 of the antisense sequence. In certain embodiments of the invention an antisense sequence includes nucleobase u in position 1 of the antisense sequence. As used herein, the term “matching position” in a sense and an antisense strand are the positions in each strand that “pair” when the two strands are duplexed strands. For example, in a 21 nucleobases sense strand and a 21 nucleobases

antisense strand, nucleobase in position 1 of the sense strand and position 21 in the antisense strand are in “matching positions”. In yet another non-limiting example in a 23 nucleobases sense strand and a 23 nucleobases antisense strand, nucleobase 2 of the sense strand and position 22 of the antisense strand are in matching positions. In another non-limiting example, in an 18 nucleobases sense strand and an 18 nucleobases antisense strand, nucleobase in position 1 of the sense strand and nucleobase 18 in the antisense strand are in matching positions, and nucleobase 4 in the sense strand and nucleobase 15 in the antisense strand are in matching positions. A skilled artisan will understand how to identify matching positions in sense and antisense strands that are or will be duplexed strands and paired strands.

The first column in Table 1 indicates a Duplex AV# for a duplex that includes the sense and antisense sequences in the same table row. For example, Table 1 discloses the duplex assigned Duplex AV# AV01118.um, which includes sense strand SEQ ID NO: 6 and antisense strand SEQ ID NO: 200. Thus, each row in Table 1 identifies a duplex of the invention, each comprising the sense and antisense sequences shown in the same row, with the assigned identifier for each duplex shown in the first column in the row.

In some embodiments of methods of the invention, an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex comprising at least one of the base sequences set forth in Table 1, including 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 sequence modifications. In some embodiments of methods of the invention an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is attached to a delivery molecule, a non-limiting example of which is a delivery compound comprising a GalNAc compound, or a GLS-15* compound.

Table 1: Unmodified FXI RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3' direction. Duplex AV#/#AD#s are the number assigned to the duplex of the two strands in the same row in the table.

Duplex AV#	Sense Strand	SEQ ID NO	Antisense Strand	SEQ ID NO
AV01117.µm	GAACACAGGUCUUUUCAGGAUA	5	UAUCCUGAAAAAGACCUUGUUC	199
AV01118.µm	GCAAGGUCUUUCAGGAUGAA	6	UUCAUCCUGAAAAAGACCUUGC	200
AV01119.µm	GAGGUCUUUUCAGGAUGAUA	7	UAUUCAUCCUGAAAAAGACCUUC	201
AV01120.µm	CUUUUUUCAGGAUGAUUUUCA	8	UGAAAAUUCAUCCUGAAAAAGAG	202
AV01121.µm	GUUUCAGGAUGAUUUUUCUUA	9	UUAAGAAAAUUCAUCCUGAAAC	203
AV01122.µm	GAGGAUGAUUUUUCUUAUUA	10	UGAUUAUAAAGAAAAUUCAUCCUC	204
AV01123.µm	CGAUGAUUUUUCUUAUUAUCAA	11	UUUGAUUAUAAAGAAAAUUCAUCCG	205
AV01124.µm	GCUUCAGUUUUUCUGGUGAUAUGA	12	UCAUUCACCCAGAAACUAGAAGC	206
AV01125.µm	GUCAGUUUUUCUGGUGAUAUGUA	13	UCACAUUCACCCAGAAACUGAGC	207
AV01126.µm	GUUUCUGGUGAAUUGUGUACUA	14	UAGUCACACAUUUCACCCAGAAC	208
AV01127.µm	GUUGUUUACUUGUGUCCUGAA	15	UUCAGGACACAGAUAACACAC	209
AV01128.µm	GGGUUUUACUUUGUCCUGAAAA	16	UUUCAGGACACAGAUAACACCC	210
AV01129.µm	CAAAAGACAGUGUUACAGAAAAA	17	UUUUUCUGUAAACACUUGUCUUUG	211
AV01130.µm	GAAAGACAGUGUUACAGAAAAA	18	UGUUUUUCUGUAAACACUUGUCUUC	212
AV01131.µm	GGACAGUUGUUACAGAAACACA	19	UGUGUUUUUCUGUAAACACUGUCC	213
AV01132.µm	GUACAGAAACACUGCCAAAGAA	20	UUCUUUGGCAGUGUUUUCUGUAC	214
AV01133.µm	GACAGAAACACUGCCAAAGAGA	21	UCUUCUUGGCAGUGUUUUCUGUC	215
AV01134.µm	CAAAACACUGCCAAAGAGUAAAA	22	UUUCACUCUUUGGCAGUGUUUG	216
AV01135.µm	GAAACACUGCCAAAGAGUAAUA	23	UAUUCACUCUUUGGCAGUGUUC	217
AV01136.µm	GACUGCCCAAGAGUGAAUAAGGA	24	UCCUAUUUCACUCUUUGGCAGUUC	218
AV01137.µm	GAGCAGCGAUUUUCUGGUAUA	25	UAUACCCAGAAAAUUCGUGUC	219
AV01138.µm	CCAGCGAUUUUCUGGUAUUUA	26	UGAAUUAACCCAGAAAUCCGUCG	220
AV01139.µm	GGAUUUUCUGGUAUUUCUUUCA	27	UGAAAGAAUUAACCCAGAAAUCC	221
AV01140.µm	GUUUUGGUAUUUCUUUCAAGCA	28	UGUUUGAAAGAAUUAACCCAGAC	222
AV01141.µm	GCUUGGUAUUUCUUUCAAGCAA	29	UUUCUUUGAAAGAAUUAACCCAGC	223
AV01142.µm	GUUGGUAUUUCUUUCAAGCAAAA	30	UUUUGCUUGAAAGAAUUAACCCAC	224
AV01143.µm	GGGUAUUUCUUUCAAGCAAUUA	31	UAUUUGCUUGAAAGAAUUAACCCC	225

AV01144. um	CGUAUUCUUUCAAGCAUUGCA	32	UGCAUUGCUUGAAAAGAAUACG	226
AV01145. um	GUUCUUUCAAGCAUUGCUCAA	33	UUGAGCAUUGCUUGAAAAGAAC	227
AV01146. um	GUUCUUUCAAGCAUUGCUACA	34	UGUGAGCAUUGCUUGAAAGAC	228
AV01147. um	CCAUUGCUCACAGCAAAUAAA	35	UUUAUUUGGUUGAGCAUUGG	229
AV01148. um	GAAUGCUCACACCAAAUAAAG	36	UCUUAAUUUGGUUGAGCAUUC	230
AV01149. um	GAUGCUCACACCAAAUAAAGCA	37	UGCUUAUUUGGUUGAGCAUC	231
AV01150. um	GCACCAAAUAAAGCGCUUGCAA	38	UUGCAAGCGCUUAUUUGGUGC	232
AV01151. um	GACCAAAUAAAGCGCUUGCAAAA	39	UUUGCAAGCGCUUAUUUGGUC	233
AV01152. um	GAAAUAAAGCGCUUGCAACAAA	40	UUUGUUUGCAAGCGCUUAUUUC	234
AV01153. um	GAAUAAAGCGCUUGCAACAAA	41	UUUUUUUGCAAGCGCUUAUUUC	235
AV01154. um	CCUUGCACAAAGACAUUUAA	42	UUAAAUUGUCUUUGUUUGCAAGG	236
AV01155. um	GGCAACAAAGACAUUUUAUGUA	43	UACAUAAAUUGUCUUUGUUUGCC	237
AV01156. um	CCAACAAAGACAUUUUAUGUGA	44	UCACAUAAAUUGUCUUUGUUUGG	238
AV01157. um	GAAACAAAGACAUUUUAUGUGGA	45	UCCACAUAAAUUGUCUUUGUUC	239
AV01158. um	GACAAAGACAUUUUAUGUGGAA	46	UUCCACAUAAAUUGUCUUUGUC	240
AV01159. um	GAAAGCAUUUAUUGUGGACCUA	47	UAGGUCCACAUAAAUUGUCUUC	241
AV01160. um	GAGACAUUUUAUUGUGGACCUAA	48	UUAGGUCCACAUAAAUUGUCUC	242
AV01161. um	GGACAUUUUAUUGUGGACCUAGA	49	UUCUAGGUCCACAUAAAUUGUCC	243
AV01162. um	CACAUUUUAUUGUGGACCUAGAA	50	UUUUAGGUCCACAUAAAUUGUG	244
AV01163. um	GAUGUGGACCUAGACAUUGAAA	51	UUUUCAUUGUCUAGGUCCACAUUC	245
AV01164. um	GUAGACAUUGAAAGGGCAUAAAA	52	UUUUUAUUGCCCUUCAUUGUCUAC	246
AV01165. um	GAGACAUUGAAAGGGCAUAAAA	53	UGUUUAUUGCCCUUCAUUGUCUC	247
AV01166. um	GGACAUUGAAAGGGCAUAAACUA	54	UAGUUUAUUGCCCUUCAUUGUCC	248
AV01167. um	GC AUUGAAAGGGCAUAAACUUA	55	UAUAGUUUAUUGCCCUUCAUUGC	249
AV01168. um	GAUGAAAGGGCAUAAACUUAUA	56	UUUAUAGUUUAUUGCCCUUCAUUC	250
AV01169. um	GUUGAAAGGGCAUAAACUUAUAAA	57	UUUAUAGUUUAUUGCCCUUCAC	251
AV01170. um	GGAAAGGGCAUAAACUUAUAAACA	58	UGUUUAUAGUUUAUUGCCCUUCC	252
AV01171. um	CAAGGGCAUAAACUUAUAAACAA	59	UUUGUUUAUAGUUUAUUGCCCUUG	253
AV01172. um	GAGGGCAUAAACUUAUAAACAGA	60	UUCUGUUUAUAGUUUAUUGCCCUUC	254
AV01173. um	CGGCAUUAACUUAUAAACAGCUA	61	UAGCUUUUAUAGUUUAUUGCCG	255
AV01174. um	CCAUAACUUAUAAACAGCUCAA	62	UUAGAGCUUUUAUAGUUUAUUGG	256
AV01175. um	CCCAAGAGUGUCUCAAGAAUUGA	63	UCAUUCUUUGAGCACUCUUUGGG	257

AV01176.µm	GCAAGAAUGCCAAAGAAAGAU	64	UAUCUUUCUUGGC AUUCUUGC	258
AV01177.µm	GAAAGAUGCCAAGAAAGAU	65	UCAUCUUUCUUGGC AUUCUUC	259
AV01178.µm	GCCACUGCCACUUUUUCACGA	66	UCGUGAAAAAGUGGCAGUGGC	260
AV01179.µm	GCACUGCCACUUUUUCACGUA	67	UACGUGAAAAAGUGGCAGUGC	261
AV01180.µm	GACUGCCACUUUUUCACGUA	68	UUACGUGAAAAAGUGGCAGUC	262
AV01181.µm	GAGAAAUUCUUUGUCUCCUUA	69	UUAAAGAGACAAAAGAUUUCUC	263
AV01182.µm	GAUCUUUGUCUCCUUAAAAACA	70	UGUUUUAAAGGAGACAAAAGUUC	264
AV01183.µm	GUUUUGUCUCCUUAAAAACA	71	UGAUUUUUAAAGGAGACAAAAC	265
AV01184.µm	GCUCUUAAAAACAUUCUAGAA	72	UUCUCAGAUUUUUAAAGGAGC	266
AV01185.µm	GCCUUAAAAACAUUCUAGAU	73	UACUCUCAGAUUUUUAAAGGC	267
AV01186.µm	GAAACAUUCUAGAUUGAUUA	74	UAAUCCACUCUCAGAUUUUC	268
AV01187.µm	GCACGCAUUAAAAAGAGCAAA	75	UUUGCUCUUUUUAUUGCGUC	269
AV01188.µm	GCGCAUUAAAAAGAGCAAAAG	76	UCUUUGCUCUUUUUAUUGCGC	270
AV01189.µm	GUAAAAAGAGCAAAAGCUCUA	77	UAAAGAGCUUUUGCUCUUUUAC	271
AV01190.µm	GAAAGCAAAAGCUCUUUCUGA	78	UCAGAAAAAGAGCUUUUGCUCUC	272
AV01191.µm	GGAGCAAAAGCUCUUUCUGUA	79	UACCAAGAAAGAGCUUUUGCUC	273
AV01192.µm	CAGCAAAAGCUCUUUCUGGUA	80	UAACCAAGAAAGAGCUUUUGCUG	274
AV01193.µm	CCAAAAGCUCUUUCUGGUAUA	81	UGAAACCAGAAAGAGCUUUUGG	275
AV01194.µm	GAAAAGCUCUUUCUGGUAUA	82	UUGAAAACCAGAAAGAGCUUUC	276
AV01195.µm	CAAGAACUUGGAUUAUUGUUGA	83	UCCAACAUAUUCAGUUUCUUG	277
AV01196.µm	GAGAACUUGGAUUAUUGUUGUA	84	UAGCAACAUAUUCAGUUUCUC	278
AV01197.µm	GUGCCAGAAACUUGUGCACCAA	85	UUUGUGCACAGUUUCUGGCGAC	279
AV01198.µm	CCCAGAAACUUGUGCACCAUA	86	UAUUUGUGCACAGUUUCUGGG	280
AV01199.µm	GCGCUGCCAGUUUUUUUACCUA	87	UAGGUAAAAAAACUUGGCAGCGC	281
AV01200.µm	CCUGCCAGUUUUUUUACCUUA	88	UAUAGGUAAAAAAACUUGGCAGG	282
AV01201.µm	GAGUGUUACUUAAAAAGCUUUA	89	UGAAAGCUUUUAAGUAACACUC	283
AV01202.µm	GUGUUAUUUUUUAAAAAGCUUUA	90	UAGAAAAAGCUUUUAAGUAACACC	284
AV01203.µm	CUUUUAUUUUUUAAAAAGCUUUA	91	UAAGAAAAAGCUUUUAAGUAACAG	285
AV01204.µm	GUACUUAAAAAGCUUUUUUACAAA	92	UUUUGAAAGAAAGCUUUUAAGUAC	286
AV01205.µm	GACUUAAAAAGCUUUUUUACAAA	93	UUUUUGAAAGAAAGCUUUUAAGUC	287
AV01206.µm	GGGAUUCUCCCAACUAAAAAUACA	94	UGUAUUUUUAGUUUGGAGAUCCC	288
AV01207.µm	CGAUUCUCCCAACUAAAAAUACUA	95	UAGUAUUUUUAGUUUGGAGAUCCG	289

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AV01143-19-1.umm	GGUAAUUCUUUCAAGCAUA	128	UAUUGCUUGAAAGAAUACC	322
AV01144-19-1.umm	UAUUCUUUCAAGCAUUGCA	129	UGCAUUGCUUGAAAGAAUA	323
AV01145-19-1.umm	UCUUUCAAGCAUUGCUCAA	130	UUGAGCAUUGCUUGAAAGA	324
AV01146-19-1.umm	CUUUCAAGCAUUGCUCACA	131	UGUGAGCAUUGCUUGAAAG	325
AV01147-19-1.umm	AAUUCUCACACCACAAAUAAA	132	UUUAUUUGGUGUGAGCAU	326
AV01148-19-1.umm	AUGCUCACACCACAAAUAGA	133	UCUUAAUUUGGUGUGAGCAU	327
AV01149-19-1.umm	UGCUCACACCACAAAUAGCA	134	UGCUUAAUUUGGUGUGAGCA	328
AV01150-19-1.umm	ACCACAAUUAAGCGCUUGCAA	135	UUGCAAGCGCUUAAUUUGGU	329
AV01151-19-1.umm	CCAAAUAAAGCGCUUGCAAAA	136	UUUGCAAGCGCUUAAUUUGG	330
AV01152-19-1.umm	AAUAAAGCGCUUGCAACAAA	137	UUUGUUUGCAAGCGCUUAUU	331
AV01153-19-1.umm	AUAAAGCGCUUGCAACAAA	138	UUUUUUUGCAAGCGCUUAU	332
AV01154-19-1.umm	UUUGCAACAAAGACAUUUAA	139	UUAAAUUGCUUUUGUUGCAC	333
AV01155-19-1.umm	CAACAAAGACAUUUUAUGUA	140	UACAUAAAUUGUCUUUGUU	334
AV01156-19-1.umm	AACAAAGACAUUUUAUGUA	141	UCACAUAAAUUGUCUUUGUU	335
AV01157-19-1.umm	ACAAAAGACAUUUUAUGUGGA	142	UCCACAUAAAUUGUCUUUGU	336
AV01158-19-1.umm	CAAAAGACAUUUUAUGUGGAA	143	UUCCACAUAAAUUGUCUUUG	337
AV01159-19-1.umm	AGACAUUUUAUGUGGACCUA	144	UAGGUCCACAUAAAUUGUCU	338
AV01160-19-1.umm	GACAUUUUAUGUGGACCUAA	145	UUAGGUCCACAUAAAUUGUC	339
AV01161-19-1.umm	ACAUUUUAUGUGGACCUAGA	146	UUAAGGUCCACAUAAAUUGU	340
AV01162-19-1.umm	CAUUUAUGUGGACCUAGAA	147	UUUUAGGUCCACAUAAAUUG	341
AV01163-19-1.umm	UGUGGACCUAGACAUUGAAA	148	UUUCAUUGUCUAGGUCCACA	342
AV01164-19-1.umm	AGACAUUGAAAGGCAUAAAA	149	UUUUAAUGCCCUUCAUUGCU	343
AV01165-19-1.umm	GACAUUGAAGGCAUUAACA	150	UGUUUAUGCCCUUCAUUGUC	344
AV01166-19-1.umm	ACAUUGAAGGCAUUAACUA	151	UAGUUUAUGCCCUUCAUGU	345
AV01167-19-1.umm	AUGAAGGCAUUAACUUAUA	152	UAUAGUUUAUGCCCUUCAU	346
AV01168-19-1.umm	UGAAGGGCAUUAACUUAUA	153	UUUAAGUUUAUGCCCUUCA	347
AV01169-19-1.umm	GAAAGGC AUUAACUUAUA	154	UUUAUAGUUUAUGCCCUUC	348
AV01170-19-1.umm	AAAGGC AUUAACUUAUAACA	155	UGUUAAUAGUUUAUGCCCUU	349
AV01171-19-1.umm	AGGCAUUAACUUAUAACAA	156	UUGUUAAUAGUUUAUGCCCU	350
AV01172-19-1.umm	GGGCAUUAACUUAUAACAGA	157	UUUUUUAAUAGUUUAUGCCCU	351
AV01173-19-1.umm	GCAUUAACUUAUAACAGCUA	158	UAGCUUUUAUAGUUUAUGGC	352
AV01174-19-1.umm	AUAAACUUAUAACAGCUCAA	159	UUAGAGCUUUUAUAGUUUAU	353

AV01175-19-1.umm	CAAGAGUGGCUCAAGAAUGA	160	UCAUUCUUGAGCACUCUUG	354
AV01176-19-1.umm	AAGAAUGCCAAAGAAAGAUVA	161	UAUCUUUCUUGGC AUUCU	355
AV01177-19-1.umm	AGAAUGCCAAAGAAAGAUVA	162	UCAUCUUUCUUGGC AUUCU	356
AV01178-19-1.umm	CACUGCCACUUUUUCACGA	163	UCGUGAAAAAGUGGCAGUG	357
AV01179-19-1.umm	ACUGCCACUUUUUCACGUA	164	UACGUGAAAAAGUGGCAGU	358
AV01180-19-1.umm	CUGCCACUUUUUCACGUAA	165	UUACGUGAAAAAGUGGCAG	359
AV01181-19-1.umm	GAAAUUCUUUGUCUCCUAA	166	UUAAAGAGACAAAAGAUUUC	360
AV01182-19-1.umm	UCUUUGUCUCCUUAAAAACA	167	UGUUUUAAAGAGACAAAAGA	361
AV01183-19-1.umm	UUGUCUCCUUAAAAACAUCA	168	UGAUUUUUUAAAGAGACAAA	362
AV01184-19-1.umm	UCCUUAAAAACAUUCUGAGAA	169	UUUCUAGAUUUUUUAAAGGA	363
AV01185-19-1.umm	CUUUAAAAACAUUCUGAGAUVA	170	UACUUCUAGAUUUUUUAAAG	364
AV01186-19-1.umm	AACAUUCUGAGAGUGG AUVA	171	UAAUCCACUUCUAGAUUUU	365
AV01187-19-1.umm	ACGCAUUUAAAAAGAGCAAAA	172	UUUGCUUUUUUAAUUGCGU	366
AV01188-19-1.umm	GC AUUAAAAAGAGCAAAAGA	173	UCUUUGCUUUUUUAAUUGC	367
AV01189-19-1.umm	AAAAAGAGCAAAAGCUCUVA	174	UAAAGAGCUUUUGCUCUUUU	368
AV01190-19-1.umm	AGAGCAAAAGCUCUUUCUGA	175	UCAGAAAAAGAGCUUUUGCUCU	369
AV01191-19-1.umm	AGCAAAAGCUCUUUCUGGUA	176	UACCAGAAAAAGCUCUUUGCU	370
AV01192-19-1.umm	GC AAAAGCUCUUUCUGGUA	177	UAACCAGAAAAAGCUCUUUGC	371
AV01193-19-1.umm	AAAAGCUCUUUCUGG UUCA	178	UGAAACCAGAAAAAGCUCUU	372
AV01194-19-1.umm	AAGCUCUUUCUGG UUCA	179	UUGAAAAACCAGAAAAAGCUCU	373
AV01195-19-1.umm	AGAACUUGGAU AUUGUGCA	180	UGCAACAAU AUUCCAGUUCU	374
AV01196-19-1.umm	GAAACUGGAU AUUGUGCUVA	181	UAGCAACAAU AUUCCAGUUC	375
AV01197-19-1.umm	GCCAGAAACUUGGCACCCAA	182	UUUGUGCACAGUUUCUGGC	376
AV01198-19-1.umm	CAGAAACUUGGCACCCAUVA	183	UAUUUGUGCACAGUUUCUG	377
AV01199-19-1.umm	GCUGGCCAGUUUUUACCUVA	184	UAGGUAAAAAAACUUGGCAGC	378
AV01200-19-1.umm	UGCCAGUUUUUUAACCUVA	185	UAUAGGUAAAAAAACUUGGCA	379
AV01201-19-1.umm	GUUUUACUUUAAAGC UUCA	186	UGAAAGC UUUUAAAGU AACAC	380
AV01202-19-1.umm	UGUUUACUUUAAAGC UUCA	187	UAGAAAAAGC UUUUAAAGU AACCA	381
AV01203-19-1.umm	GUUUACUUUAAAGC UUCUVA	188	UAAAGAAAGC UUUUAAAGU AAC	382
AV01204-19-1.umm	ACUUUAAAGC UUUUCUUCAAAA	189	UUUUAAAGAAAGC UUUUAAAGU	383
AV01205-19-1.umm	CUUUAAAGC UUUUCUUCAAAA	190	UUUUUAAAGAAAGC UUUUAAAG	384
AV01206-19-1.umm	GAUCUCCCAACUUAAAAUACA	191	UGUAUUUUUAGUUUGAGAUUC	385

AV01207-19-1. um	AUCUCCAACUAAAAUACUA	192	UAGUAAUUUAGUUGGAGAU	386
AV01208-19-1. um	UCUCCAACUAAAAUACUUA	193	UAGUAAUUUAGUUGGAGAU	387
AV01209-19-1. um	AUCUCUGGUAUACACAUUAA	194	UUAAUUGUUAUCCAGAGAU	388
AV01210-19-1. um	UCUCUGGUAUACACAUUAAA	195	UUUAAUUGUUAUCCAGAGA	389
AV01211-19-1. um	CUUCUGGAUACACAUUAAAGA	196	UCUUAAUUGUUAUCCAGAG	390
AV01212-19-1. um	UCUGGAUACACAUUAAAGGA	197	UCCUUAAUGUGUAUCCAGA	391
AV01213-19-1. um	GUGUAAAABUGGAUAAUGAA	198	UUCAUUAUCCAUUUUACAC	392
AV05205. um	GUUCAAGAUGAUUUUUCUUAUA	715	UAUAAAGAAAAUACAUCUUGAAC	1001
AV05206. um	GUCAAGAUGAUUUUUCUUAUAA	716	UUAAUAAAGAAAAUACAUCUUGAC	1002
AV05207. um	GAGUUUCUGUGUAUUGUGUA	717	UCACACAUUACAACCAAGAAACUC	1003
AV05208. um	CGGUAAUUCUUUCAAGCAUUGA	718	UCAUUGCUUGAAAGAAUACCG	1004
AV05209. um	GCAAGCAAUUGCUCACACCAAA	719	UUUGGUGUGAGCAUUGCUUGC	1005
AV05210. um	GAAAGCAAUUGCUCACACCAAAA	720	UUUUUGUGUGAGCAUUGCUUC	1006
AV05211. um	GUGCAACAAAGACAUUUUAUGA	721	UCAUAAAUGUCUUUGUUGCAC	1007
AV05212. um	CACAUGAAGGGCAUAAACUAA	722	UUAGUUUAUUGCCCUUCAUGUG	1008
AV05213. um	GGGGCAUAAACUUAUAACAGCA	723	UGCUGUUAUAGUUUAUUGCCCC	1009
AV05214. um	GUAGAUGUACCACCAAAAUUCA	724	UGAUUUUUUGUGUACACUCAC	1010
AV05215. um	GGAGUGUACCACCAAAAUUCA	725	UUGAUUUUUGUGUGUACACUCC	1011
AV05216. um	CAGUGUACCACCAAAAUUCAAA	726	UUUGAUUUUGUGUGUACACTUG	1012
AV05217. um	CGGUAGAUGCACCUAAAGAUUA	727	UAAUCUUAGGUGACUCUACCG	1013
AV05218. um	CUCACCUAAAGAUUUUGCGUGA	728	UCACGCAAAAUCUUAGGUGAG	1014
AV05219. um	GCACCUAAAGAUUUUGCGUGUA	729	UACACGCAAAAUCUUAGGUGC	1015
AV05220. um	GCCUAAAGAUUUUGCGUGUCUA	730	UAGACACGCAAAAUCUUAGGC	1016
AV05221. um	GCUAAAGAUUUUGCGUGUCUAA	731	UUAGACACGCAAAAUCUUAGC	1017
AV05222. um	GAAAGAUUUUGCGUGUCUACAA	732	UUUGUAGACACGCAAAAUCUUC	1018
AV05223. um	GCAAGUGGCAUUUUAAAUUCAAA	733	UUUGAUUUUAAAUUGCCACUCC	1019
AV05224. um	GAGUGGCAUUUUAAAUUCAUUA	734	UAUUGAUUUUAAAUUGCCACUC	1020
AV05225. um	GUUUAAAUUCAAUUCUGAAAAUUA	735	UUAAUUUCAGAUUGAUUUUAAAC	1021
AV05226. um	GUAAAUAUCAUUCUGAAAAUAAA	736	UUUUAAUUUCAGAUUUUGAUUUAC	1022
AV05227. um	GCACAUUCUUUCUUUGGGGUUA	737	UAAACCCCAAAGAAAGAUUGGC	1023
AV05228. um	GCAUUCUUUCUUUGGGGUUCA	738	UUGAACCCCAAAGAAAGAUUGC	1024
AV05229. um	GAUUCUUUCUUUGGGGUUCAAA	739	UUUGAACCCCCAAAGAAAGAUUC	1025

AV05230. um	GUUCUUUGGGGUUCAAGAAAA	740	UUUUUCUUGAACCCCAAAAGAAC	1026
AV05231. um	GUUCUUUGGGGUUCAAGAAAAUA	741	UAUUUCUUUGAACCCCAAAAGAC	1027
AV05232. um	GCUUUUGGGGUUCAAGAAAAUA	742	UUUAUUUCUUUGAACCCCAAAAGC	1028
AV05233. um	CGGUUCAAGAAAAUAUAUAUCA	743	UGAUUAUAUUUCUUUGAACCG	1029
AV05234. um	GGAAAAUAUAUCCAUUGAUA	744	UGAUCAUGGAUAUAUAUUUC	1030
AV05235. um	GCAGUAUAAAAUUGGCAGAAAA	745	UUUUUCUGCCAUUUUAUACUC	1031
AV05236. um	GAGUAUAAAAUUGGCAGAAAAGA	746	UCUUUCUGCCAUUUUAUACUC	1032
AV05237. um	CGUAUUAUAUUUGCCUUUGUA	747	UAACAAAGGCAAUUAUCAUACCG	1033
AV05238. um	GGAUUAUUGCCUUUGUUGAAAAA	748	UGUUUCAACCAAGGCAAUUAUCC	1034
AV05239. um	CAUAUUUGCCUUUGUUGAAACUA	749	UAGUUUCAACCAAGGCAAUUAUG	1035
AV05240. um	GAUUUGCCUUUGUUGAAACUUGA	750	UCCAGUUUCAACCAAGGCAAUUC	1036
AV05241. um	CCCUUUGUUGAAAAACUGGAAAA	751	UGUUUCCAGUUUCAACCAAGGG	1037
AV05242. um	GGUUGAAAACUUGGAAACCAACA	752	UUUGUGUUUCCAGUUUCAACC	1038
AV05243. um	GGGAAACCAACAGUUAUAUAACA	753	UGUAAUUCAACUGUGGUUUUCC	1039
AV05244. um	GAAACCAAGUUAUAUAUAACA	754	UUUGUUAUUUCAACUGUGGUUC	1040
AV05245. um	GCCACAGUUAUAUAUAACAAGAA	755	UUUCUGUUAUUUCAACUGUGGC	1041
AV05246. um	GCAAAAUAACUCCCAAGAAAGA	756	UCUUUCUGGAGAGUAUUUUUC	1042
AV05247. um	GCUCUCCAGAAAAAGCCAAGAUUA	757	UAUCUUUGGCUUUUCUGGAGAGC	1043
AV05248. um	GAAAGCCAAGAUACCCUUAUAUA	758	UACUAAAGGUAUCUUUGGCUUC	1044
AV05249. um	CAAGAGAUACAGAGGACAUUA	759	UUAUUGUCCUCUGUAUCUCUUG	1045
AV05250. um	CAGAUACAGAGGACAUAAAAA	760	UUUUUAUUGUCCUCUGUAUCUG	1046
AV05251. um	GACAGAGGACAUAAAAUAUAACA	761	UGUUAAUUUAUUGUCCUCUGUC	1047
AV05252. um	GCAGAGGACAUAAAAUAUAACCA	762	UGGUUAUUUAUUGUCCUCUGC	1048
AV05253. um	CAGGACAUAAAAUAUAACCAUA	763	UAUGGUAUUUUUAUUGUCCUG	1049
AV05254. um	CACAUAAAAUAACCCAUUAAGA	764	UUUUUAUUGGUAUUUUUAUUGUG	1050
AV05255. um	GCAUAAAAUAACCCAUUAAGAA	765	UUUUUAUUGGUAUUUUUAUUGC	1051
AV05256. um	GACCCAUUAAGAUUCUUGUA	766	UACACAGAUCAUCUUUAUUGGUC	1052
AV05257. um	CGACUUGAUUUUCUGAGAAAAA	767	UUUUUCUCCAGAAUCCAGUCCG	1053
AV05258. um	CACUUGAUUUUCUGAGAAAAACA	768	UGUUUUUCUCCAGAAUCCAGUG	1054
AV05499. um	GUCAUUUCAGAGAGGAUGAAAA	769	UUUUCAUCCUCCUUGAAUUGAC	1055
AV05500. um	GAAAGUUUUUUUCAGGAUGAUA	770	UAUCAUCCUGAAAAAGACCUUC	1056
AV05501. um	GCUUUUUCAGGAUGAUUUUUUA	771	UAGAAAAUUAUCCUUGAAAAAGC	1057

AV05502. um	GGGAUGAUUUUUCUUUAUCAA	772	UUGAUAUAAAGAAAAUCAUCCC	1058
AV05503. um	GGAUUGUUUACUUGUGUCCUA	773	UAGGACACAAAGUAAACCAUCC	1059
AV05504. um	GGCCAAGAGUGAAUAGGACAA	774	UUGUCCUAUUCACUCUUUGGCC	1060
AV05505. um	GUUUUCUGGGUAUUUCUUCAAA	775	UUUGAAAGAAUACCCAGAAAC	1061
AV05506. um	GUUCUGGGUAUUUCUUCAAGA	776	UCUUGAAGAUAUACCCAGAAC	1062
AV05507. um	GC AAAUAAGCGCUUGCAACAA	777	UUUGUAGCAAGCGCUUAUUUGC	1063
AV05508. um	GGCUUGCAACAAGACAUUUUA	778	UAAAUUUCUUUUUUUGCAAGCC	1064
AV05509. um	GC AAAAGCAUUUAUUGUGGACA	779	UGUCCACAUAAAUGUCUUUUGC	1065
AV05510. um	GU AUUGUGAGCCUAGACAUUGAA	780	UUCAUUGUCUAGGUCCACAUAC	1066
AV05511. um	CUUGCC AAGAGUGUCUCAAGAA	781	UUUUUAGGACACUCUUUGGCAAG	1067
AV05512. um	CCCAAGAAAAGAUGCACGGAUUA	782	UAUCCGUGCAUCCUUUUUGGG	1068
AV05513. um	GG AAAUUCUUUUUGUCUCCUUAAA	783	UUUUAAGGAGACAAAAGAUUUCC	1069
AV05514. um	CAAAUUCUUUUUGUCUCCUUAAAA	784	UUUUAAAGGAGACAAAAGAUUUUG	1070
AV05515. um	GAAUUCUUUUUGUCUCCUUAAAAA	785	UUUUUAAAGGAGACAAAAGAUUC	1071
AV05516. um	GCUUUUUGUCUCCUUAAAAACAUA	786	UAUUGUUUUAAAGGAGACAAAAGC	1072
AV05517. um	GUUUUGUCUCCUUAAAAACAUCUA	787	UAGAUUGUUUUAAAGGAGACAAAC	1073
AV05518. um	GUUGUCUCCUUAAAAACAUCUGA	788	UCAGAUUGUUUUAAAGGAGACAC	1074
AV05519. um	GGUCUCCUUUAAAAACAUCUGAA	789	UUCAGAUUGUUUUAAAGGAGACC	1075
AV05520. um	GUCCUUUAAAAACAUCUGAGAGA	790	UUCUCUAGAUUGUUUUAAAGGAC	1076
AV05521. um	GUUAAAAACAUCUGAGAGUGGA	791	UCCACUCUCAGAUUGUUUUAAAC	1077
AV05522. um	GAGCUCUUUUUCUGUUUUCAGUA	792	UACUGAAAAACGAAAAAGAGCUC	1078
AV05523. um	GGAAACUUGGAUUAUUUGUUGCUGA	793	UCAAGCAACAAUAUCCAGUUCC	1079
AV05524. um	CAGGAGGCAUCUCUGGGAUACA	794	UGUAUCCAGAGAUUGCCUCCUG	1080
AV05525. um	CGCAUUCUCUGGAUACACAUUA	795	UAAUUGUUAUCCAGAGAUUGCG	1081
AV05526. um	CUUUGUUAAAAUUGGAUAAUUGA	796	UCAUUUAUCCAUUUUUACACAAG	1082
AV05527. um	GGUGUAAAUAUGGAUAAUUGAGA	797	UUCUCAUUUAUCCAUUUUUACACC	1083
AV05528. um	CUGUACCAACAAAAUUCAAAGCA	798	UGCUUUGAUUUUUUGGUGUACAG	1084
AV05529. um	GGCAAGGAUUCGUUGGAGGAAACA	799	UGUUUCCUCCCAACGABUCCUGGC	1085
AV05530. um	CUAGAGUCACCCUAAAGAUUUUA	800	UAAAAUCUUUAGGUGACUCUAG	1086
AV05531. um	GGGCAUUUUUAAAUAUCAUUCUGA	801	UCAGAUUUUGAUUUUAAAAUUGCCC	1087
AV05532. um	CGCAUUUUUAAAUAUCAUUCUGAA	802	UUCAGAUUUUGAUUUUAAAAUUGCG	1088
AV05533. um	CCAUUUUUAAAUAUCAUUCUGAAAA	803	UUUUCAGAUUUUGAUUUUAAAAUUGG	1089

AV05534. um	CGACACAUCCUUCUUUGGGGA	804	UCCCCAAAGAAAGAUUGUGCG	1090
AV05535. um	GCUUUCUUUGGGUUCAAGAA	805	UUUUUGAACCCCAAGAAAGC	1091
AV05536. um	GUUUUGGGUUCAAGAAAUAAA	806	UUUAUUUUUGAACCACCAC	1092
AV05537. um	CUUCAAGAAAUAAUAUCCAA	807	UUUGAUUUUAUUUUUUUGAAG	1093
AV05538. um	GUCAAGAAAUAAUAUCCAUUA	808	UAUUGAUUUUAUUUUUUUGAG	1094
AV05539. um	GGGUAUUGAUUUUCCUUUGUA	809	UACAAGGCAUUAUUAUACCCC	1095
AV05540. um	GUUUUUGCCUUUUUGAAACUGA	810	UCAGUUUACAAGGCAAUUAC	1096
AV05541. um	GCUUUUUGAAACUUGGAAACCA	811	UGGUUUUCCAAGUUUCAACAAGC	1097
AV05542. um	CGAAACACACAGUUAUUACAA	812	UUUUAAUUUACUUUGUUUUUG	1098
AV05543. um	GUUUUUCAAGAAAGCCAAAGAUAA	813	UUUAUUUUUGGUUUUUUGGAGAC	1099
AV05544. um	GUUUCAAGAAAGCCAAAGAUACCA	814	UUGUAUUUUUUUGGUUUUUUGGAC	1100
AV05545. um	CAAAAGCCAAAGAUUACCCUUAGA	815	UUUAAGGGUAUUUUUUUGGUUUUG	1101
AV05546. um	GGCCAAAGAUUACCCUUAGUGAA	816	UUCAUUAAAGGUUAUUUUUGGCC	1102
AV05547. um	GCAAAGAUUACCCUUAGUGACCA	817	UUGUACUUAAAGGUUAUUUUUGC	1103
AV05548. um	GAAAGAUUACCCUUAGUGACCAA	818	UUUGUACUUAAAGGUUAUUUUUG	1104
AV05549. um	GGAAAGAGUUGCCAGAAGAGAUUA	819	UAUUUUUUUUUGGUUUUUUUUGCC	1105
AV05550. um	CUUUUUCAAGAAAGAUUACAGAGA	820	UUUUUUUUUUUUUUUUUUUGGACAG	1106
AV05551. um	GGAAAGAGAUUACAGAGGACAUUA	821	UAUUUUUUUUUUUUUUUUUUUGCC	1107
AV05552. um	GAGAGAUUACAGAGGACAUUAAA	822	UUUUUUUUUUUUUUUUUUUUUGCC	1108
AV05553. um	GGAUUACAGAGGACAUUAAAUA	823	UUUUUUUUUUUUUUUUUUUUUGCC	1109
AV05554. um	CAUACAGAGGACAUUAAAUAUA	824	UUUUUUUUUUUUUUUUUUUUUG	1110
AV05555. um	GGGACAUUAAAUAUAAACCAUUA	825	UUUUUUUUUUUUUUUUUUUUUGCC	1111
AV05556. um	GAAAAUAUAAACCAUUAAGAUUAAA	826	UUUUUUUUUUUUUUUUUUUUUGCC	1112
AV05557. um	GAAAUUAACCAUUAAGAUUUA	827	UUUUUUUUUUUUUUUUUUUUUGCC	1113
AV05558. um	GUAAACCAUUAAGAUUUGAUUGA	828	UUUUUUUUUUUUUUUUUUUUUGCC	1114
AV05559. um	GAAACCAUUAAGAUUUGAUUGA	829	UUUUUUUUUUUUUUUUUUUUUGCC	1115
AV05560. um	GGUACGUUGGACUUGAUUUUGA	830	UUUUUUUUUUUUUUUUUUUUUGCC	1116
AV05561. um	CUUGACUUGGACUUGAUUUUGA	831	UUUUUUUUUUUUUUUUUUUUUGCC	1117
AV05562. um	GGGAUUUUUUUUUUUUUUUUUUUU	832	UUUUUUUUUUUUUUUUUUUUUGCC	1118
AV05563. um	CGAUUUUUUUUUUUUUUUUUUUUU	833	UUUUUUUUUUUUUUUUUUUUUGCC	1119
AV05564. um	CAUUUUUUUUUUUUUUUUUUUUUU	834	UUUUUUUUUUUUUUUUUUUUUGCC	1120
AV05565. um	GGCAUUUUUUUUUUUUUUUUUUUU	835	UUUUUUUUUUUUUUUUUUUUUGCC	1121

AV05566.µm	GGCUAGAAGAAAAACAACUGA	836	UCAGUUUGUUUUUCUUCUAGCC	1122
AV05567.µm	CCUAGAAGAAAAACAACUGUA	837	UACAGUUUUUUUUUUUUUUUAGG	1123
AV05568.µm	GUAGAAGAAAAACAACUGUCA	838	UGACAGUUUUUUUUUUUUUUUAC	1124
AV05569.µm	GAGAAGAAAAACAACUGUCAA	839	UUGACAGUUUUUUUUUUUUUUUC	1125
AV05570.µm	CAAGAAAAACAACUGUCACAA	840	UUGUGACAGUUUUUUUUUUUUUG	1126
AV06227.µm	AAAAUUGCUAGAAGAAAAACAAA	841	UUUUUUUUUUUUUUUUUUUUUUUU	1127
AV06228.µm	AAAAUUGCUAGAAGAAAAACAAA	842	UUUUUUUUUUUUUUUUUUUUUUUU	1128
AV06229.µm	AAUUGCUAGAAAAACAACAACA	843	UGUUUUUUUUUUUUUUUUUUUUUU	1129
AV06230.µm	AUUGCUAGAAGAAAAACAACAUA	844	UAGUUUUUUUUUUUUUUUUUUUUUU	1130
AV06231.µm	UGCUAGAAGAAAAACAACAUGA	845	UCAGUUUUUUUUUUUUUUUUUUUU	1131
AV06232.µm	GCUAGAAGAAAAACAACAUGUA	846	UACAGUUUUUUUUUUUUUUUUUUUU	1132
AV06233.µm	CUAGAAGAAAAACAACAUGUCA	847	UGACAGUUUUUUUUUUUUUUUUUU	1133
AV06234.µm	UAGAAGAAAAACAACAUGUCAA	848	UUGACAGUUUUUUUUUUUUUUUUUU	1134
AV06235.µm	AGAAGAAAAACAACAUGUCACA	849	UGUGACAGUUUUUUUUUUUUUUUU	1135
AV06236.µm	GAAAGAAAAACAACAUGUCACAA	850	UUGUGACAGUUUUUUUUUUUUUUUU	1136
AV06237.µm	AAGAAAAACAACAUGUCACAAA	851	UUUUUUUUUUUUUUUUUUUUUUUU	1137
AV06238.µm	AGAAAAACAACAUGUCACAAGA	852	UUUUUUUUUUUUUUUUUUUUUUUU	1138
AV06239.µm	GAAAAACAACAUGUCACAAGUA	853	UUUUUUUUUUUUUUUUUUUUUUUU	1139
AV06240.µm	AAAAACAACAUGUCACAAGUUA	854	UUUUUUUUUUUUUUUUUUUUUUUU	1140
AV06241.µm	AAAAACAACAUGUCACAAGUUGA	855	UUUUUUUUUUUUUUUUUUUUUUUU	1141
AV01126-1.µm	GCGUCAGUUUUUUUUUUUUUUUU	856	UUUUUUUUUUUUUUUUUUUUUUUU	1142
AV01138-1.µm	CGAGCGAUUUUUUUUUUUUUUUUU	857	UUUUUUUUUUUUUUUUUUUUUUUU	1143
AV05205-19-1.µm	UCAGGAUGAUUUUUUUUUUUUUUU	858	UUUUUUUUUUUUUUUUUUUUUUUU	1144
AV05206-19-1.µm	CAGGAUGAUUUUUUUUUUUUUUU	859	UUUUUUUUUUUUUUUUUUUUUUUU	1145
AV05207-19-1.µm	GUUUUUUUUUUUUUUUUUUUUUUU	860	UUUUUUUUUUUUUUUUUUUUUUUU	1146
AV05208-19-1.µm	GUUUUUUUUUUUUUUUUUUUUUUU	861	UUUUUUUUUUUUUUUUUUUUUUUU	1147
AV05209-19-1.µm	AAGCAUUGCUUUCACACCAAAA	862	UUUUUUUUUUUUUUUUUUUUUUUU	1148
AV05210-19-1.µm	AGCAUUGCUUUCACACCAAAA	863	UUUUUUUUUUUUUUUUUUUUUUUU	1149
AV05211-19-1.µm	GCAACAAGAGACAUUUUUUUUUUU	864	UUUUUUUUUUUUUUUUUUUUUUUU	1150
AV05212-19-1.µm	CAUUAAGGGAUUAUAUAUAUAUA	865	UUUUUUUUUUUUUUUUUUUUUUUU	1151
AV05213-19-1.µm	GGCAUUAUAUAUAUAUAUAUAUA	866	UUUUUUUUUUUUUUUUUUUUUUUU	1152
AV05214-19-1.µm	GAGUGUACCAACCAAAAUUAUAUA	867	UUUUUUUUUUUUUUUUUUUUUUUU	1153

AV05215-19-1.umm	AGUGUACCAACCAAAAUCAA	868	UUGAUUUUGGUGUACACU	1154
AV05216-19-1.umm	GUUGACCAACCAAAAUCAA	869	UUUGAUUUUGGUGUACAC	1155
AV05217-19-1.umm	GUAGAGUCACCUAAGAUUA	870	UAAUCUUAGGUGACUCUAC	1156
AV05218-19-1.umm	CACCUAAGAUUUUGCGUGA	871	UCACGCAAAAUCCUUAGGUG	1157
AV05219-19-1.umm	ACCUAAGAUUUUUGCGUGUA	872	UACACGCAAAAUCCUUAGGU	1158
AV05220-19-1.umm	CUAAGAUUUUGCGUGUCUA	873	UAGACACGCAAAAUCCUAG	1159
AV05221-19-1.umm	UAAGAUUUUUGCGUGUCUAA	874	UUAAGACACGCAAAAUCCUUA	1160
AV05222-19-1.umm	AGAUSUUUGCGUGUCUACAA	875	UUGUAGACACGCAAAAUUCU	1161
AV05223-19-1.umm	AGUGGCAUUUUAAAUCAAA	876	UUUGAUUUUAAAUAUGCCACU	1162
AV05224-19-1.umm	GUUGCAUUUUAAAUCAAUA	877	UAUUGAUUUAAAUAUGCCAC	1163
AV05225-19-1.umm	UUAAAUCAAUUCUGAAAUAUA	878	UUAAUUUCAGAUUGAUUUUA	1164
AV05226-19-1.umm	AAAUCCAUCUGAAAUAUAUA	879	UUUUAAUUUCAGAUUUUAUU	1165
AV05227-19-1.umm	ACAUUCUUUCUUUGGGGCUUA	880	UAAACCCCAAAAGAAAGAUGU	1166
AV05228-19-1.umm	AUCUUUCUUUGGGGCUCAA	881	UUGAACCCCAAAAGAAAGAU	1167
AV05229-19-1.umm	UCUUUCUUUGGGGCUCAAAA	882	UUUGAAACCCCAAAAGAAAGA	1168
AV05230-19-1.umm	UCUUUGGGGCUUCAAGAAAUA	883	UUUUUCUUGAACCCCAAAAGA	1169
AV05231-19-1.umm	CUUUUGGGGCUUCAAGAAUAUA	884	UAUUUCUUUGAAACCCCAAAAG	1170
AV05232-19-1.umm	UUUUUGGGGCUUCAAGAAUAUA	885	UUAAUUUCUUUGAAACCCCAAA	1171
AV05233-19-1.umm	GUUCAAGAAAUAAUAUAUAUA	886	UGAUUUAAUUUUUCUUUGAAC	1172
AV05234-19-1.umm	AAAUAAUAUAUCCAUUGAUUA	887	UGAUUCAUUGGAUUUAUUUAUU	1173
AV05235-19-1.umm	AGUAUAAAUUUGGCAGAAAAA	888	UUUUUCUGCCAUUUUUUAUACU	1174
AV05236-19-1.umm	GUAAUAAAUUUGGCAGAAAAGA	889	UCUUUCUGCCAUUUUUUAUAC	1175
AV05237-19-1.umm	GUAAUGAUUAUUUGCCUUUGUA	890	UAACAAGGCAAUUAUCAUAC	1176
AV05238-19-1.umm	AUAUUUGCCUUUGUUGAAACA	891	UGUUUCAACCAAGGCAAUUAU	1177
AV05239-19-1.umm	UAUUUGCCUUUGUUGAAACUA	892	UAGUUUCAACCAAGGCAAUUA	1178
AV05240-19-1.umm	UUUGCCUUUGUUGAAACUUGA	893	UCCAGUUUCAACCAAGGCAA	1179
AV05241-19-1.umm	CUUGUUUGAAACUUGGAAACA	894	UGUUUCCAGUUUUUCAACAAG	1180
AV05242-19-1.umm	UUUGAAACUUGGAAACCAACAA	895	UUUGUGUUUUCCAAGUUUCAAA	1181
AV05243-19-1.umm	GAAACCAACAGUGAAUUUACA	896	UGUAAUUUCAUCUGUGGUUUC	1182
AV05244-19-1.umm	ACCACAGUGAAUUUACACACAA	897	UUUGUGAAUUUCAUCUGUGGU	1183
AV05245-19-1.umm	CACAGUGAAUUUACACACAGAA	898	UUUCUGUGAAUUUCAUCUGUG	1184
AV05246-19-1.umm	AAAAUACUUCUCCAGAAAAAGA	899	UUUUUUUCUGGAGAGAUUUUU	1185

AV05247-19-1.umm	UCUCCAGAAAGCCCAAGAU	900	UAUCUUGGCUUUCUGGAGA	1186
AV05248-19-1.umm	AGCCAAAGAUACCCCUUAGUA	901	UACUAAAGGUAUCUUGGCU	1187
AV05249-19-1.umm	AGAGAUACAGAGGACAUAA	902	UUAUGUCCUCUGUAUCUCU	1188
AV05250-19-1.umm	GAUACAGAGACAUAAAA	903	UUUUUAUGUCCUCUGUAUC	1189
AV05251-19-1.umm	CAGAGGACAUAAAAUACA	904	UGUUUAUUUAUGUCCUCUG	1190
AV05252-19-1.umm	AGAGGACAUAAAAUAACCA	905	UGGUUAUUUAUGUCCUCU	1191
AV05253-19-1.umm	GGACAUAAAAUAACCCAU	906	UAUGGUUAUUUAUGUCC	1192
AV05254-19-1.umm	CAUAAAAUAAACCCAUAGA	907	UCUUUAUGGUAUUUUUAUG	1193
AV05255-19-1.umm	AUAAAAUAAACCCAUAGAA	908	UUCUUUAUGGUAUUUUUAU	1194
AV05256-19-1.umm	CCCAUAAAGAUGAUUCUGUA	909	UCACAGAUCAUCCUUAUGGG	1195
AV05257-19-1.umm	ACUGGAUUCUGGAGAAAA	910	UUUUUUCUCCAGAAUCCAGU	1196
AV05258-19-1.umm	CUUGAUUUCUGGAGAAAA	911	UGUUUUUUCUCCAGAAUCCAG	1197
AV05499-19-1.umm	CAUUCAGAGGAGGAUUGAAA	912	UUUUCAUCCUCCUCUGAAUG	1198
AV05500-19-1.umm	AGGUCUUUUUCAGGAUUGAU	913	UAUUCAUCCUGAAAAAGACCU	1199
AV05501-19-1.umm	UUUUUCAGGAUUAUUUUUCA	914	UAGAAAAUUCAUCCUGAAAA	1200
AV05502-19-1.umm	GAUGAUUUUUUCUUUAUACAA	915	UUGAUUAUAAAGAAAAUUCAU	1201
AV05503-19-1.umm	AUUGUUUAUUUUUGUUCUA	916	UAGGACACAAGUAAACCAU	1202
AV05504-19-1.umm	CCAAAGAGUGAAUAGGACAA	917	UUUGUCCUUAUUCACUUCUUG	1203
AV05505-19-1.umm	UUUUUGGUAUUUUUCUUA	918	UUUUAAAAAGAAUACCCAGAA	1204
AV05506-19-1.umm	UUUUUGGUAUUUUUCUUA	919	UUUUUGAAAAAGAAUACCCAGAA	1205
AV05507-19-1.umm	AAAAUAAAGCGCUUUGCAACAA	920	UUUUUGCAAGCGCUUUAUUU	1206
AV05508-19-1.umm	CUUUGCAACAAAAAGACAUUU	921	UAAAUUGUCUUUUUGUUCAAG	1207
AV05509-19-1.umm	AAAGACAUUUUAUGUGGACA	922	UGUCCACAUAAAUUGUCUUU	1208
AV05510-19-1.umm	AUUGGAGACCUAGACAUUGAA	923	UUCAUUGUCUAGGUCCACAU	1209
AV05511-19-1.umm	UGCCAAAGAGUGUCCUCAAAGAA	924	UUUUUGAGCACUCCUUUGGCA	1210
AV05512-19-1.umm	CAAGAAAAAGAUUGCACGGAU	925	UAUCCGUGCAUCCUUUCUUG	1211
AV05513-19-1.umm	AAAAUCCUUUUUGUCCUUUA	926	UUUUAAAGGAGACAAAAAGAUUU	1212
AV05514-19-1.umm	AAUCCUUUUUGUCCUUUA	927	UUUUAAAGGAGACAAAAAGAUUU	1213
AV05515-19-1.umm	AUCCUUUUUGUCCUUUA	928	UUUUUAAGGAGAGACAAAGAUUU	1214
AV05516-19-1.umm	UUUUUGUCCUUUA	929	UAUUGUUUUUAAGGAGACAA	1215
AV05517-19-1.umm	UGUCCUUUUUA	930	UAGAUUUUUUAAGGAGACA	1216
AV05518-19-1.umm	GUUCCUUUUUA	931	UCAGAUUUUUUAAGGAGAC	1217

AV05519-19-1.umm	UCUCCUUAAAAACAUCUGAA	932	UUCAGAUUUUUAAAGAGA	1218
AV05520-19-1.umm	CCUUAAAAACAUCUGAGAGA	933	UCUCUCAGAUUUUUAAAG	1219
AV05521-19-1.umm	UAAAAACAUCUGAGAGUGGA	934	UCCACUCUCAGAUUUUUUA	1220
AV05522-19-1.umm	GCUCUUUCUGGUUUUCAGUA	935	UACUGAAAACCAAGAAAGAGC	1221
AV05523-19-1.umm	AACUGGAUAAUUGUUUGCUGA	936	UCAGCAACAUAUCCAGUU	1222
AV05524-19-1.umm	GGAAGCAUCUCUGGAUACA	937	UGUAUCCAGAGAUUGCCUC	1223
AV05525-19-1.umm	CAUCUCUGGAUACACAUA	938	UAAUGUGUAUCCAGAGAUUG	1224
AV05526-19-1.umm	UGUGUAAAAAUGGAUAAUGA	939	UCAUUAAUCCAUUUUACACA	1225
AV05527-19-1.umm	UGUAAAAAUGGAUAAUGAGA	940	UCUCAUUAAUCCAUUUUACA	1226
AV05528-19-1.umm	GUACCACCAAAAUCAAGCA	941	UGCUUGAUUUUUGUGGUAC	1227
AV05529-19-1.umm	CAGGAUCCGUUGAGGAACA	942	UGUUCCUCCAAACGADUCCUG	1228
AV05530-19-1.umm	AGAUGUCACCUAAAGAUUUUA	943	UAAAAUCUUAGGUGACUCU	1229
AV05531-19-1.umm	GC AUUUUUAAAAUCCAUCUGA	944	UCAGAUUGAUUUUAAAAUUG	1230
AV05532-19-1.umm	CAUUUUUAAAAUCCAUCUGAA	945	UUCAGAUUGAUUUUAAAAUUG	1231
AV05533-19-1.umm	AUUUUUAAAAUCCAUCUGAAAA	946	UUUCAGAUUUGAUUUUAAAAU	1232
AV05534-19-1.umm	ACACAUCUUUUUUUGGGGA	947	UCCCCAAAAAGAAAGAUUGU	1233
AV05535-19-1.umm	UUUUUUUUUGGGUUUCAAGAA	948	UUUUUUUUAACCCCAAGAAAA	1234
AV05536-19-1.umm	UUUGGGUUUCAAGAAAUUAAA	949	UUUAUUUUUUUGAAGACCCCA	1235
AV05537-19-1.umm	UCAAGAAAUAAUAAAUCCAA	950	UUUGAUUUUAUUUUUUUGA	1236
AV05538-19-1.umm	CAAGAAAUAAUAAAUCCAUUA	951	UAUUGAUUUUAUUUUUUUG	1237
AV05539-19-1.umm	GGUAAUGAUAAUUGCCUUUGUA	952	UACAAGGCAAUUAUCAUACC	1238
AV05540-19-1.umm	AUUUGCCUUUGUUAAAAUCUGA	953	UCAGUUUUCAACAAGGCCAAU	1239
AV05541-19-1.umm	UUUUUUUUAACUUGGAACCA	954	UGGUUUUCCAGUUUUCAACAA	1240
AV05542-19-1.umm	AAACCACAGUUGAAUUUACAA	955	UUUUAAUUUACAUUGUGUUU	1241
AV05543-19-1.umm	CUCCAGAAAAAGCCAAAGAUAA	956	UUUAUUUUUGGCUUUUUUGAG	1242
AV05544-19-1.umm	CCAGAAAAAGCCAAAGAUACCA	957	UUUUUUUUUUUGGCUUUUUUGG	1243
AV05545-19-1.umm	AAAGCCAAAGAUACCCUUUAGA	958	UUUAAGGUAUUUUUUUGGCUU	1244
AV05546-19-1.umm	CCAAAGAUUACCCUUUAGUAAA	959	UUCAUUUAAAGGUUUUUUUUGG	1245
AV05547-19-1.umm	AAGAUUAACCCUUUAGUGACCA	960	UUUUUUUUUUUAAAGGUUUUUUU	1246
AV05548-19-1.umm	AGAUUAACCCUUUAGUGACCAA	961	UUUUUUUUUUUAAAGGUUUUUUU	1247
AV05549-19-1.umm	AAAGAUUGCCAAAGAGAGAUUA	962	UUUUUUUUUUUUUGGCUUUUUUU	1248
AV05550-19-1.umm	GCCAGAGAGAGAUUACAGAGA	963	UUUUUUUUUUUUUUUUUUUGG	1249

AV05551-19-1.umm	AAAGAGUACAGAGGACAUUA	964	UAUUGUCCUCUGUAUUCUCUU	1250
AV05552-19-1.umm	GAGAUACAGAGGACAUUAAA	965	UUUAUGUCCUCUGUAUCUC	1251
AV05553-19-1.umm	AUACAGAGGACAUUAAAUA	966	UAUUUAUGUCCUCUGUAU	1252
AV05554-19-1.umm	UACAGAGGACAUUAAAUA	967	UUUAUUUAUGUCCUCUGUA	1253
AV05555-19-1.umm	GACAUAAAUAUAAACCAUAA	968	UUUAUGGUAUUUUUAUGUC	1254
AV05556-19-1.umm	AAAUAAACCCAUAAAGAUCAA	969	UUCAUCUUUAUGGUUAUUU	1255
AV05557-19-1.umm	AAUAAACCAUAAAGAUCAA	970	UAUCAUCUUUAUGGUUAUU	1256
AV05558-19-1.umm	AAACCAUAAAGAUUUCUGA	971	UCAGAUCAUCUUUAUGGGUU	1257
AV05559-19-1.umm	ACCCAUAAAGAUUUCUGUA	972	UACAGAUCAUCUUUAUGGGU	1258
AV05560-19-1.umm	UACGUUGGACUGGAUUUCUGA	973	UCAGAUAUCCAGUCCACGUA	1259
AV05561-19-1.umm	GGACUGGAAUUCUGGAGAAA	974	UUUUCUCCAGAAUCCAGUCC	1260
AV05562-19-1.umm	GAAUUCUGGAGAAAAACUCAA	975	UUAGAUUUUUUCCUCCAGAAUC	1261
AV05563-19-1.umm	AUUUCUGGAGAAAAACUCAAA	976	UUUUGAGUUUUUCCUCCAGAAU	1262
AV05564-19-1.umm	UUUCUGGAGAAAAACUCAGA	977	UCUUAGAUUUUUUCCUCCAGAA	1263
AV05565-19-1.umm	CAUUGCUUCCUCCACAGUAA	978	UUACUUGUGGAGGAAAGCAUG	1264
AV05566-19-1.umm	CUAGAAGAAAAACAACUCUGA	979	UCAGUUUUUUUUUUUUUUUAG	1265
AV05567-19-1.umm	UAGAAGAAAAACAACUCUGA	980	UACAAGUUUUUUUUUUUUUUUA	1266
AV05568-19-1.umm	AGAAGAAAAACAACUCUGUA	981	UGACAGUUUUUUUUUUUUUUUCU	1267
AV05569-19-1.umm	GAAAGAAAAACAACUCUGCAA	982	UUAGACAGUUUUUUUUUUUUUCC	1268
AV05570-19-1.umm	AGAAAAACAACUCUGUCACAA	983	UUUGUGACAGUUUUUUUUUUUUUCU	1269
AV06227-19-1.umm	AAUUGCUAAGAAAGAAAAACAAA	984	UUUUUGUUUUUUUUUUUUUUUAGCAUU	1270
AV06228-19-1.umm	AUUGCUAAGAAAGAAAAACAAA	985	UUUUUGUUUUUUUUUUUUUUUAGCAU	1271
AV06229-19-1.umm	UGCUAAGAAAGAAAAACAACA	986	UGUUUUUUUUUUUUUUUUUUUAGCA	1272
AV06230-19-1.umm	GCUAGAAGAAAAACAACUA	987	UAGUUUUUUUUUUUUUUUUUUUAGC	1273
AV06231-19-1.umm	CUAGAAGAAAAACAACUGA	988	UUAGUUUUUUUUUUUUUUUUUUUAG	1274
AV06232-19-1.umm	UAGAAGAAAAACAACUGUA	989	UUACAGUUUUUUUUUUUUUUUUUUA	1275
AV06233-19-1.umm	AGAAGAAAAACAACUGUCA	990	UUAGACAGUUUUUUUUUUUUUUUCU	1276
AV06234-19-1.umm	GAAAGAAAAACAACUGUCA	991	UUAGACAGUUUUUUUUUUUUUUUC	1277
AV06235-19-1.umm	AAAGAAAAACAACUGUCACA	992	UUUGACAGUUUUUUUUUUUUUUUCU	1278
AV06236-19-1.umm	AGAAAAACAACUGUCACAA	993	UUUGUGACAGUUUUUUUUUUUUUCU	1279
AV06237-19-1.umm	GAAAAACAACUGUCACAAA	994	UUUUUGACAGUUUUUUUUUUUUUC	1280
AV06238-19-1.umm	AAAAACAACUGUCACAAGA	995	UUUUUGUGACAGUUUUUUUUUUUU	1281

AV06239-19-1. um	AAACAACUCGUCACAAAGUA	996	UACUUGUGACAGUUGUU	1282
AV06240-19-1. um	AACAACUCGUCACAAAGUUA	997	UACUUGUGACAGUUGUU	1283
AV06241-19-1. um	ACAACUCGUCACAAAGUUGA	998	UCAACUUGUGACAGUUGU	1284
AV01126-1-19-1. um	GUCAGUUUCUGUGAUAUGA	999	UCAUUCACCAAGAAACUGAC	1285
AV01138-1-19-1. um	AGCGAUUUCUGGGUAUUCA	1000	UGAAUACCCAGAAAUCCGU	1286
AV01139-1. um	GGAUUUCUGGGUAUUCUUCU	1729	AGAAAGAAUACCCAGAAAUCC	1730
AV01139-1-19-1. um	AUUUCUGGGUAUUCUUCU	1733	AGAAAGAAUACCCAGAAAU	1734

Sense strand sequences of AV01124, AV01126, AV01138, AV01141, AV01152, AV01180, and AV01204 are shown in table1, corresponding respectively position of 148-168, 155-175, 385-405, 394-414, 424-444, 541-561, 1146-1166 of SEQ ID NO: 1.

Table 2 shows certain chemically modified FXI RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, an RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a cell and/or subject. In some embodiments of methods of the invention, an RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises a duplex identified in a row in Table 2, column one and includes the sequence modifications show in the sense and antisense strand sequences in the same row in Table 2, columns four and seven, respectively. In some embodiments of methods of the invention, a sequence shown in Table 2 may be attached to (also referred to herein as “conjugated to”) a compound capable of delivering the RNAi agent to a cell and/or tissue in a subject. A non-limiting example of a delivery compound that may be used in certain embodiments of the invention is a GalNAc-containing compound or a GLS-15-containing compound. In Table 2, the first column indicates the Duplex AV# of the base sequences as shown in Table 1. Table 2 discloses Duplex AV# and also shows chemical modifications included in sense and antisense sequence of the duplexes. For example, Table 1 shows base single-strand sequences SEQ ID NO: 6 (sense) and SEQ ID NO: 200 (antisense), which together are the double-stranded duplex identified as: Duplex AV# AV01118. um and Table 2 lists Duplex AV# AV01118, which indicates that the duplex of SEQ ID NO: 394 and SEQ ID NO:491 includes base sequences of SEQ ID NO: 6 and SEQ ID NO: 200, respectively, but with the chemical modifications shown in the sense and antisense sequences shown in columns four and seven, respectively. The “Sense strand SS#” in Table 2 column two is the assigned identifier for the

Sense Sequence (including modifications) shown column 4 in the same row. The “Antisense strand AS#” in Table 2 column 5 is the assigned identifier for the Antisense sequence (including modifications) shown in column seven.

Table 2: provides chemically modified FXI RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3' . These sequences were used in certain *in vitro* testing studies described herein.

Duplex AV#	Sense strand SS#	SEQ ID NO	Sense Strand	Antisense strand AS#	SEQ ID NO	Antisense Strand
AV01117	AV01117-SS	393	g*a*acaaggUfcUfhuUfcaagg*a*u*a	AV01117-AS	490	u*At*ucCfugaaAfaCfcuuGfu*u*c
AV01118	AV01118-SS	394	g*c*aaagucUfuUfucAfggau*g*a*a	AV01118-AS	491	u*Uf*caUficcugaaAfaGfaccUfhu*g*c
AV01119	AV01119-SS	395	g*a*ggucuuUfuCfagCfangau*u*a	AV01119-AS	492	u*At*auCfauccugAfaAfagcCfc*u*c
AV01120	AV01120-SS	396	c*u*cuuuueAfgGfaufauuuu*c*a	AV01120-AS	493	u*G*a*aAfaucaucCfuGfaaaAfg*a*g
AV01121	AV01121-SS	397	g*u*uucaaggAfuGfaufhuucur*a*a	AV01121-AS	494	u*Uf*a*aGfaaaaucAfuCfcugAfa*a*c
AV01122	AV01122-SS	398	g*a*ggauugUfuUfucUfuanau*c*a	AV01122-AS	495	u*G*a*auAfaaagaaAfaUfcauCfc*u*c
AV01123	AV01123-SS	399	c*g*uaagauuUfuCfuAfuauca*a*a	AV01123-AS	496	u*Uf*u*gaAfaanaagAfaAfaucAfu*c*g
AV01124	AV01124-SS	400	g*c*u*ucaaguUfuCfugCfugau*g*a	AV01124-AS	497	u*Cf*auUfcaacagAfaAfucgAfa*g*c
AV01125	AV01125-SS	401	g*u*c*cauguuUfuCfugGfaauu*g*a	AV01125-AS	498	u*Cf*acAfuucaccAfgAfaacUfug*a*c
AV01126	AV01126-SS	402	g*u*ucugguGfaAfuGfugau*c*u*a	AV01126-AS	499	u*At*guCfaacauUfcaAfccaGfa*a*c
AV01127	AV01127-SS	403	g*u*gguuuaCfuUfugGfuucug*a*a	AV01127-AS	500	u*Uf*caGfg(aUNA)cacaAfgUfaaaCfc*a*c
AV01128	AV01128-SS	404	g*g*guuuacUfuGfugUficcug*a*a	AV01128-AS	501	u*Uf*ucAfggacacAfaGfuaaAfc*c*c
AV01129	AV01129-SS	405	c*a*aaagacaGfuGfuAfcagaa*a*a	AV01129-AS	502	u*Uf*uuCfuguaacAfcUfguCfu*u*g
AV01130	AV01130-SS	406	g*a*agacaguUfuUfuaCfaagaa*c*a	AV01130-AS	503	u*Gf*uuUficcuguaacAfaCfaucGfu*u*c
AV01131	AV01131-SS	407	g*g*acagugUfuAfcagfaaaca*c*a	AV01131-AS	504	u*Gf*ugUfuuucuguAfaCfaucGfu*c*c
AV01132	AV01132-SS	408	g*u*acagaaAfcAfccGfccaag*a*a	AV01132-AS	505	u*Uf*cuUfug(gUNA)caguGfuUfucugfu*a*c
AV01133	AV01133-SS	409	g*a*acagaaCfaCfugCfcaag*a*g*a	AV01133-AS	506	u*Cf*ucUfu(gUNA)gcagUfuUfuucUfg*u*c
AV01134	AV01134-SS	410	c*a*aaacacuGfcCfaaGfaugug*a*a	AV01134-AS	507	u*Uf*ucAfccuugGfcAfguGfu*u*g
AV01135	AV01135-SS	411	g*a*acacugCfcAfaaAfguga*u*a	AV01135-AS	508	u*At*uuCfaucuuGfgCfaugGfu*u*c
AV01136	AV01136-SS	412	g*a*cuuccaAfgaAfguGfauaa*g*a	AV01136-AS	509	u*Cf*cuAfuucacuCfuUfggcAfg*u*c
AV01137	AV01137-SS	413	g*a*gcagcGfuUfucUfgeguu*a*a	AV01137-AS	510	u*At*uaCfccaagaaAfuCfugGfc*u*c
AV01138	AV01138-SS	414	c*c*agcguUfuCfugGfignaau*c*a	AV01138-AS	511	u*Gf*aaUfaaccagAfaAfuagCfu*g*g
AV01139	AV01139-SS	415	g*g*auuuucGfgGfuUfuuuu*c*a	AV01139-AS	512	u*Gf*aaAfgaauacCfcAfgaAfu*c*c

AV01140	AV01140-SS	416	g ^{*u} *cugguvAfuUfcuUfucaga ^{*c} *a	AV01140-AS	513	u [*] G ^{*c} uUfugaagaAfuAfcccAf ^{*g} *a ^{*c}
AV01141	AV01141-SS	417	g ^{*c} *ugguuaUfuCfuUfcaagc ^{*a} *a	AV01141-AS	514	u [*] U ^{*g} cUfuugaagAfaUfaccCfa ^{*g} *c
AV01142	AV01142-SS	418	g ^{*u} *ugguauUfcUfuUfucfAagca ^{*a} *a	AV01142-AS	515	u [*] U ^{*g} cUfuugaagAfaAfuacCfc ^{*a} *c
AV01143	AV01143-SS	419	g ^{*g} *ggauuChUfuUfucAfaga ^{*a} *u ^{*a}	AV01143-AS	516	u [*] A ^{*u} uGfcuuagaAf ^{*g} AfaaCfc ^{*c} *c
AV01144	AV01144-SS	420	c ^{*g} *uauuCuUfuCfaCfcauag ^{*c} *a	AV01144-AS	517	u [*] G ^{*c} aUfu(gUNA)cuuGfAfaAfgaaUfa ^{*c} *g
AV01145	AV01145-SS	421	g ^{*u} *ucuuuCaFaGfcaAfugcu ^{*a} *a	AV01145-AS	518	u [*] U ^{*g} aaGfcauugCuUfuGfaaaGfa ^{*a} *c
AV01146	AV01146-SS	422	g ^{*u} *cuuueAf ^{*g} CfaCfcaUf ^{*g} uca ^{*c} *a	AV01146-AS	519	u [*] G ^{*g} uAGfc(UNA)auugCfuUfgaagAf ^{*g} *a ^{*c}
AV01147	AV01147-SS	423	c ^{*c} *aauugcuCfaCfcaCfaaua ^{*a} *a	AV01147-AS	520	u [*] U ^{*u} aUfuugugUf ^{*g} Af ^{*g} caUfu ^{*c} *g
AV01148	AV01148-SS	424	g ^{*a} *aagcuAfcAfccAfauaa ^{*g} *a	AV01148-AS	521	u [*] C ^{*u} uAfuuugugGfuGfagcAfu ^{*u} *c
AV01149	AV01149-SS	425	g ^{*a} *u ^{*g} cucaCfaCfcaAfaua ^{*g} *c ^{*a}	AV01149-AS	522	u [*] G ^{*c} cuUfauuugUf ^{*g} Uf ^{*g} agCfa ^{*u} *c
AV01150	AV01150-SS	426	g ^{*c} *accaaUfaAf ^{*g} cGfcuu ^{*g} *a ^{*a}	AV01150-AS	523	u [*] U ^{*g} cAf ^{*a} (gUNA)cguUfaUfuugGfu ^{*c} *g
AV01151	AV01151-SS	427	g ^{*a} *ccaauAf ^{*a} Gf ^{*c} gCfuugca ^{*a} *a	AV01151-AS	524	u [*] U ^{*g} uGfAagcgcUfuAfuuGf ^{*g} *u ^{*c}
AV01152	AV01152-SS	428	g ^{*a} *aauaagCf ^{*g} CfuGfcaaca ^{*a} *a	AV01152-AS	525	u [*] U ^{*u} uGfuugcaagCf ^{*g} CfuuaUfu ^{*u} *c
AV01153	AV01153-SS	429	g ^{*a} *aauaagCf ^{*c} Ufu ^{*g} Cfcaaca ^{*a} *a	AV01153-AS	526	u [*] U ^{*u} uGfuugcaagCf ^{*c} Ufu ^{*g} uUfu ^{*u} *c
AV01154	AV01154-SS	430	c ^{*c} *c ^{*u} ugcaCfaAfa ^{*g} Afcauu ^{*a} *a	AV01154-AS	527	u [*] U ^{*a} aAfuuugcuUf ^{*g} Ufu ^{*g} caAfa ^{*g} *g
AV01155	AV01155-SS	431	g ^{*g} *caacaAf ^{*g} AfcaUfuua ^{*g} *u ^{*a}	AV01155-AS	528	u [*] A ^{*c} aUfaaauGfuUfuugUf ^{*g} *c ^{*c}
AV01156	AV01156-SS	432	c ^{*c} *c ^{*a} acaagCfaCfaUfuua ^{*g} *u ^{*a}	AV01156-AS	529	u [*] C ^{*a} cAfuaaagUf ^{*c} UfuugUfu ^{*g} *g
AV01157	AV01157-SS	433	g ^{*a} *acaagAf ^{*c} AfuUfaug ^{*g} *u ^{*a}	AV01157-AS	530	u [*] C ^{*c} caCfauaauGfuCfuuaGfu ^{*u} *c
AV01158	AV01158-SS	434	g ^{*a} *caagaCfaUfuAfugug ^{*g} *a ^{*a}	AV01158-AS	531	u [*] U ^{*c} cAfcauaaUf ^{*g} Uf ^{*c} uUf ^{*g} *c
AV01159	AV01159-SS	435	g ^{*a} *aga ^{*c} auUfuAfu ^{*g} Uf ^{*g} agc ^{*u} *a	AV01159-AS	532	u [*] A ^{*g} gUf ^{*c} (UNA)acauAf ^{*a} Afu ^{*g} Cfu ^{*u} *c
AV01160	AV01160-SS	436	g ^{*a} *ga ^{*c} auUfaUfuGf ^{*g} agcu ^{*a} *a	AV01160-AS	533	u [*] U ^{*f} *agGfu(cUNA)cacaUfaAf ^{*a} u ^{*g} Uf ^{*c} *c
AV01161	AV01161-SS	437	g ^{*g} *acaauAfuGfuGf ^{*a} ca ^{*g} *a	AV01161-AS	534	u [*] C ^{*u} aGf ^{*g} (uUNA)ccacAfuAf ^{*a} auGfu ^{*c} *c
AV01162	AV01162-SS	438	c ^{*a} *cauuuUf ^{*g} Uf ^{*g} Af ^{*c} cuag ^{*a} *a	AV01162-AS	535	u [*] U ^{*c} uAf ^{*g} u ^{*c} caCfaUfaaUf ^{*g} *u ^{*g}
AV01163	AV01163-SS	439	g ^{*a} *u ^{*g} ugcaCfcUfa ^{*g} Afcaug ^{*a} *a	AV01163-AS	536	u [*] U ^{*u} uAf ^{*u} gcucaGf ^{*g} Uf ^{*c} caCfa ^{*u} *c
AV01164	AV01164-SS	440	g ^{*u} *aga ^{*c} auGfaAf ^{*g} cGfcauaa ^{*a} *a	AV01164-AS	537	u [*] U ^{*u} uAf ^{*u} gcccUf ^{*c} Afu ^{*g} Cfu ^{*a} *c
AV01165	AV01165-SS	441	g ^{*a} *ga ^{*c} auGfaGf ^{*g} gCfauaa ^{*c} *a	AV01165-AS	538	u [*] G ^{*u} uUfaugcccUfuCfaugUf ^{*c} *c
AV01166	AV01166-SS	442	g ^{*g} *acaugAf ^{*g} cGf ^{*c} Gfcauaa ^{*c} *u ^{*a}	AV01166-AS	539	u [*] A ^{*g} uUfuauugcccUfuUfcauGfu ^{*c} *c
AV01167	AV01167-SS	443	g ^{*c} *au ^{*g} aa ^{*g} Gf ^{*c} GfcauAfa ^{*c} ua ^{*u} *a	AV01167-AS	540	u [*] A ^{*u} aGfuuaugCfcCfu ^{*c} uAfu ^{*g} *c
AV01168	AV01168-SS	444	g ^{*a} *u ^{*g} aa ^{*g} Gf ^{*c} AfaAfa ^{*c} ua ^{*a} *a	AV01168-AS	541	u [*] U ^{*u} aAf ^{*g} uuuauGf ^{*c} Cfcu ^{*c} uAfu ^{*u} *c
AV01169	AV01169-SS	445	g ^{*u} *ga ^{*a} ggcCfaUfaaAfa ^{*c} ua ^{*a} *a	AV01169-AS	542	u [*] G ^{*u} uAf ^{*a} u ^{*g} uuuAf ^{*u} gfc ^{*c} Ufu ^{*c} *c
AV01170	AV01170-SS	446	g ^{*g} *aa ^{*g} ggcAfuAf ^{*a} aaCfuuaa ^{*c} *a	AV01170-AS	543	u [*] G ^{*c} uUfauuugUf ^{*g} Cf ^{*c} uUfu ^{*c} *c
AV01171	AV01171-SS	447	c ^{*a} *ag ^{*g} ggcaUfaAfa ^{*c} Ufaaa ^{*a} *a	AV01171-AS	544	u [*] U ^{*f} *guUfauuugcuUfaUf ^{*g} cCfu ^{*u} *g
AV01172	AV01172-SS	448	g ^{*a} *gg ^{*c} cauAf ^{*a} Af ^{*c} uAfaa ^{*a} *g ^{*a}	AV01172-AS	545	u [*] C ^{*f} *u ^{*g} Ufuuaa ^{*g} UfuAf ^{*u} g ^{*c} Cfc ^{*u} *c
AV01173	AV01173-SS	449	c ^{*g} *gcauaAfcUfaaAfa ^{*c} agc ^{*u} *a	AV01173-AS	546	u [*] A ^{*g} *gcUf ^{*g} uuuaGfuUfuauGf ^{*c} *c ^{*g}

AV01174	AV01174-SS	450	c*c*auaaacUfaUfaaCfaaguc*a*a	AV01174-AS	547	u*U*gaGfc(u)UNA)guuaUfaGfuuuAfu*g*g
AV01175	AV01175-SS	451	c*c*c*caagugUfgCfucAfagaau*g*a	AV01175-AS	548	u*C*auUfcuuugagCfaCfucUfg*g*g
AV01176	AV01176-SS	452	g*c*a*agaauGfcCfaaGfaaaga*u*a	AV01176-AS	549	u*Al*ucUfuucuuGfcAfucUfu*g*c
AV01177	AV01177-SS	453	g*a*a*agaugCfcAfaGfaagaug*g*a	AV01177-AS	550	u*C*auCfuuuuuGfgCfaauCfu*u*c
AV01178	AV01178-SS	454	g*c*cacugCfaCfuUfuucac*g*a	AV01178-AS	551	u*C*guGfaaagaUfgGfcagUfg*g*c
AV01179	AV01179-SS	455	g*c*a*agucGfcUfuUfuacg*u*a	AV01179-AS	552	u*Al*cugUfgaaaaGfuGfgcaGfu*g*c
AV01180	AV01180-SS	456	g*a*cugcacaCfuUfuUfcaagu*a*a	AV01180-AS	553	u*U*acGfuugaaaaAfguUfgcAfgu*u*c
AV01181	AV01181-SS	457	g*a*a*gaauCfuUfguCfucuu*a*a	AV01181-AS	554	u*U*aaGfugaacaAfaGfauuUfc*u*c
AV01182	AV01182-SS	458	g*a*ucuuugUfcUfcUfuuaa*c*a	AV01182-AS	555	u*G*f*uuUfuuaagGfaCfaaGfa*u*c
AV01183	AV01183-SS	459	g*u*unugucUfcUfaAfaacau*c*a	AV01183-AS	556	u*G*f*auGfuuuuaGfgAfgaCfa*a*c
AV01184	AV01184-SS	460	g*c*c*uccuaAfaAfcaUfcugag*a*a	AV01184-AS	557	u*U*f*cuCfaagauGfuUfaagGfa*g*c
AV01185	AV01185-SS	461	g*c*c*cuuaaAfcAfucUfgagag*u*a	AV01185-AS	558	u*Al*f*cuCfucagauGfuUfuuaAfgu*g*c
AV01186	AV01186-SS	462	g*a*a*acauCfUfaAfgaGfuggau*u*a	AV01186-AS	559	u*Al*f*auCfcaucucCfaGfaugUfu*u*c
AV01187	AV01187-SS	463	g*c*a*agcauUfaAfaaAfgaagca*a*a	AV01187-AS	560	u*U*f*ugCfucuuuuUfaAfugcGfu*g*c
AV01188	AV01188-SS	464	g*c*c*agcauaAfaAfaGfagafgcaaa*g*a	AV01188-AS	561	u*C*f*uuUfgucuuUfuUfaauGfc*g*c
AV01189	AV01189-SS	465	g*u*aaaaagAfIgCfaaAfugcu*u*a	AV01189-AS	562	u*Al*f*agAfugcuuugCfuCfuuuUfu*a*c
AV01190	AV01190-SS	466	g*a*a*agcaAfaGfcuCfuuuu*g*a	AV01190-AS	563	u*C*f*agAfaagagCfuUfgucCfu*u*c
AV01191	AV01191-SS	467	g*g*gaagcaagGfcUfcUfucugg*u*a	AV01191-AS	564	u*Al*f*ccAfgaagaGfcUfuugCfu*c*c
AV01192	AV01192-SS	468	c*a*agcaagCfuCfuUfjuggu*u*a	AV01192-AS	565	u*Al*f*acCfagaagAfugCfuugGfc*u*g
AV01193	AV01193-SS	469	c*c*a*agaucCfuUfucUfjuguu*c*a	AV01193-AS	566	u*G*f*aaAfccagaaAfguAfguUfu*g*g
AV01194	AV01194-SS	470	g*a*a*agucUfuUfucGfguuu*c*a	AV01194-AS	567	u*U*f*gaAfaccagAfaGfagCfu*u*c
AV01195	AV01195-SS	471	c*a*a*gaucGfgAfuaUfuguu*g*c*a	AV01195-AS	568	u*G*f*caAfcauanCfcAfguuCfu*u*g
AV01196	AV01196-SS	472	g*a*a*gaucGfaUfaUfjugugc*u*a	AV01196-AS	569	u*Al*f*gcAfacaauUfjcCfaguUfc*u*c
AV01197	AV01197-SS	473	g*u*gcagaaAfacCfugUfgcaac*a*a	AV01197-AS	570	u*U*f*ggUfg(c)UNA)acagUfuUfucugGfc*a*c
AV01198	AV01198-SS	474	c*c*c*agaaacCfuGfugCfaacca*u*a	AV01198-AS	571	u*Al*f*uuGfugagacAfguUfuucUfg*g*g
AV01199	AV01199-SS	475	g*c*c*gcugacAfguUfuUfuuaac*u*a	AV01199-AS	572	u*Al*f*ggUfaaaaaCfuGfgcaGfc*g*c
AV01200	AV01200-SS	476	c*c*c*ugcagUfuUfuUfaccua*u*a	AV01200-AS	573	u*Al*f*uaGfugaaaaAfaCfugcCfa*g*g
AV01201	AV01201-SS	477	g*a*a*guuuacCfuUfaaAfgcuuu*c*a	AV01201-AS	574	u*G*f*aaAfgcuuuaAfguUfaacAfic*g*c
AV01202	AV01202-SS	478	g*g*uguuacUfuAfaaGfcuuu*c*a	AV01202-AS	575	u*Al*f*gaAfagcuuuAfaGfuuaCfa*g*c
AV01203	AV01203-SS	479	c*u*guuuacUfaAfagCfuuuu*c*a	AV01203-AS	576	u*Al*f*agAfagcuUfaAfguaaAfic*g*g
AV01204	AV01204-SS	480	g*u*acuuaaAfugCfuUfcuuc*a*a	AV01204-AS	577	u*U*f*ugAfagaagCfuUfuuaGfu*a*c
AV01205	AV01205-SS	481	g*a*a*cuuaaGfcUfuUfcuuc*a*a	AV01205-AS	578	u*U*f*uuGfaagaaGfcUfuuaAfgu*u*c
AV01206	AV01206-SS	482	g*g*guuucCfaAfcuAfaaaua*c*a	AV01206-AS	579	u*G*f*uaUfuuaaguUfgGfaagUfc*c*c
AV01207	AV01207-SS	483	c*g*auucucAfacCfuAfaaaua*c*a	AV01207-AS	580	u*Al*f*guAfuuuuagUfuGfgagAfu*c*g

AV01208	AV01208-SS	484	c*a*ucuccaAfcUfaaAfauc <u>u</u> *u*a	AV01208-AS	581	u* <u>A</u> *a <u>g</u> UfauuuaGfuUfgegaGfa* <u>u</u> *g
AV01209	AV01209-SS	485	c*c*auucucuGfgyAfuacCfa <u>cau</u> *a*a	AV01209-AS	582	u* <u>U</u> *a <u>l</u> UfgyguauCfcAlgegaAfu* <u>g</u> *g
AV01210	AV01210-SS	486	g*a*ucucugGfaUfaCfcauua* <u>a</u> *a	AV01210-AS	583	u* <u>U</u> *aAfuuguuaUfcCfaggaGfa* <u>u</u> *c
AV01211	AV01211-SS	487	g <u>u</u> *u*cucugGAfuAfcaCfa <u>uua</u> *g*a	AV01211-AS	584	u* <u>C</u> *u <u>u</u> AfauguguAfuCfca <u>g</u> Alge* <u>a</u> *c
AV01212	AV01212-SS	488	g*c*ucuggaUfaCfcaAfuua <u>g</u> *g*a	AV01212-AS	585	u* <u>C</u> *cuUfaaugu <u>g</u> UfaUfcaGfa* <u>g</u> *c
AV01213	AV01213-SS	489	g <u>u</u> *u*guuuaAfaUfigAfuua <u>g</u> *a*a	AV01213-AS	586	u* <u>U</u> *caUfuauccaUfuUfuacAlc* <u>a</u> *c
AV05205	AV05205-SS	1287	g <u>u</u> *u*ucagegaUfigAfuUfu <u>cuua</u> *u*a	AV05205-AS	1428	u* <u>A</u> *uaageAfaauCfaUfcCfu <u>ga</u> *a*c
AV05206	AV05206-SS	1288	g <u>u</u> *u*cageguGfaUfuUfu <u>cuua</u> *a*a	AV05206-AS	1429	u* <u>U</u> *auaaGfaaaUfca <u>fu</u> Cfcu <u>g</u> *a*c
AV05207	AV05207-SS	1289	g*a*guuucuGfgyUfigAfaug <u>u</u> *g*a	AV05207-AS	1430	u* <u>C</u> *cacacAfuucaCfcAl <u>g</u> Alaac* <u>u</u> *c
AV05208	AV05208-SS	1290	c*g*guauuuUfuUfcAfagca <u>u</u> *g*a	AV05208-AS	1431	u* <u>C</u> *auugCfuugaAfaGfaAfuac* <u>c</u> *g
AV05209	AV05209-SS	1291	g*c*aaageaaUfigCfuCfa <u>cca</u> *a*a	AV05209-AS	1432	u* <u>U</u> *u <u>g</u> guGfu <u>g</u> gaCfaUfuGfcu <u>u</u> *g*c
AV05210	AV05210-SS	1292	g*a*agecauGfcUfcaAlcaca <u>a</u> *a	AV05210-AS	1433	u* <u>U</u> *u <u>g</u> guUfiguugaGfcAfuUf <u>g</u> cu* <u>u</u> *c
AV05211	AV05211-SS	1293	g <u>u</u> *u*gaacaaAfagGfaCfa <u>uuu</u> au* <u>g</u> *a	AV05211-AS	1434	u* <u>C</u> *auaaAfuu <u>g</u> cuUfuUf <u>g</u> Ufu <u>g</u> c* <u>a</u> *c
AV05212	AV05212-SS	1294	c*a*caugaaGfgyGfcAfua <u>ac</u> u* <u>a</u> *a	AV05212-AS	1435	u* <u>U</u> *a <u>g</u> uuUfaugcCfcUfuCfa <u>u</u> g* <u>u</u> *g
AV05213	AV05213-SS	1295	g*g*gecauaAfcaCfuAfuac <u>ag</u> *c*a	AV05213-AS	1436	u* <u>G</u> *a <u>u</u> guUfa <u>u</u> agUfuUfaUf <u>g</u> c* <u>c</u> *c
AV05214	AV05214-SS	1296	g <u>u</u> *u*gaugguAfcCfaCfa <u>aa</u> au* <u>c</u> *a	AV05214-AS	1437	u* <u>G</u> *a <u>u</u> uuUfgyugGfuAfcAf <u>eu</u> c* <u>a</u> *c
AV05215	AV05215-SS	1297	g*g*ageguuGfcAfcCfaa <u>au</u> *a*a	AV05215-AS	1438	u* <u>U</u> *a <u>u</u> uuUfgyugGfuUfaCfa <u>cu</u> * <u>a</u> *c
AV05216	AV05216-SS	1298	c*a*guuuaCfcaCfcAfaa <u>uc</u> *a*a	AV05216-AS	1439	u* <u>U</u> *u <u>g</u> uuUfuugUfigGfuAfcac* <u>u</u> *g
AV05217	AV05217-SS	1299	c*g*guuagUfcaAfcCfaa <u>g</u> au* <u>u</u> *a	AV05217-AS	1440	u* <u>A</u> *a <u>u</u> cuUfagguGfaCfuCfuac* <u>c</u> *g
AV05218	AV05218-SS	1300	c*u*ca <u>cu</u> aAfgaAfuUfu <u>g</u> cu <u>g</u> * <u>a</u> *a	AV05218-AS	1441	u* <u>C</u> *acGfc(aUNA)aa <u>u</u> CfuUfaGf <u>g</u> u <u>g</u> * <u>a</u> *g
AV05219	AV05219-SS	1301	g*c*acuaaGfaUfuUfu <u>g</u> cu <u>g</u> * <u>u</u> *a	AV05219-AS	1442	u* <u>A</u> *caCfgy(cUNA)aa <u>u</u> UfcUfuAfg <u>u</u> * <u>g</u> *c
AV05220	AV05220-SS	1302	g*c*cuaga <u>g</u> UfuUfuGf <u>g</u> cu <u>g</u> * <u>u</u> *a	AV05220-AS	1443	u* <u>A</u> *gaCfa(cUNA)gca <u>a</u> AfaUfcUfuag* <u>g</u> *c
AV05221	AV05221-SS	1303	g*c*uaaguuUfuUf <u>g</u> Cfgy <u>cu</u> * <u>a</u> *a	AV05221-AS	1444	u* <u>U</u> *a <u>g</u> acAfcegaAfaAfuCfu <u>u</u> * <u>u</u> *c
AV05222	AV05222-SS	1304	g*a*aga <u>uu</u> UfgyCfgyUfgy <u>cu</u> * <u>a</u> *a	AV05222-AS	1445	u* <u>U</u> *a <u>g</u> acAfcegaCfaAfaAfu <u>cu</u> * <u>u</u> *c
AV05223	AV05223-SS	1305	g*c*guugcAfuUfuUfaa <u>uc</u> *a*a	AV05223-AS	1446	u* <u>U</u> *u <u>g</u> uuUfuaaAfuuGfcCfa <u>cu</u> * <u>g</u> *c
AV05224	AV05224-SS	1306	g*a*ugc <u>g</u> UfuUfuAfaa <u>uc</u> *u*a	AV05224-AS	1447	u* <u>A</u> *uug <u>g</u> UfuuaAfaUf <u>g</u> Cfca <u>u</u> * <u>u</u> *c
AV05225	AV05225-SS	1307	g <u>u</u> *u*uaaauCfaAfuCfu <u>g</u> aa <u>u</u> *a*a	AV05225-AS	1448	u* <u>U</u> *a <u>u</u> uuCfagauUf <u>g</u> AfuUfuaa* <u>a</u> *c
AV05226	AV05226-SS	1308	g <u>u</u> *u*aaaucaAfuCfuGfaa <u>aa</u> *a*a	AV05226-AS	1449	u* <u>U</u> *u <u>u</u> auUfuca <u>g</u> AluUf <u>g</u> Afu <u>u</u> *a*c
AV05227	AV05227-SS	1309	g*c*acau <u>cu</u> UfuCfuUfu <u>g</u> gu <u>u</u> * <u>u</u> *a	AV05227-AS	1450	u* <u>A</u> *acCfc(cUNA)aa <u>g</u> AfaAl <u>g</u> Afu <u>g</u> * <u>u</u> *c
AV05228	AV05228-SS	1310	g*c*aa <u>cuu</u> uCfuUfuGfgy <u>cu</u> * <u>a</u> *a	AV05228-AS	1451	u* <u>U</u> *gaAfc(cUNA)ca <u>a</u> Al <u>g</u> AfaAfg <u>u</u> * <u>g</u> *c
AV05229	AV05229-SS	1311	g*a*ucuuu <u>cu</u> UfuUfgyGfgy <u>cu</u> *a*a	AV05229-AS	1452	u* <u>U</u> *uugaaCfccaAfaGfaAfa <u>g</u> * <u>u</u> *c
AV05230	AV05230-SS	1312	g <u>u</u> *u*cuuugGfgyGfuUfca <u>g</u> aa* <u>a</u> *a	AV05230-AS	1453	u* <u>U</u> *u <u>cu</u> UfagacCfcCfaAl <u>g</u> aa* <u>a</u> *c
AV05231	AV05231-SS	1313	g <u>u</u> *u*cuuugCfgyUfuCfaa <u>g</u> aa* <u>u</u> *a	AV05231-AS	1454	u* <u>A</u> *u <u>uu</u> cuUfuagaaCfcCfcAla <u>g</u> * <u>a</u> *c
AV05232	AV05232-SS	1314	g*c*uuugcGfuUfcAfagaa <u>u</u> *a*a	AV05232-AS	1455	u* <u>U</u> *a <u>uu</u> uChuu <u>g</u> AfcCfcCfaa* <u>g</u> *c

AV05233	AV05233-SS	1315	c* <u>g</u> *guucacGfAfaUfaauat*c*a	AV05233-AS	1456	u*Gf*auaUfuaauUfcUfuGfaac*c* <u>g</u>
AV05234	AV05234-SS	1316	g* <u>g</u> *aaauaUfaAfucCfcaugau*c*a	AV05234-AS	1457	u*Gf*aucaUffguuUfaUfuAfuuu*c*c
AV05235	AV05235-SS	1317	g*c* <u>g</u> uaauaAfAafuGfcaagaa*a*a	AV05235-AS	1458	u*Uf*uuucGfcauUfuUfuUfaUfauc* <u>g</u> *c
AV05236	AV05236-SS	1318	g*a* <u>g</u> uaauaAfAufgGfcaagaa*a* <u>g</u> *a	AV05236-AS	1459	u*CF*uuucUfccaUfuUfuAfuaac*u*c
AV05237	AV05237-SS	1319	c* <u>g</u> * <u>g</u> uaugaUfaUfuGfcauu <u>g</u> *u*a	AV05237-AS	1460	u*Af*caagGfccaUfaUfcAfuaac*c* <u>g</u>
AV05238	AV05238-SS	1320	g* <u>g</u> *auauuGfCfufuGfuaagaa*c*c*a	AV05238-AS	1461	u*Gf*uuucAfacaGfGfCfaAfuaa*c*c
AV05239	AV05239-SS	1321	c*a* <u>g</u> aaugGfUfuUfuUfugaac*u*a	AV05239-AS	1462	u*Af*guuUfacaAfGfGfCfaAfuaa*u* <u>g</u>
AV05240	AV05240-SS	1322	g*a* <u>g</u> aaugGfUfuUfuGfcaacug*c* <u>g</u> *a	AV05240-AS	1463	u*CF*caugUfuaaAfAafGfcaaa*u*c
AV05241	AV05241-SS	1323	c*c*c*uuugGfAfaAfcaFuaagaa*c*c*a	AV05241-AS	1464	u*Gf*uuucCfagaUfcAfcaCfaag*c* <u>g</u>
AV05242	AV05242-SS	1324	g* <u>g</u> *uuuaaCfuGfGfAfaacac*a*a	AV05242-AS	1465	u*Uf* <u>g</u> ugGfuaucAfGufuUfcaac*c*c
AV05243	AV05243-SS	1325	g* <u>g</u> * <u>g</u> aaacAfC AfGfUfgaaua*c*c*a	AV05243-AS	1466	u*Gf*aaauUfcauGfuGfGfuauc*c*c
AV05244	AV05244-SS	1326	g*a* <u>g</u> cccaGfuGfAfauaac*a*a	AV05244-AS	1467	u*Uf* <u>g</u> ugUfaucAfCufgUfugu*u*c
AV05245	AV05245-SS	1327	g*c*c*acaguGfAfuUfaca <u>g</u> *a*a	AV05245-AS	1468	u*Uf*cuugGfuaauUfcAfCufugu*c* <u>g</u> *c
AV05246	AV05246-SS	1328	g*c*c*aaauaCfuCfuCfcaagaa*a* <u>g</u> *a	AV05246-AS	1469	u*CF*uuucUf g gGfAfGfUfaUfuuu*c* <u>g</u> *c
AV05247	AV05247-SS	1329	g*c*c*ucuccaGfAfaGfcaagaa*u*a	AV05247-AS	1470	u*Af*uuucGfcauuUfcUfGfGfaagaa*c* <u>g</u> *c
AV05248	AV05248-SS	1330	g*a* <u>g</u> cccaGfAfuUfCfcauu <u>g</u> *u*a	AV05248-AS	1471	u*Af*cuuaGfignaUfcUfuGfcau*u*c
AV05249	AV05249-SS	1331	c*a* <u>g</u> agaauAfC AfGfAfgaagaa*a*a	AV05249-AS	1472	u*Uf* <u>g</u> auugCfcauGfuAfucfcau*u* <u>g</u>
AV05250	AV05250-SS	1332	c*a* <u>g</u> auaacaGfAfgfAfcauaa*a*a	AV05250-AS	1473	u*Uf*fuuaUfguccUfcUfGfUfauc*u* <u>g</u>
AV05251	AV05251-SS	1333	g*a* <u>g</u> aaugGfAfC AfuAfauaa*a*c*a	AV05251-AS	1474	u*Gf*uuauUfuaaGfuCfCfcau*u*c
AV05252	AV05252-SS	1334	g*c*c* <u>g</u> agaagCfAfuAfauaac*c*c*a	AV05252-AS	1475	u*Gf*guuaUfuuaUfGfUfcfcau*c* <u>g</u> *c
AV05253	AV05253-SS	1335	c*a* <u>g</u> gaacauAfAfaUfAfaacca*u*a	AV05253-AS	1476	u*Af* <u>g</u> ugGfufuaUfuAfufcau*c* <u>g</u>
AV05254	AV05254-SS	1336	c*a* <u>g</u> auaauAfAfaCfcauaa*a* <u>g</u> *a	AV05254-AS	1477	u*CF*uuauGfignaAfUfuUfUfaug*u* <u>g</u>
AV05255	AV05255-SS	1337	g*c*c* <u>g</u> auaaaUfaAfCfcauaa <u>g</u> *a*a	AV05255-AS	1478	u*Uf*cuuaUf g gguUfaUfuUfauc* <u>g</u> *c
AV05256	AV05256-SS	1338	g*a* <u>g</u> cccaAfGfAfuGfcau <u>g</u> * <u>g</u> *a	AV05256-AS	1479	u*CF*acagAfuaucfuaUfUf g gGfu*c
AV05257	AV05257-SS	1339	c* <u>g</u> * <u>g</u> acugGfUfuCfuGfagaagaa*a*a	AV05257-AS	1480	u*Uf*uuucUfcaagAfAufCfaga <u>g</u> *c* <u>g</u>
AV05258	AV05258-SS	1340	c*a* <u>g</u> ugauUfcUfGfGfaagaa*c*c*a	AV05258-AS	1481	u*Gf*uuuUfcaGfAfaufCcaag*u* <u>g</u>
AV05499	AV05499-SS	1341	g* <u>u</u> *cauuaGfAfgfAfcau <u>g</u> *a*a	AV05499-AS	1482	u*Uf* <u>u</u> cauCfcaucUfcUfGfAfaag*a*c
AV05500	AV05500-SS	1342	g*a* <u>g</u> ugauUfuUfCfAfgaugaa*u*a	AV05500-AS	1483	u*Af* <u>u</u> cauCfcauAfAafGfcau*u*c
AV05501	AV05501-SS	1343	g*c*c*uuuucGfGfAfufgaauuuc*u*a	AV05501-AS	1484	u*Af* <u>g</u> aaafucauUfcUfGfAfaa* <u>g</u> *c
AV05502	AV05502-SS	1344	g* <u>g</u> * <u>g</u> aaugauUfuUfcUfuaaua*c*a	AV05502-AS	1485	u*Uf* <u>g</u> aaUfagaAfAfuCfcauc*c*c
AV05503	AV05503-SS	1345	g* <u>g</u> * <u>g</u> aaugauUfaCfuUfuguuc*u*a	AV05503-AS	1486	u*Af* <u>g</u> gAfC(aUfA)caagUfaAfcaCfcau*c*c
AV05504	AV05504-SS	1346	g* <u>g</u> *ccaaGfUfGfAfaugaa*c*a	AV05504-AS	1487	u*Uf* <u>g</u> uccUfauucAfUfcUfugu*c*c
AV05505	AV05505-SS	1347	g* <u>u</u> *uuucGfGfAfufUfcauua*a*a	AV05505-AS	1488	u*Uf* <u>u</u> gaafgaauAfCfCfAfga*a*c
AV05506	AV05506-SS	1348	g* <u>u</u> *uuucGfGfUfuCfuaucaa*c* <u>g</u> *a	AV05506-AS	1489	u*CF*uuugaAfaga

AV05507	AV05507-SS	1349	g ^{*c} *aanaaGfcGfcUfhuGfcaac ^{*a} *a	AV05507-AS	1490	u [*] U [*] gugGfIaagGfcUfhuAfhuu ^{*g} *c
AV05508	AV05508-SS	1350	g ^{*g} *cuuGafCfAfaAfgaauu ^{*u} *a	AV05508-AS	1491	u [*] A [*] aaugUfrcuuGfhuUfjGcfIaag ^{*c} *c
AV05509	AV05509-SS	1351	g ^{*c} *aaagacAfhuUfhuAfhuuggga ^{*c} *a	AV05509-AS	1492	u [*] G [*] ucCfa(cUNA)auaaAfhuGfhuCfhuu ^{*g} *c
AV05510	AV05510-SS	1352	g ^{*u} *aanguGfcCfhuAfgaauu ^{*g} *a	AV05510-AS	1493	u [*] U [*] caugUfcaagGfhuCfcAfcau ^{*a} *c
AV05511	AV05511-SS	1353	c ^{*u} *ugcGfGfGfhuGfcaag ^{*a} *a	AV05511-AS	1494	u [*] U [*] cuugAfgaacUfCfhuGfga ^{*a} *g
AV05512	AV05512-SS	1354	c ^{*c} *caagaaAfgaAfhuGfcaag ^{*u} *a	AV05512-AS	1495	u [*] A [*] ucCf(guUNA)gcauCfhuCfhuug ^{*g} *g
AV05513	AV05513-SS	1355	g ^{*g} *aaauCfhuGfhuCfhucau ^{*a} *a	AV05513-AS	1496	u [*] U [*] uaagGfIagacAfAafgaAfhuu ^{*c} *c
AV05514	AV05514-SS	1356	c ^{*a} *aaauCfUfUfCfhucau ^{*a} *a	AV05514-AS	1497	u [*] U [*] uaaGfIaggaCfaAfagfauu ^{*a} *g
AV05515	AV05515-SS	1357	g ^{*a} *aaauuGfhuCfhucau ^{*a} *a	AV05515-AS	1498	u [*] U [*] uaaAfIaggaAfCfAfagfauu ^{*u} *c
AV05516	AV05516-SS	1358	g ^{*c} *uuugGfUfCfhuUfaaaca ^{*u} *a	AV05516-AS	1499	u [*] A [*] uugUfhuagGfIaGfIa ^{*g} *c
AV05517	AV05517-SS	1359	g ^{*u} *ugucCfhuUfaAfcau ^{*u} *a	AV05517-AS	1500	u [*] A [*] ggaugUfhuuaAfIggGfIaGfIa ^{*a} *c
AV05518	AV05518-SS	1360	g ^{*u} *ugucCfhuUfaAfcau ^{*u} *a	AV05518-AS	1501	u [*] Cf [*] agauGfuuuAfIaGfIaGfIa ^{*a} *c
AV05519	AV05519-SS	1361	g ^{*g} *ucucCfhuUfaAfcau ^{*g} *a	AV05519-AS	1502	u [*] U [*] caagUfIguuUfaAfIggGfIaGfIa ^{*c} *c
AV05520	AV05520-SS	1362	g ^{*u} *ccuaaAfAcfUfCfugga ^{*g} *a	AV05520-AS	1503	u [*] Cf [*] ucUfC(aUNA)gaugUfhuUfhuAfagga ^{*a} *c
AV05521	AV05521-SS	1363	g ^{*u} *uaaacAfhuCfhuGfagga ^{*g} *a	AV05521-AS	1504	u [*] Cf [*] caCfhu(cUNA)ucagAfhuGfhuUfhuu ^{*a} *c
AV05522	AV05522-SS	1364	g ^{*a} *gucuuUfCfUfGfhuuca ^{*u} *a	AV05522-AS	1505	u [*] A [*] cuGaAfaccaGfIaAfIaGfIaGfIa ^{*u} *c
AV05523	AV05523-SS	1365	g ^{*g} *aaucGfhuAfhuUfIguu ^{*g} *a	AV05523-AS	1506	u [*] Cf [*] agCfIa(aUNA)cauAfhuCfCfIguu ^{*c} *c
AV05524	AV05524-SS	1366	c ^{*a} *aggaGfcAfhuCfhuGfhuu ^{*c} *a	AV05524-AS	1507	u [*] G [*] uaucCfIaggaAfhuGfCfhu ^{*u} *g
AV05525	AV05525-SS	1367	c ^{*g} *caucUfIggGfIaaca ^{*u} *a	AV05525-AS	1508	u [*] A [*] auguGfhuucCfIaGfIaGfIa ^{*g} *g
AV05526	AV05526-SS	1368	c ^{*u} *uuguaAfAafhuGfhuu ^{*g} *a	AV05526-AS	1509	u [*] Cf [*] auuaUfccaUfhuUfIaCfIa ^{*a} *g
AV05527	AV05527-SS	1369	g ^{*g} *uuaaAfhuGfhuAfhuu ^{*g} *a	AV05527-AS	1510	u [*] Cf [*] ucauUfauccAfhuUfhuUfIa ^{*c} *c
AV05528	AV05528-SS	1370	c ^{*u} *guaccaCfCfAfAfaAuca ^{*g} *c	AV05528-AS	1511	u [*] G [*] cuugAfhuuGfIggUfIggGfhuac ^{*a} *g
AV05529	AV05529-SS	1371	g ^{*c} *caggaUfIggGfhuGfhuu ^{*c} *a	AV05529-AS	1512	u [*] G [*] uucCf(cuUNA)ccaCfIgaAfhuCfhu ^{*g} *c
AV05530	AV05530-SS	1372	c ^{*u} *aggaUfCfhuAfaguu ^{*u} *a	AV05530-AS	1513	u [*] A [*] aaauCfhuagGfhuGfIaCfhu ^{*a} *g
AV05531	AV05531-SS	1373	g ^{*g} *gcauuUfAfaUfcau ^{*u} *a	AV05531-AS	1514	u [*] Cf [*] agauUfIgaauUfaAfAfhg ^{*c} *c
AV05532	AV05532-SS	1374	c ^{*g} *cauuAfAafuAfauu ^{*g} *a	AV05532-AS	1515	u [*] U [*] caagUfhuuUfhuAfAafuug ^{*c} *g
AV05533	AV05533-SS	1375	c ^{*c} *cauuuAfAafuAfauu ^{*g} *a	AV05533-AS	1516	u [*] U [*] ucagAfhuuUfhuAfAafau ^{*g} *g
AV05534	AV05534-SS	1376	c ^{*g} *acacCfhuUfhuCfhuuug ^{*g} *a	AV05534-AS	1517	u [*] Cf [*] ccCf(aUNA)agaaAfgaAfhuGfhu ^{*c} *g
AV05535	AV05535-SS	1377	g ^{*c} *uuuUfIggGfhuGfhuu ^{*g} *a	AV05535-AS	1518	u [*] U [*] cuugAfIaccCfAfAfaGfIa ^{*g} *c
AV05536	AV05536-SS	1378	g ^{*u} *uuugGfhuCfAfaAfgaau ^{*a} *a	AV05536-AS	1519	u [*] U [*] uaauUfcauGfAfaCfCfca ^{*a} *c
AV05537	AV05537-SS	1379	c ^{*u} *ucaagAfAafuAfhuu ^{*c} *a	AV05537-AS	1520	u [*] U [*] ggaUfauuaUfhuUfCfhuu ^{*a} *g
AV05538	AV05538-SS	1380	g ^{*u} *caagAfhuAfAfaUfauc ^{*u} *a	AV05538-AS	1521	u [*] A [*] uugaUfhuuAfhuUfhuCfhuu ^{*a} *c
AV05539	AV05539-SS	1381	g ^{*g} *ggaugAfhuAfhuUfIggcu ^{*u} *a	AV05539-AS	1522	u [*] A [*] caAf(gUNA)cauAfhuCfIafcc ^{*c} *c
AV05540	AV05540-SS	1382	g ^{*u} *auugCfhuGfhuUfIgaau ^{*g} *a	AV05540-AS	1523	u [*] Cf [*] aguuUfcaacAfAfaGfIgaau ^{*a} *c

AV05541	AV05541-SS	1383	g ^{*c} *uuguuGfaAfcUfggaaac ^{*c} *a	AV05541-AS	1524	u [*] G [*] guUfu(cUNA)caaguUfuCfaAfcaaa ^{*g} *c
AV05542	AV05542-SS	1384	c ^{*g} *aaaccaCfaGfuGfauuac ^{*a} *a	AV05542-AS	1525	u [*] U [*] guaaUfucaacUfguGfuuu ^{*c} *g
AV05543	AV05543-SS	1385	g ^{*u} *ucuccagAfaAfgcCfaagau ^{*a} *a	AV05543-AS	1526	u [*] U [*] auuuUfggcuUfuCfuGfzg ^{*a} *c
AV05544	AV05544-SS	1386	g ^{*u} *ccagaaAfgcCfaAfauguac ^{*c} *a	AV05544-AS	1527	u [*] G [*] guuuCfuugcuCfuUfuCfuug ^{*a} *c
AV05545	AV05545-SS	1387	c ^{*a} *aagcccaAfGaAfuAfcccuua ^{*g} *a	AV05545-AS	1528	u [*] C [*] uaAf(gUNA)guuuCfuUfGfGfcuu ^{*u} *g
AV05546	AV05546-SS	1388	g ^{*g} *ccaagUfaCfcCfuuaug ^{*a} *a	AV05546-AS	1529	u [*] U [*] caacuAfagggUfaUfcUfuug ^{*c} *c
AV05547	AV05547-SS	1389	g ^{*c} *aagaauaCfcCfuUfauguac ^{*c} *a	AV05547-AS	1530	u [*] G [*] guCfa(cUNA)uaagGfguUfaUfcuu ^{*g} *c
AV05548	AV05548-SS	1390	g ^{*a} *aaguuacCfcUfuAfuguac ^{*a} *a	AV05548-AS	1531	u [*] U [*] gguUfc(aUNA)cuagGfGfuAfuuu ^{*u} *c
AV05549	AV05549-SS	1391	g ^{*g} *aagaguGfcCfaGfaagau ^{*u} *a	AV05549-AS	1532	u [*] Al [*] uucUfuucugGfcAfcUfcuu ^{*c} *c
AV05550	AV05550-SS	1392	c ^{*u} *ugccagaaAfGaAfgAfuacaga ^{*g} *a	AV05550-AS	1533	u [*] C [*] uucugUfaucuCfuUfcUfggc ^{*a} *g
AV05551	AV05551-SS	1393	g ^{*g} *aagagaUfaCfaGfaagga ^{*u} *a	AV05551-AS	1534	u [*] Al [*] uugucCfuucugUfaUfcUfcuu ^{*c} *c
AV05552	AV05552-SS	1394	g ^{*a} *gagaaCfaGfaGfaacaua ^{*a} *a	AV05552-AS	1535	u [*] U [*] uauugUfcuucUfgUfaUfcuc ^{*u} *c
AV05553	AV05553-SS	1395	g ^{*g} *auacagAfgCfaCfauaaa ^{*u} *a	AV05553-AS	1536	u [*] Al [*] uuuuAfugucCfuCfuGfaau ^{*c} *c
AV05554	AV05554-SS	1396	c ^{*a} *a*uaagagGfgAfcAfuaau ^{*a} *a	AV05554-AS	1537	u [*] U [*] fauuuUfaugucCfcUfcUfguu ^{*a} *g
AV05555	AV05555-SS	1397	g ^{*g} *gagcauaAfaAfuAfaccuu ^{*a} *a	AV05555-AS	1538	u [*] U [*] faugGfuuuuUfuUfaUfguu ^{*c} *c
AV05556	AV05556-SS	1398	g ^{*a} *aaauaaCfcCfaUfaagau ^{*a} *a	AV05556-AS	1539	u [*] U [*] caucUfuauGfguUfuAfuuu ^{*u} *c
AV05557	AV05557-SS	1399	g ^{*a} *aaauaaCfcAfuAfaugu ^{*u} *a	AV05557-AS	1540	u [*] Al [*] ucauCfuuaugfGfuUfauu ^{*u} *c
AV05558	AV05558-SS	1400	g ^{*u} *u*aaaccaUfaAfgaAfuuguu ^{*g} *a	AV05558-AS	1541	u [*] C [*] aguuCfaucUfaUfGfGfu ^{*a} *c
AV05559	AV05559-SS	1401	g ^{*a} *accuuAfaGfaUfgaucu ^{*u} *a	AV05559-AS	1542	u [*] Al [*] caagaUfcuacUfuAfuGfguu ^{*c} *c
AV05560	AV05560-SS	1402	g ^{*g} *uacuuGfaCfuGfauuu ^{*g} *a	AV05560-AS	1543	u [*] C [*] agaaUfcuagUfcCfaCfua ^{*c} *c
AV05561	AV05561-SS	1403	c ^{*u} *uggaucugGfaUfuCfuugga ^{*a} *a	AV05561-AS	1544	u [*] U [*] fuucCfaagaaUfcCfaGfu ^{*a} *g
AV05562	AV05562-SS	1404	g ^{*g} *gaaucUfgAfgAfaaacu ^{*a} *a	AV05562-AS	1545	u [*] U [*] gaaUfuucUfcAfgAfauc ^{*c} *c
AV05563	AV05563-SS	1405	c ^{*g} *aauucugGfaGfaAfaucua ^{*a} *a	AV05563-AS	1546	u [*] U [*] fuugUfuucUfcCfaGfaau ^{*c} *g
AV05564	AV05564-SS	1406	c ^{*a} *a*uuucugAfgAfaAfaucua ^{*g} *a	AV05564-AS	1547	u [*] C [*] uuuagGfuuuuCfuCfcAfgaa ^{*u} *g
AV05565	AV05565-SS	1407	g ^{*g} *caugcuUfcCfuCfaacau ^{*a} *a	AV05565-AS	1548	u [*] U [*] acuugUfggagGfaAfgCfaug ^{*c} *c
AV05566	AV05566-SS	1408	g ^{*g} *cuagaaGfaAfaAfaaacu ^{*g} *a	AV05566-AS	1549	u [*] C [*] aguuUfguuuUfcUfuCfuag ^{*c} *c
AV05567	AV05567-SS	1409	c ^{*c} *uagaaGfaAfaAfaaacu ^{*u} *a	AV05567-AS	1550	u [*] Al [*] caaguUfuuuUfuCfuUfcua ^{*g} *g
AV05568	AV05568-SS	1410	g ^{*u} *u*agaaGfaAfaAfaaacu ^{*c} *a	AV05568-AS	1551	u [*] G [*] acagUfuugcuUfuUfcUfuuc ^{*a} *c
AV05569	AV05569-SS	1411	g ^{*a} *agaaGfaCfaAfaacugc ^{*a} *a	AV05569-AS	1552	u [*] U [*] fgaacGfuuuUfuUfuCfuuc ^{*u} *c
AV05570	AV05570-SS	1412	c ^{*a} *a*agaaGfaAfaCfuugcua ^{*a} *a	AV05570-AS	1553	u [*] U [*] fgaaCfauguuUfgUfuUfuuc ^{*u} *g
AV06227	AV06227-SS	1413	a ^{*a} *a*auagcuAfgAfaGfaaacaa ^{*a} *a	AV06227-AS	1554	u [*] U [*] fuuguuUfuucUfuAfgCfauu ^{*u} *u
AV06228	AV06228-SS	1414	a ^{*a} *a*auagcuAfgAfaGfaaacaa ^{*a} *a	AV06228-AS	1555	u [*] U [*] fuuguuUfuucUfuUfaGfcau ^{*u} *u
AV06229	AV06229-SS	1415	a ^{*a} *a*ugcuagAfaGfaAfaaacaa ^{*c} *a	AV06229-AS	1556	u [*] G [*] fuuuuUfuucUfuCfuAfgca ^{*u} *u
AV06230	AV06230-SS	1416	a ^{*u} *ugcuagAfgAfaAfaaacaa ^{*u} *a	AV06230-AS	1557	u [*] Al [*] guuuGfuuuuUfuUfcUfaug ^{*a} *u

AV06231	AV06231-SS	1417	u [*] g [*] cuagaaGfaAfaAfcacaau [*] g [*] a	AV06231-AS	1558	u [*] C [*] aguuUfguuuUfcUfuCfuag [*] c [*] a
AV06232	AV06232-SS	1418	g [*] c [*] uugaaGfaAfaCfaaacuu [*] u [*] a	AV06232-AS	1559	u [*] A [*] caguUfuguuUfuCfuUfcau [*] g [*] c
AV06233	AV06233-SS	1419	c [*] u [*] agaaGfaAfaAfcAfaacuu [*] c [*] a	AV06233-AS	1560	u [*] G [*] acagUfuuguUfuUfcUfuuu [*] a [*] g
AV06234	AV06234-SS	1420	u [*] g [*] agaaGfaCfaAfaucuu [*] a [*] a	AV06234-AS	1561	u [*] U [*] gacaGfuuuUfuUfuCfuuc [*] u [*] a
AV06235	AV06235-SS	1421	a [*] g [*] agaaAfcAfaAfcuucac [*] c [*] a	AV06235-AS	1562	u [*] G [*] ugacAfguuGfuUfuUfcuu [*] c [*] u
AV06236	AV06236-SS	1422	g [*] a [*] agaaaCfaAfaCfuugcac [*] a [*] a	AV06236-AS	1563	u [*] U [*] guagCfauguUfuUfuUfuuu [*] c [*] c
AV06237	AV06237-SS	1423	a [*] a [*] gaaaAfaAfcUfugacac [*] a [*] a	AV06237-AS	1564	u [*] U [*] ugugAfcaguUfuGfuUfuuc [*] u [*] u
AV06238	AV06238-SS	1424	a [*] g [*] aaaaAfaCfuGfuacacac [*] g [*] a	AV06238-AS	1565	u [*] C [*] uugGfaacagUfuUfuUfuuu [*] c [*] u
AV06239	AV06239-SS	1425	g [*] a [*] aaacAfcUfGUfcaaac [*] u [*] a	AV06239-AS	1566	u [*] A [*] cuuGUfgacaGfuUfuGfuuu [*] u [*] c
AV06240	AV06240-SS	1426	a [*] a [*] aacaaCfuGfuCfaaac [*] u [*] a	AV06240-AS	1567	u [*] A [*] acuGfuagcAfgUfuUfuuu [*] u [*] u
AV06241	AV06241-SS	1427	a [*] a [*] acaacUfGUfcAfcaguu [*] g [*] a	AV06241-AS	1568	u [*] C [*] aacuUfuguCfaGfuUfuuu [*] u [*] u

Table 3 shows certain chemically modified FXI RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, RNAi agents shown in Table 3 are administered to a cell and/or subject. In some embodiments of the invention, an RNAi agent with a polynucleotide sequence shown in Table 3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises a duplex identified in a row in Table 3, column one and includes the sequence modifications and/or delivery compound show in the sense and antisense strand sequences in the same row in Table 3, columns four and seven, respectively. The sequences were used in certain *in vivo* testing studies described elsewhere herein. In some embodiments of the invention, a sequence shown in Table 3 may be attached to (also referred to herein as “conjugated to”) a compound for delivery, a non-limiting example of which is a GalNAc-containing compound, with a delivery compound identified in Table 3 as “GLX-n” on sense strands in column four. As used herein, “GLX-n” is used to represent either a “GLS-n^{*}” or a “GLO-n” delivery compound (“X” can be either “S” or “O”) and GLX-0 can be any of the “GLS-n^{*}” and “GLO-n” delivery compounds that can be attached to 3'-end of oligonucleotide during synthesis. As used herein and shown in Table 3, “GLX-n” is used to indicate the attached GalNAc-containing compound is any one of compounds GLS-1^{*}, GLS-2^{*}, GLS-3^{*}, GLS-4^{*}, GLS-5^{*}, GLS-6^{*}, GLS-7^{*}, GLS-8^{*}, GLS-9^{*}, GLS-10^{*}, GLS-11^{*}, GLS-12^{*}, GLS-13^{*}, GLS-14^{*}, GLS-15^{*}, GLS-16^{*}, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, The structure of each of which is provided elsewhere herein. One skilled in the art will be able to prepare

and use a dsRNA compound of the invention in which the attached delivery compound is one of GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16. Column one of Table 3 provides a Duplex AD# assigned to the duplex of the sense and antisense sequences in that row of the table. For example, Duplex AD# AD00764 is the duplex of sense strand SEQ ID NO: 587 and antisense strand SEQ ID NO: 651. Each line in Table 3 provides a sense strand and an antisense strand, and discloses the duplex of the sense and antisense strands shown. The “Sense strand SS#” in Table 3 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 4 in the same row. The “Antisense strand AS#” in Table 3 column 5 is the assigned identifier for the Antisense sequence (including modifications) shown in column seven. An identifier for certain attached GalNAc-containing “GLO-n” or “GLS-n*” compounds is shown as GLS-5*, GLS-15* or GLX-0, and it will be understood that another of the “GLO-n” or “GLS-n*” compounds may be substituted for the compound shown as GLO-0, with the resulting compound included in an embodiment of a method and/or a composition of the invention.

Table 3 provides chemically modified FXI RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. The sequences were used in certain *in vivo* testing studies described elsewhere herein. A delivery molecule used in the *in vivo* studies is indicated as “GLO-n” or “GLS-n*” at the 3'-end or 5'-end of each sense strand.

Duplex AD#	Sense strand SS#	SEQ ID NO	Sense Strand	Antisense strand AS#	SEQ ID NO	Antisense Strand
AD00764	AD00764-SS	587	(GLS-15*)(invab*)gcaagguccUfuUfucAfggaugaa*a*(invab)	AD00764-AS	651	u*Uf*caUfucugaaAtaGfacUfu*g*c
AD00765	AD00765-SS	588	(GLS-15*)(invab*)ggguuacUfuUfucUfuanauc*a*(invab)	AD00765-AS	652	u*Gf*auAtuaagaAtaUfcauCfc*u*c
AD00766	AD00766-SS	589	(GLS-15*)(invab*)ggguuacUfuGfugUfcccuga*a*(invab)	AD00766-AS	653	u*Uf*ucAfggacacAtaGfuaaAfc*c*c
AD00767	AD00767-SS	590	(GLS-15*)(invab*)caaaagacaGfuGfuUfcaaga*a*(invab)	AD00767-AS	654	u*Uf*uuCfuguaacAfcUfguUfu*u*g
AD00768	AD00768-SS	591	(GLS-15*)(invab*)gcuugguaUfuCfuUfcaagca*a*(invab)	AD00768-AS	655	u*Uf*gcUfugaagAtaUfacCfa*g*c
AD00769	AD00769-SS	592	(GLS-15*)(invab*)gaaauagcGfcUfuGfcaacaaa*a*(invab)	AD00769-AS	656	u*Uf*uuGfuugcaGfcGfcuuAfu*u*c
AD00770	AD00770-SS	593	(GLS-15*)(invab*)gacaagcaCfaUfuUfugugga*a*(invab)	AD00770-AS	657	u*Uf*ccAfcuaaaUfguUfuuUfg*u*c

[illegible]

AD01012	AD01012-SS	624	(GLS-15*)(invab*)guuugucUfcUfuAfaacauc*a*(invab)	AD01012-AS	688	u*Gf*auguUfuuaGfgaAfgaAfcac*a*c
AD01013	AD01013-SS	625	(GLS-15*)(invab*)guuaaaagAfgcAfaAfaucuu*a*(invab)	AD01013-AS	689	u*Af*agagCfuugCfuCfuUfuuu*a*c
AD01014	AD01014-SS	626	(GLS-15*)(invab*)caagaucUfgAfuAfuugugc*a*(invab)	AD01014-AS	690	u*Gf*caacAfauucUfcAfguUfucuu*a*c
AD01015	AD01015-SS	627	(GLS-15*)(invab*)ccugccgUfuUfuUfuacuan*a*(invab)	AD01015-AS	691	u*Af*uaagUfaaaAfacCfuGfgea*a*c
AD01016	AD01016-SS	628	(GLS-15*)(invab*)gaguguaCfuUfaAfaucuuu*a*(invab)	AD01016-AS	692	u*Gf*aaagCfuuaAfguUfaAfcac*a*c
AD01017	AD01017-SS	629	(GLS-15*)(invab*)cuuguaCfuUfaAfaCfuuuu*a*(invab)	AD01017-AS	693	u*Af*agaaAfgeuuUfaAfguUfaac*a*c
AD01018	AD01018-SS	630	(GLS-15*)(invab*)guacuuaAfgeCfuUfucuuca*a*(invab)	AD01018-AS	694	u*Uf*ugaaGfaagCfuUfuAfaagu*a*c
AD01019	AD01019-SS	631	(GLS-15*)(invab*)gacuuaaGfcUfuUfucuaaa*a*(invab)	AD01019-AS	695	u*Uf*uuugaAfgaaGfcUfuUfaagu*a*c
AD01020	AD01020-SS	632	(GLS-15*)(invab*)ccaucucUfgAfuAfcacuuu*a*(invab)	AD01020-AS	696	u*Uf*aaugUfguauCfcAfgaAfguu*a*c
AD01477	AD01477-SS	633	(GLS-15*)(invab*)guacguuUfcUfgUfgaagug*a*(invab)	AD01477-AS	697	u*Cf*acauUfcaccAfgAfaAfcuug*a*c
AD01478	AD01478-SS	634	(GLS-15*)(invab*)guucugguAfuUfcUfuucaagc*a*(invab)	AD01478-AS	698	u*Gf*cuugAfaagaAfuAfcCfcag*a*c
AD01479	AD01479-SS	635	(GLS-15*)(invab*)guucuuuAfaGfcAfaugcuc*a*(invab)	AD01479-AS	699	u*Uf*gaagAfuugCfuUfuGfaAfaag*a*c
AD01480	AD01480-SS	636	(GLS-15*)(invab*)ccauugucAfaCfaCfaaauaa*a*(invab)	AD01480-AS	700	u*Uf*uaauUfgeugUfgAfgeCfaau*a*c
AD01481	AD01481-SS	637	(GLS-15*)(invab*)gaugucAfcAfcCfaaauag*a*(invab)	AD01481-AS	701	u*Cf*uaauUfugeguGfuGfaGfcuu*a*c
AD01482	AD01482-SS	638	(GLS-15*)(invab*)gaugcucAfaCfaAfaaauagc*a*(invab)	AD01482-AS	702	u*Gf*cuuaUfuugUfgUfgAfgca*u*c
AD01483	AD01483-SS	639	(GLS-15*)(invab*)gcaccaaUfaAfgCfcuugca*a*(invab)	AD01483-AS	703	u*Uf*gcAfag(UfNA)ccguUfaUfuUfguu*a*c
AD01484	AD01484-SS	640	(GLS-15*)(invab*)gaccaaauAfaGfcGfcuugca*a*(invab)	AD01484-AS	704	u*Uf*ugcaAfgcgcUfuAfuUfugeu*a*c
AD01485	AD01485-SS	641	(GLS-15*)(invab*)gaccaucCfaCfuUfuucaagc*a*(invab)	AD01485-AS	705	u*Cf*guugaAfaagUfgGfcAfgeu*a*c
AD01486	AD01486-SS	642	(GLS-15*)(invab*)gacugccAfcUfuUfuucaagc*a*(invab)	AD01486-AS	706	u*Af*cguuAfaaaGfuGfcCfagu*a*c
AD01487	AD01487-SS	643	(GLS-15*)(invab*)guguguaCfuUfaAfaAfgcuuuc*u*(invab)	AD01487-AS	707	u*Af*gaagGfcuuUfaGfuAfaaa*c*c
AD00990-1	AD00990-SS	644	(GLS-15*)(invab*)gucucagUfuCfuGfeguagau*a*(invab)	AD00990-AS	708	u*Cf*auucAfcagAfaAfcUfgaa*a*c
AD00991-1	AD00991-SS	645	(GLS-15*)(invab*)guucugguCfaAfuGfugugau*a*(invab)	AD00991-AS	709	u*Af*gucaCfacauUfcAfcCfaaga*a*c
AD00997-1	AD00997-SS	646	(GLS-15*)(invab*)ccagcgauUfuCfuGfeguauuc*a*(invab)	AD00997-AS	710	u*Gf*auaaCfccagAfaAfuCfgeu*a*c
AD00998-1	AD00998-SS	647	(GLS-15*)(invab*)gacugccAfuUfuUfucaagca*a*(invab)	AD00998-AS	711	u*Uf*acguGfaaaAfgUfgGfcau*a*c
AD00999-1	AD00999-SS	648	(GLS-15*)(invab*)gcuugguUfuCfuUfucaagca*a*(invab)	AD00999-AS	712	u*Uf*guuuGfaagAfaUfaCfcau*a*c
AD01002-1	AD01002-SS	649	(GLS-15*)(invab*)gaaauagCfcCfuUfugcaaa*a*(invab)	AD01002-AS	713	u*Uf*uguuGfcaagCfcCfuUfaau*a*c
AD01016-1	AD01016-SS	650	(GLS-15*)(invab*)guguguaCfuUfaAfaaguuc*a*(invab)	AD01016-AS	714	u*Gf*aaagCfuuaAfgUfaAfcac*a*c
AD02349	AD02349-SS	1731	(GLS-15*)(invab*)guucgguUfgAfuUfuucuuu*a*(invab)	AD02349-AS	1648	u*Af*uaagAfaauCfaUfcCfuga*a*c
AD02350	AD02350-SS	1732	(GLS-15*)(invab*)gucagguGfaUfuUfuucuuu*a*(invab)	AD02350-AS	1649	u*Uf*auaaGfaaaUfcAfauCfcuag*a*c
AD02351	AD02351-SS	1569	(GLS-15*)(invab*)gaguuuUfgUfgAfaugugc*a*(invab)	AD02351-AS	1650	u*Cf*acacAfuaaCfcAfgeAfaiac*a*c
AD02352	AD02352-SS	1570	(GLS-15*)(invab*)gaaagcaUfgCfuCfaacacaa*a*(invab)	AD02352-AS	1651	u*Uf*ugguGfugaCfaUfuGfcuu*a*c
AD02353	AD02353-SS	1571	(GLS-15*)(invab*)gaaagcauGfcUfcAfcaacaa*a*(invab)	AD02353-AS	1652	u*Uf*uuugUfgugaGfcAfuUfguu*a*c

AD02354	AD02354-SS	1572	(GLS-15*)(invab*)cacaugaaGfcGfcAfuuaaaua*a*(invab)	AD02354-AS	1653	u*Uf*aguuUfaugCfcUfuCfaug*u*g
AD02355	AD02355-SS	1573	(GLS-15*)(invab*)gagcauaAfaCfuAfuacagc*a*(invab)	AD02355-AS	1654	u*Gf*cuuuUfaugUfuUfaUfgc*c*c
AD02356	AD02356-SS	1574	(GLS-15*)(invab*)gguagagUfcAfcCfuagauu*a*(invab)	AD02356-AS	1655	u*Af*aucuUfaagGfaCfuCfuac*c*g
AD02357	AD02357-SS	1575	(GLS-15*)(invab*)ggaauuuUfgCfuUfgucuaa*a*(invab)	AD02357-AS	1656	u*Uf*guagAfcagCfaAfaAfuauu*a*c
AD02358	AD02358-SS	1576	(GLS-15*)(invab*)gcaugagAfuUfuUfaauca*a*(invab)	AD02358-AS	1657	u*Uf*ugauUfuuaAfuGfcCfauc*u*g
AD02359	AD02359-SS	1577	(GLS-15*)(invab*)gagugagAfuUfuAfaucanu*a*(invab)	AD02359-AS	1658	u*Af*uuuUfuuaAfaUfgCfcac*u*c
AD02360	AD02360-SS	1578	(GLS-15*)(invab*)guuaaucaAfuCfuGfaaauaa*a*(invab)	AD02360-AS	1659	u*Uf*uanUfuacagAfuUfgAfuuu*a*c
AD02361	AD02361-SS	1579	(GLS-15*)(invab*)gucuuugGfgUfuCfaagaaau*a*(invab)	AD02361-AS	1660	u*Af*uuucUfuugaCfcCfcAfaag*u*c
AD02362	AD02362-SS	1580	(GLS-15*)(invab*)cgguucaAfaAfaUfaauauc*a*(invab)	AD02362-AS	1661	u*Gf*auuaUfuauUfcUfuGfaac*c*g
AD02363	AD02363-SS	1581	(GLS-15*)(invab*)gcauuaaAfaAfuGfgagaa*a*(invab)	AD02363-AS	1662	u*Uf*uuuGfccauUfuUfaUfauc*u*g
AD02364	AD02364-SS	1582	(GLS-15*)(invab*)gaaacacaGfuGfaAfuuaaca*a*(invab)	AD02364-AS	1663	u*Uf*guuAfaucAfcUfgUfgu*u*c
AD02365	AD02365-SS	1583	(GLS-15*)(invab*)gcaacagaGfaAfuUfaacaga*a*(invab)	AD02365-AS	1664	u*Uf*cuuGfuauUfcAfcUfgu*g*c
AD02366	AD02366-SS	1584	(GLS-15*)(invab*)caggaauAfaAfaUfaaccan*a*(invab)	AD02366-AS	1665	u*Af*uuuUfuauUfuAfuAfuucc*u*g
AD02369	AD02369-SS	1585	(GLS-15*)(invab*)gaaaguuUfuUfcAfggaugau*a*(invab)	AD02369-AS	1666	u*Af*ucauCfcugaAfaAfgafccu*u*c
AD02370	AD02370-SS	1586	(GLS-15*)(invab*)gcuuuuCaGfgAfuGfauuuuu*a*(invab)	AD02370-AS	1667	u*Af*gaauAfucauCfcUfgAfaaa*g*c
AD02371	AD02371-SS	1587	(GLS-15*)(invab*)gaggaugauUfuUfcUfuauuca*a*(invab)	AD02371-AS	1668	u*Uf*gaauUfaagaAfaAfuCfauc*c*c
AD02372	AD02372-SS	1588	(GLS-15*)(invab*)ggauguuUfaCfuUfgugcu*a*(invab)	AD02372-AS	1669	u*Af*ggAfc(aUNA)caagUfaAfaCfauc*c
						*c
AD02373	AD02373-SS	1589	(GLS-15*)(invab*)gucugcaAfgAfuUfgaauagg*a*(invab)	AD02373-AS	1670	u*CF*cuauUfaucUfuUfgGfcag*u*c
AD02374	AD02374-SS	1590	(GLS-15*)(invab*)gagcaagaGfuGfaAfuagaca*a*(invab)	AD02374-AS	1671	u*Uf*guccUfauuCfcUfcUfuugc*c*c
AD02375	AD02375-SS	1591	(GLS-15*)(invab*)ggaauuuCfGfgAfuAfuuuuc*a*(invab)	AD02375-AS	1672	u*Gf*aaagAfaucCfcAfgAfaau*c*c
AD02376	AD02376-SS	1592	(GLS-15*)(invab*)guuuuugGfuAfuUfcuuuca*a*(invab)	AD02376-AS	1673	u*Uf*ugaAfgaaUfcCfcAfgaa*a*c
AD02377	AD02377-SS	1593	(GLS-15*)(invab*)guuucuggUfaUfuCfuuucaag*a*(invab)	AD02377-AS	1674	u*CF*uuuAfaagaUfaCfcCfaaga*a*c
AD02378	AD02378-SS	1594	(GLS-15*)(invab*)cguuuuUfuCfaAfgcaaugc*a*(invab)	AD02378-AS	1675	u*Gf*caUfu(gUNA)cuugAfaAfgAfaua*c
						*g
AD02379	AD02379-SS	1595	(GLS-15*)(invab*)gcaauaaGfcGfcUfuagaca*a*(invab)	AD02379-AS	1676	u*Uf*guuGfagcGfcUfuAfuuu*g*c
AD02380	AD02380-SS	1596	(GLS-15*)(invab*)gagcaagaAfaAfgaauuu*a*(invab)	AD02380-AS	1677	u*Af*aaugUfcuuuGfuUfgCfaag*c*c
AD02381	AD02381-SS	1597	(GLS-15*)(invab*)gcaagacAfuUfuAfuugagac*a*(invab)	AD02381-AS	1678	u*Gf*ucCfa(cUNA)auaaAfuGfuCfuuu*g
						*c
AD02382	AD02382-SS	1598	(GLS-15*)(invab*)guuugagAfcCfuAfgacauu*a*(invab)	AD02382-AS	1679	u*Uf*caugUfcuagGfuCfcAfcu*a*c
AD02383	AD02383-SS	1599	(GLS-15*)(invab*)cuugcaCfaGfuGfucagaa*a*(invab)	AD02383-AS	1680	u*Uf*cuugAfgacUfcUfuGfgaa*a*g
AD02384	AD02384-SS	1600	(GLS-15*)(invab*)cccaagaaAfgAfuGfcaagaa*a*(invab)	AD02384-AS	1681	u*Af*ucCfg(uUNA)gcauCfuUfuCfuug*g
						*g
AD02385	AD02385-SS	1601	(GLS-15*)(invab*)ggaauuUfuGfuCfuuccuuaa*a*(invab)	AD02385-AS	1682	u*Uf*uaagGfagacAfaAfgAfuuu*c*c
AD02386	AD02386-SS	1602	(GLS-15*)(invab*)cagcaagCfuCfuUfuuguu*a*(invab)	AD02386-AS	1683	u*Af*accaGfaagAfgCfuUfuugc*u*g

AD02387	AD02387-SS	1603	(GLS-15*)(invab*)gcaucccAfaCfuAfaaauac*a*(invab)	AD02387-AS	1684	u*A [†] guauUfuuagUfuGfagAfgau*c [†] g
AD02388	AD02388-SS	1604	(GLS-15*)(invab*)cuuguaAfaAfuGfguaua [†] g*a*(invab)	AD02388-AS	1685	u*C [†] auuaUfccaUfuUfaCfaca*c [†] g
AD02389	AD02389-SS	1605	(GLS-15*)(invab*)cucacuaAfgaAfuUfuugug [†] g*a*(invab)	AD02389-AS	1686	u*C [†] acGfc(aUNA)aaauCfuUfaGfgu [†] g*a
						[†] g
AD02390	AD02390-SS	1606	(GLS-15*)(invab*)gcaacuuaGfaUfuUfugcgu [†] g*a*(invab)	AD02390-AS	1687	u*A [†] caCf(cUNA)aaauUfcUfuAfggu [†] g
						[†] c
AD02391	AD02391-SS	1607	(GLS-15*)(invab*)gccaagaUfuUfuGfeggu [†] g*a*(invab)	AD02391-AS	1688	u*A [†] gcaCfa(cUNA)gccaAfaUfcUfuag [†] g
						[†] c
AD02392	AD02392-SS	1608	(GLS-15*)(invab*)gcauuuAfaAfuCfaaucu [†] g*a*(invab)	AD02392-AS	1689	u*U [†] ca [†] gUfu [†] gauUfuAfaAfaug [†] c [†] g
AD02393	AD02393-SS	1609	(GLS-15*)(invab*)gcaacuUfuCfuUfu [†] g [†] g [†] g [†] u [†] a*(invab)	AD02393-AS	1690	u*A [†] acCfc(cUNA)aaagAfaAfgAfu [†] g [†] g
						[†] c
AD02394	AD02394-SS	1610	(GLS-15*)(invab*)gcauuuUfuUfuGf [†] g [†] g [†] u [†] ca*a*(invab)	AD02394-AS	1691	u*U [†] gAfc(cUNA)ccaaAfgAfaAfgau [†] g
						[†] c
AD02395	AD02395-SS	1611	(GLS-15*)(invab*)guu [†] cuu [†] gCf [†] gGfuUfcaaga [†] a*a*(invab)	AD02395-AS	1692	u*U [†] u [†] cuUfgaacCfcCfaAfa [†] g [†] a*a*c
AD02396	AD02396-SS	1612	(GLS-15*)(invab*)gaguuaaAfaUf [†] gGfcaaga [†] a [†] g*a*(invab)	AD02396-AS	1693	u*C [†] uu [†] Uf [†] gcaUfuUfuAfuac [†] u [†] c
AD02397	AD02397-SS	1613	(GLS-15*)(invab*)gguau [†] gUfaUfuGf [†] ccuu [†] g [†] a*a*(invab)	AD02397-AS	1694	u*A [†] acaaGf [†] gcaUfaUfcAfuac [†] c [†] g
AD02398	AD02398-SS	1614	(GLS-15*)(invab*)ggaau [†] gCfcUfuGfu [†] gga [†] a [†] c*a*(invab)	AD02398-AS	1695	u*G [†] uu [†] Ufa [†] caaGf [†] gCfaAfuau [†] c [†] c
AD02399	AD02399-SS	1615	(GLS-15*)(invab*)ggaaccaCfaGfuGfaaua [†] a*a*(invab)	AD02399-AS	1696	u*U [†] guauUfuacUf [†] gUf [†] gGfu [†] u [†] c [†] g
AD02400	AD02400-SS	1616	(GLS-15*)(invab*)gcaauaCfuCfuCfcaaga [†] a [†] g*a*(invab)	AD02400-AS	1697	u*C [†] uu [†] Uf [†] gagAfgUfaUfu [†] u [†] g [†] c
AD02401	AD02401-SS	1617	(GLS-15*)(invab*)caagccaAfgAfuAfc [†] cuu [†] a [†] g*a*(invab)	AD02401-AS	1698	u*C [†] uaAfg(gUNA)guauCfuUf [†] gGfcu [†] u [†] g
						[†] g
AD02402	AD02402-SS	1618	(GLS-15*)(invab*)gacaggaAfcAfuAfaauaac [†] a*a*(invab)	AD02402-AS	1699	u*G [†] uuauUfuauGfuCfcUfcu [†] g [†] u [†] c
AD02403	AD02403-SS	1619	(GLS-15*)(invab*)gaccauaAfgAfuGfauc [†] u [†] g [†] a*a*(invab)	AD02403-AS	1700	u*C [†] acagAfucauCfuUfaUf [†] g [†] g [†] u [†] c
AD02404	AD02404-SS	1620	(GLS-15*)(invab*)gacu [†] ggaUfuCfuGfaga [†] aa [†] a*a*(invab)	AD02404-AS	1701	u*U [†] uu [†] Uf [†] ccagAfaUfcCfagu [†] c [†] g
AD00990-2	AD00990-2-SS	1621	(GLS-15*)(invab*)g [†] gca [†] g [†] u [†] UfuCfuGf [†] gga [†] u [†] g [†] a*a*(invab)	AD00990-2-AS	1702	u*C [†] au [†] Uf [†] ccagAfaAfcUf [†] gac [†] g [†] c
AD00990	AD00990-SS	1622	(GLS-15*)(invab*)gcauca [†] gUfuCfuGf [†] gga [†] u [†] g [†] a*a*(invab)	AD00990-AS	1703	u*C [†] au [†] Uf [†] ccagAfaAfcUf [†] gaa [†] g [†] c
AD00991	AD00991-SS	1623	(GLS-15*)(invab*)guu [†] cu [†] ggaGfaAfuGfu [†] gga [†] cu [†] a*a*(invab)	AD00991-AS	1704	u*A [†] gucaCfaccuUfcAfcCfaga [†] a*a*c
AD00997-2	AD00997-2-SS	1624	(GLS-15*)(invab*)g [†] ga [†] g [†] gaUfuCfuGf [†] gga [†] u [†] u [†] c [†] a*(invab)	AD00997-2-AS	1705	u*G [†] auaCfccaGfaAfuCf [†] gcu [†] c [†] g
AD00997	AD00997-SS	1625	(GLS-15*)(invab*)cca [†] ggaUfuCfuGf [†] gga [†] u [†] u [†] c [†] a*(invab)	AD00997-AS	1706	u*G [†] auaCfccaGfaAfuCf [†] gcu [†] c [†] g
AD02432	AD02432-SS	1626	(GLS-15*)(invab*)gaucuuGfuCfuCfcuu [†] aa [†] a*a*(invab)	AD02432-AS	1707	u*U [†] uu [†] Uf [†] ga [†] gAfcAfaAfgau [†] u [†] c
AD02433	AD02433-SS	1627	(GLS-15*)(invab*)gcuu [†] gucUfcCfuUfaaa [†] cau [†] a*(invab)	AD02433-AS	1708	u*A [†] u [†] guuUfuagGfaGfaCf [†] aa [†] c [†] c
AD02434	AD02434-SS	1628	(GLS-15*)(invab*)g [†] cu [†] cu [†] UfaAfaAfa [†] cau [†] cu [†] a*a*(invab)	AD02434-AS	1709	u*U [†] ca [†] gUf [†] guuUfaAfgGfaga [†] c [†] c
AD02435	AD02435-SS	1629	(GLS-15*)(invab*)g [†] ca [†] ggaUf [†] gUfuGfaga [†] g [†] aa [†] c [†] a*(invab)	AD02435-AS	1710	u*G [†] uuCfc(uNA)ccaCf [†] gAfuCf [†] cu [†] g [†] g
						[†] c
AD02436	AD02436-SS	1630	(GLS-15*)(invab*)gcuu [†] cu [†] Uf [†] gGf [†] gGfu [†] ca [†] g [†] a*a*(invab)	AD02436-AS	1711	u*U [†] cu [†] gAfa [†] ccCfaAfaGf [†] aa [†] g [†] c

AD02437	AD02437-SS	1631	(GLS-15*)(invab*)gucaaagaaAfuAfaUfaauccau*a*(invab)	AD02437-AS	1712	u*Af*uugaUfuauuAfuUfuCfuug*a*c
AD02438	AD02438-SS	1632	(GLS-15*)(invab*)gegguaugAfuAfuUfgccuugu*a*(invab)	AD02438-AS	1713	u*Af*caAf(gUNA)caauAfuCfaUfac*c
						*c
AD02439	AD02439-SS	1633	(GLS-15*)(invab*)ggaucagAfgGfaCfaaauaau*a*(invab)	AD02439-AS	1714	u*Af*uuuuAfuugcCfuCfuGfuau*c*c
AD02440	AD02440-SS	1634	(GLS-15*)(invab*)cauacagaGfgAfcAfuaaua*a*(invab)	AD02440-AS	1715	u*Uf*auuuUfauguCfcUfcUfgua*u*g
AD02441	AD02441-SS	1635	(GLS-15*)(invab*)gggaauaAfaAfuAfaccuaua*a*(invab)	AD02441-AS	1716	u*Uf*auugGfuauuUfuUfaUfguc*c*c
AD02442	AD02442-SS	1636	(GLS-15*)(invab*)cuugcuugGfaUfuCfuaggaa*a*(invab)	AD02442-AS	1717	u*Uf*ucucCfagaalUfcCfaGfuac*a*g
AD02443	AD02443-SS	1637	(GLS-15*)(invab*)ggcuagaaGfaAfaAfcaacuug*a*(invab)	AD02443-AS	1718	u*CF*aguuUfguuUfcUfuCfuag*c*c
AD02444	AD02444-SS	1638	(GLS-15*)(invab*)ccuagaagAfaAfaCfaaacuugu*a*(invab)	AD02444-AS	1719	u*Af*caaguUfuguuUfuCfuUfcua*g*g
AD02445	AD02445-SS	1639	(GLS-15*)(invab*)guagaaagAfaAfcAfacuugc*a*(invab)	AD02445-AS	1720	u*Gf*acagUfuuguUfuUfcUfcu*a*c
AD02446	AD02446-SS	1640	(GLS-15*)(invab*)gaagaaagAfaCfaAfacuugca*a*(invab)	AD02446-AS	1721	u*Uf*gaacaGfuuuuUfuUfuCfuuc*u*c
AD02447	AD02447-SS	1641	(GLS-15*)(invab*)caagaaagAfaAfaCfugucaca*a*(invab)	AD02447-AS	1722	u*Uf*guugaCfaguUfgUfuUfcu*u*g
AD02375-1	AD02375-1-SS	1642	(GLS-15*)(invab*)ggauuucGfgGfuAfuuuuc*u*(invab)	AD02375-1-AS	1723	a*Gf*aaagAfauacCfcAfgaAfaau*c*c
AD01606	AD01606-SS	1643	g*g*guauUfCfUfuucaagcau(L96)	AD01606-AS	1724	(phos)a*Uf*ugcUfugaaggaAfuAfccc*a*g
AD01607	AD01607-SS	1644	a*u*uuucuGfGfGfuauuucua(L96)	AD01607-AS	1725	(phos)u*Gf*aaGfauacccAfgaAfaau*c*g
AD00726	AD00726-SS	1645	u*c*agGfaUfGfAfuuuucuuau*u*(L96)	AD00726-AS	1726	u*Af*uAfagfAaAfuCfaUfcCfuGfa*a*a
AD00727	AD00727-SS	1646	g*g*guauUfCfUfuucaagcau(L96)	AD00727-AS	1727	a*Uf*ugcUfugaaggaAfuAfccc*a*g
AD00728	AD00728-SS	1647	a*u*uuucuGfGfGfuauuucua(L96)	AD00728-AS	1728	u*Gf*aaagfAauacccAfgaAfaau*c*c

L96 is refers to the compound GaINaC3 in Jayaprakash, et al., (2014) J. Am. Chem. Soc., 136, 16958–16961.

In certain embodiments of the invention a dsRNA (also referred to herein as a “duplex”) is one disclosed in one of Tables 1-3. Each row in Tables 1-3 discloses a duplex comprising the sequence of the sense strand and the sequence of the antisense strand in that table row. In addition to the duplexes disclosed in Tables 1-3, it will be understood that in some embodiments, a duplex of the invention may include sense and antisense sequences shown in Tables 1-3, that differ by zero, one, two, or three nucleotides shown in a sequence shown in Tables 1-3. It will be understood that the sequence of the sense strand and the sequence of the antisense strand in a duplex of the invention may be independently selected. Thus, a dsRNA of the invention may comprise a sense strand and an antisense strand of a duplex disclosed in a row in Tables 1-3. Alternatively, in a dsRNA of the invention, one or both of the selected sense and antisense strand in the dsRNA may include sequences shown in Tables 1-3 but with one or both of the sense and antisense sequences including 1, 2, 3, or more nucleobase substitutions from the parent sequence. The selected sequences may in some embodiments be longer or shorter than their parent sequence. As non-limiting examples, in some embodiments, a sense strand in a duplex of the invention may be SEQ ID NO: 6, 7, 9 longer than SEQ ID NO: 102, 103, 105, respectively. Thus, dsRNA agents included in the invention can but need not include exact sequences of the sense and antisense pairs disclosed as duplexes in Tables 1-3.

In some embodiments, a dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a FXI RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand. In some instances, the region of complementarity to the FXI RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3. In some embodiments of a dsRNA agent of the invention, the antisense strand of the dsRNA is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, an antisense strand of a dsRNA agent of the invention is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments a dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In other embodiments, a dsRNA agent of the invention comprises a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some instances, a dsRNA agent of the invention comprises an antisense strand sequence set forth in any one of Tables 1-3. Some embodiments of a dsRNA agent of the invention comprises the sense and antisense sequences

disclosed as duplex in any of Tables 1-3. As described herein, it will be understood that the sense and antisense strands in a duplex of the invention may be independently selected.

Mismatches

It is known to skilled in art, mismatches are tolerated for efficacy in dsRNA, especially the mismatches are within terminal region of dsRNA. Certain mismatches tolerate better, for example mismatches with wobble base pairs G:U and A:C are tolerated better for efficacy (Du et al., A systematic analysis of the silencing effects of an active siRNA at all single-nucleotide mismatched target sites. *Nucleic Acids Res.* 2005 Mar 21;33(5):1671-7. Doi: 10.1093/nar/gki312. *Nucleic Acids Res.* 2005;33(11):3698). Some embodiments of methods and compounds of the invention a FXI dsRNA agent may contain one or more mismatches to the FXI target sequence. In some embodiments, FXI dsRNA agent of the invention includes no mismatches. In certain embodiments, FXI dsRNA agent of the invention includes no more than 1 mismatch. In some embodiments, FXI dsRNA agent of the invention includes no more than 2 mismatches. In certain embodiments, FXI dsRNA agent of the invention includes no more than 3 mismatches. In some embodiments of the invention, an antisense strand of a FXI dsRNA agent contains mismatches to a FXI target sequence that are not located in the center of the region of complementarity. In some embodiments, the antisense strand of the FXI dsRNA agent includes 1, 2, 3, 4, or more mismatches that are within the last 5, 4, 3, 2, or 1 nucleotide from one or both of the 5' or 3' end of the region of complementarity. Methods described herein and/or methods known in the art can be used to determine whether a FXI dsRNA agent containing a mismatch to a FXI target sequence is effective in inhibiting the expression of the FXI gene.

Complementarity

As used herein, unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence (e.g., FXI dsRNA agent sense strand or targeted FXI mRNA) in relation to a second nucleotide sequence (e.g., FXI dsRNA agent antisense strand or a single-stranded antisense polynucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize [form base pair hydrogen bonds under mammalian physiological conditions (or similar conditions *in vitro*)] and form a duplex or double helical structure under certain conditions with an oligonucleotide or polynucleotide including the second nucleotide sequence. Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. A skilled artisan will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base

pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification.

Complementary sequences, for example, within a FXI dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. It will be understood that in embodiments when two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs are not regarded herein as mismatches with regard to the determination of complementarity. For example, a FXI dsRNA agent comprising one oligonucleotide 19 nucleotides in length and another oligonucleotide 20 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 19 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein. Thus, as used herein, “fully complementary” means that all (100%) of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

The term “substantially complementary” as used herein means that in a hybridized pair of nucleobase sequences, at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The term “substantially complementary” can be used in reference to a first sequence with respect to a second sequence if the two sequences include one or more, for example at least 1, 2, 3, 4, or 5 mismatched base pairs upon hybridization for a duplex up to 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs (bp), while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g., inhibition of FXI gene expression via a RISC pathway.

The term, “partially complementary” may be used herein in reference to a hybridized pair of nucleobase sequences, in which at least 75%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. In some embodiments, “partially complementary” means at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide.

The terms “complementary,” “fully complementary,” “substantially complementary,” and “partially complimentary” are used herein in reference to the base matching between the sense strand and the antisense strand of a FXI dsRNA agent, between the antisense strand of a FXI dsRNA agent and a sequence of a target FXI mRNA, or between a single-stranded antisense oligonucleotide and a sequence of a target FXI mRNA. It will be understood that the term “antisense strand of a FXI dsRNA agent” may refer to the same sequence of an “FXI antisense polynucleotide agent”.

As used herein, the term “substantially identical” or “substantial identity” used in reference to a nucleic acid sequence means a nucleic acid sequence comprising a sequence with at least about 85% sequence identity or more, preferably at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the identical nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. The inventions disclosed herein encompasses nucleotide sequences substantially identical to those disclosed herein. e.g., in Tables 1-3. In some embodiments, the sequences disclosed herein are exactly identical, or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identical to those disclosed herein, e.g., in Tables 1-3.

As used herein, the term “strand comprising a sequence” means an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature. The term “double-stranded RNA” or “dsRNA,” as used herein, refers to an RNAi that includes an RNA molecule or complex of molecules having a hybridized duplex region comprising two anti-parallel and substantially or fully complementary nucleic acid strands, which are referred to as having “sense” and “antisense” orientations with respect to a target FXI RNA. The duplex region can be of any length that permits specific degradation of a desired target FXI RNA through a RISC pathway but will typically range from 9 to 30 base pairs in length, e.g., 15-30 base pairs in length. Considering a duplex between 9 and 30 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20 base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base pairs, 20-23 base

pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. FXI dsRNA agents generated in the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of a FXI dsDNA agent comprises a sequence that is substantially complementary to a region of a target FXI RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a "hairpin loop") between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. In some embodiments of the invention, a hairpin loop comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more unpaired nucleotides. Where the two substantially complementary strands of a FXI dsRNA agent are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than a hairpin loop, the connecting structure is referred to as a "linker." The term "siRNA" is also used herein to refer to a dsRNA agent as described herein.

In some embodiments of the invention a FXI dsRNA agent may include a sense and antisense sequence that have no-unpaired nucleotides or nucleotide analogs at one or both terminal ends of the dsRNA agent. An end with no unpaired nucleotides is referred to as a "blunt end" and as having no nucleotide overhang. If both ends of a dsRNA agent are blunt, the dsRNA is referred to as "blunt ended." In some embodiments of the invention, a first end of a dsRNA agent is blunt, in some embodiments a second end of a dsRNA agent is blunt, and in certain embodiments of the invention, both ends of a FXI dsRNA agent are blunt.

In some embodiments of dsRNA agents of the invention, the dsRNA does not have one or two blunt ends. In such instances there is at least one unpaired nucleotide at the end of a strand of a dsRNA agent. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least 1, 2, 3, 4, 5, 6, or more nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. It will be understood that in some embodiments a nucleotide overhang is on a sense strand of a dsRNA agent, on an antisense strand of a dsRNA agent, or on both ends of a dsRNA agent and nucleotide(s) of an overhang can be present on the 5' end, 3' end or both ends of either an antisense or sense strand of a dsRNA. In certain embodiments of the invention, one or more of the nucleotides in an overhang is replaced with a nucleoside thiophosphate.

As used herein, the term “antisense strand” or “guide strand” refers to the strand of a FXI dsRNA agent that includes a region that is substantially complementary to a FXI target sequence. As used herein the term “sense strand,” or “passenger strand” refers to the strand of a FXI dsRNA agent that includes a region that is substantially complementary to a region of the antisense strand of the FXI dsRNA agent.

Modifications

In some embodiments of the invention the RNA of a FXI RNAi agent is chemically modified to enhance stability and/or one or more other beneficial characteristics. Nucleic acids in certain embodiments of the invention may be synthesized and/or modified by methods well established in the art, for example, those described in “Current protocols in Nucleic Acid Chemistry,” Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, which is incorporated herein by reference. Modifications that can be present in certain embodiments of FXI dsRNA agents of the invention include, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation, conjugation, inverted linkages, etc.) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in certain embodiments of FXI dsRNA agents, FXI antisense polynucleotides, and FXI sense polynucleotides of the invention include, but are not limited to RNAs comprising modified backbones or no natural internucleoside linkages. As a non-limiting example, an RNA having a modified backbone may not have a phosphorus atom in the backbone. RNAs that do not have a phosphorus atom in their internucleoside backbone may be referred to as oligonucleosides. In certain embodiments of the invention, a modified RNA has a phosphorus atom in its internucleoside backbone.

It will be understood that the term “RNA molecule” or “RNA” or “ribonucleic acid molecule” encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. The terms “ribonucleoside” and “ribonucleotide” may be used interchangeably herein. An RNA molecule can be modified in the nucleobase structure or in the ribose-phosphate backbone structure, e.g., as described herein below, and molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleoside, a nucleoside comprising a 5' phosphorothioate group, a

terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. In some embodiments of the invention, an RNA molecule comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or up to the full length of the FXI dsRNA agent molecule's ribonucleosides that are modified ribonucleosides. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule.

DsRNA agents, FXI antisense polynucleotides, and/or FXI sense polynucleotides of the invention may, in some embodiments comprise one or more independently selected modified nucleotide and/or one or more independently selected non-phosphodiester linkage. As used herein the term "independently selected" used in reference to a selected element, such as a modified nucleotide, non-phosphodiester linkage, etc., means that two or more selected elements can but need not be the same as each other.

As used herein, a "nucleotide base," "nucleotide," or "nucleobase" is a heterocyclic pyrimidine or purine compound, which is a standard constituent of all nucleic acids, and includes the bases that form the nucleotides adenine, guanine, cytosine, thymine, and uracil. A nucleobase may further be modified to include, though not intended to be limiting: universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. The term "ribonucleotide" or "nucleotide" may be used herein to refer to an unmodified nucleotide, a modified nucleotide, or a surrogate replacement moiety. Those in the art will recognize that guanine, cytosine, adenine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety.

In one embodiment, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability to form the required duplex structure and that permit or mediate the specific degradation of a target RNA via a RISC pathway. In certain embodiments of the invention, a FXI RNA interference agent includes a single stranded RNA that interacts with a target FXI RNA sequence to direct the cleavage of the target FXI RNA.

Modified RNA backbones can include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having

inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. Means of preparing phosphorus-containing linkages are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents, certain modified FXI antisense polynucleotides, and/or certain modified FXI sense polynucleotides of the invention.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Means of preparing modified RNA backbones that do not include a phosphorus atom are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents, certain modified FXI antisense polynucleotides, and/or certain modified FXI sense polynucleotides of the invention.

In certain embodiments of the invention, RNA mimetics are included in FXI dsRNAs, FXI antisense polynucleotides, and/or FXI sense polynucleotides, such as, but not limited to: replacement of the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units with novel groups. In such embodiments, base units are maintained for hybridization with an appropriate FXI nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Means of preparing RNA mimetics are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents of the invention.

Some embodiments of the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular -CH₂-NH-CH₂-, -CH₂-N(CH₃)-O-CH₂- [known as a methylene (methylimino) or MMI backbone], -CH₂-O-N(CH₃)-CH₂-, -CH₂-N(CH₃)-N(CH₃)-CH₂- and -N(CH₃)-CH₂- [wherein the native phosphodiester backbone is represented as -O-P-O-CH₂-]. Means of preparing RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones are routinely practiced in the art and such methods can be used to prepare certain

modified FXI dsRNA agents, certain FXI antisense polynucleotides, and/or certain FXI sense polynucleotides of the invention.

Modified RNAs can also contain one or more substituted sugar moieties. FXI dsRNAs, FXI antisense polynucleotides, and/or FXI sense polynucleotides of the invention may comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of a FXI dsRNA agent, or a group for improving the pharmacodynamic properties of a FXI dsRNA agent, FXI antisense polynucleotide, and/or FXI sense polynucleotide, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O-CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78:486-504) i.e., an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH₂-O-CH₂-N(CH₂)₂. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents of the invention.

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of a FXI dsRNA agent, FXI antisense polynucleotide, and/or FXI sense polynucleotide of the invention, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked FXI dsRNAs, FXI antisense polynucleotides, or FXI sense polynucleotides, and the 5' position of 5' terminal nucleotide. FXI dsRNA agents, FXI antisense polynucleotides, and/or FXI sense polynucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents, FXI antisense polynucleotides, and/or FXI sense polynucleotides of the invention.

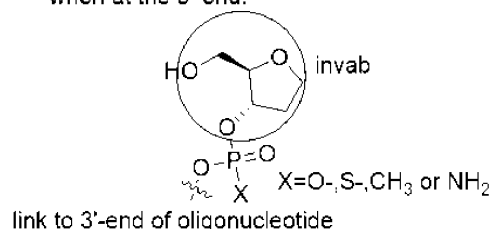
A FXI dsRNA agent, FXI antisense polynucleotide, and/or FXI sense polynucleotide may, in some embodiments, include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine and guanine, and the pyrimidine bases thymine, cytosine and uracil. Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Additional nucleobases that may be included in certain embodiments of FXI dsRNA agents of the invention are known in the art, see for example: *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, English et al., *Angewandte Chemie, International Edition*, 1991, 30, 613, Sanghvi, Y S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Means of preparing dsRNAs, FXI antisense strand polynucleotides and/or FXI sense strand polynucleotides that comprise nucleobase modifications and/or substitutions such as those described herein are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents, FXI sense polynucleotides, and/or FXI antisense polynucleotides of the invention.

Certain embodiments of FXI dsRNA agents, FXI antisense polynucleotides, and/or FXI sense polynucleotides of the invention include RNA modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide with a modified ribose moiety comprising an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids in a FXI dsRNA agent, FXI antisense polynucleotides, and/or FXI sense polynucleotides of the invention may increase stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) *Nucleic Acids Research* 33(1):439-447; Mook, O R. et al., (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. et al., (2003) *Nucleic Acids Research* 31(12):3185-3193). Means of preparing dsRNA agents, FXI antisense polynucleotides, and/or FXI sense polynucleotides that comprise locked nucleic acid(s) are routinely practiced in the art and such methods can be used to prepare certain modified FXI dsRNA agents of the invention.

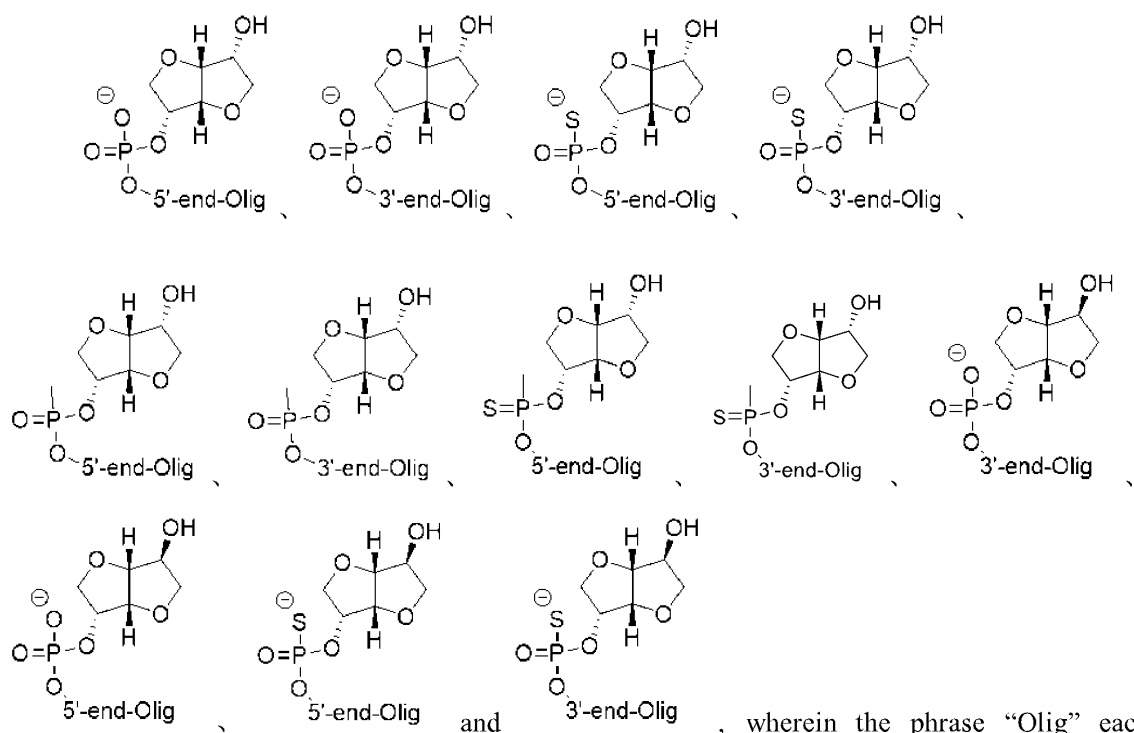
Certain embodiments of FXI dsRNA compounds, sense polynucleotides, and/or antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, 2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-Ome nucleotide, a nucleotide comprising a 5'-phosphorothioate group, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide. In some embodiments, a FXI dsRNA compound includes an E-vinylphosphonate nucleotide at the 5' end of the antisense strand, also referred to herein as the guide strand.

Certain embodiments of FXI dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide. It is known to skilled in art, including an abasic or inverted abasic nucleotide at the end of oligonucleotide enhances stability (Czaderna et al. Structural variations and stabilizing modifications of synthetic siRNAs in mammalian cells. *Nucleic Acids Res.* 2003;31(11):2705-2716. doi:10.1093/nar/gkg393). In some embodiments, a FXI dsRNA compound includes one or more inverted abasic residues (invab) at either 3'-end or 5'-end, or both 3'-end and 5'-end. Exemplified inverted abasic residues (invab) include, but are not limited to the following:

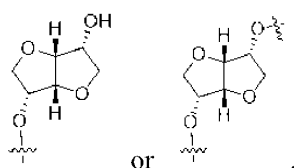
when at the 3'-end:



Certain embodiments of FXI dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: isomannide nucleotide or stereoisomer of said isomannide nucleotide. Specific examples of isomannide nucleotides or stereoisomers of said isomannide nucleotides include, but are not limited to:



Exemplified isomannide residues (imann) include, but are not limited to, the following:



In certain embodiments, the isomannide nucleotides may further conjugate to one or more targeting groups or delivery molecules, such as GalNAc moieties.

Certain embodiments of FXI dsRNA compounds, antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises unlocked nucleic acid nucleotide (UNA) or/and glycol nucleic acid nucleotide (GNA). It is known to skilled in art, UNA and GNA are thermally destabilizing chemical modifications, can significantly improves the off-target profile of a siRNA compound (Janas, et al., Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity. Nat Commun. 2018;9(1):723. doi:10.1038/s41467-018-02989-4; Laursen et al., Utilization of unlocked nucleic acid (UNA) to enhance siRNA performance in vitro and in vivo. Mol BioSyst. 2010;6:862–70).

Another modification that may be included in the RNA of certain embodiments of FXI dsRNA agents, FXI antisense polynucleotides, and/or FXI sense polynucleotides of the invention, comprises

chemically linking to the RNA one or more ligands, moieties or conjugates that enhance one or more characteristics of the FXI dsRNA agent, FXI antisense polynucleotide, and/or FXI sense polynucleotide, respectively. Non-limiting examples of characteristics that may be enhanced are: FXI dsRNA agent, FXI antisense polynucleotide, and/or FXI sense polynucleotide activity, cellular distribution, delivery of a FXI dsRNA agent, pharmacokinetic properties of a FXI dsRNA agent, and cellular uptake of the FXI dsRNA agent. In some embodiments of the invention, a FXI dsRNA agent comprises one or more targeting groups or linking groups, which in certain embodiments of FXI dsRNA agents of the invention are conjugated to the sense strand. A non-limiting example of a targeting group is a compound comprising N-acetyl-galactosamine (GalNAc). The terms “targeting group”, “targeting agent”, “linking agent”, “targeting compound”, “delivery molecule”, “delivery compound” and “targeting ligand” may be used interchangeably herein. In certain embodiments of the invention a FXI dsRNA agent comprises a targeting compound that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments of the invention a FXI dsRNA agent comprises a targeting compound that is conjugated to the 3'-terminal end of the sense strand. In some embodiments of the invention, a FXI dsRNA agent comprises a targeting group that comprises GalNAc. In certain embodiments of the invention a FXI dsRNA agent does not include a targeting compound conjugated to one or both of the 3'-terminal end and the 5'-terminal end of the sense strand. In certain embodiments of the invention a FXI dsRNA agent does not include a GalNAc containing targeting compound conjugated to one or both of the 5'-terminal end and the 3'-terminal end of the sense strand.

Additional targeting and linking agents are well known in the art, for example, targeting and linking agents that may be used in certain embodiments of the invention include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86: 6553-6556), cholic acid (Manoharan et al., Biorg. Med. Chem. Lett., 1994, 4:1053-1060), a thioether, e.g., beryl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Lett., 1993, 3:2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10:1111-1118; Kabanov et al., FEBS Lett., 1990, 259:327-330; Svinarchuk et al., Biochimie, 1993, 75:49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937).

Certain embodiments of a composition comprising a FXI dsRNA agent, FXI antisense polynucleotide, and/or FXI sense polynucleotide may comprise a ligand that alters distribution, targeting, or etc. of the FXI dsRNA agent. In some embodiments of a composition comprising a FXI dsRNA agent of the invention, the ligand increases 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 species absent such a ligand. A ligand useful in a composition and/or method of the invention may be a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); a carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. A ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid or polyamine. Examples of polyamino acids are a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolid) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

A ligand included in a composition and/or method of the invention may comprise a targeting group, non-limiting examples of which are a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody that binds to a specified cell type such as a kidney cell or a liver cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine 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.

Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g., cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (e.g., antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto,

PEG (e.g., PEG-40K), MPEG, [MPEG]₂, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g., biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu³⁺ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

A ligand included in a composition and/or method of the invention may be a protein, e.g., glycoprotein, or peptide, for example a molecule with a specific affinity for a co-ligand, or an antibody, for example an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, cardiac cell, or bone cell. A ligand useful in an embodiment of a composition and/or method of the invention can be a hormone or hormone receptor. A ligand useful in an embodiment of a composition and/or method of the invention can be a lipid, lectin, carbohydrates, vitamin, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, or multivalent fucose. A ligand useful in an embodiment of a composition and/or method of the invention can be a substance that can increase uptake of the FXI dsRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, e.g., by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. Non-limiting examples of this type of agent are: taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, and myoservin.

In some embodiments, a ligand attached to a FXI dsRNA agent of the invention functions as a pharmacokinetic (PK) modulator. An example of a PK modulator that may be used in compositions and methods of the invention includes but is not limited to: a lipophiles, a bile acid, a steroid, a phospholipid analogue, a peptide, a protein binding agent, PEG, a vitamin, cholesterol, a fatty acid, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, a phospholipid, a sphingolipid, naproxen, ibuprofen, vitamin E, biotin, an aptamer that binds a serum protein, etc. Oligonucleotides comprising a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, e.g., oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone may also be used in compositions and/or methods of the invention as ligands.

FXI dsRNA agent compositions

In some embodiments of the invention, a FXI dsRNA agent is in a composition. A composition of the invention may include one or more FXI dsRNA agent and optionally one or more of a pharmaceutically acceptable carrier, a delivery agent, a targeting agent, detectable label, etc. A non-limiting example of a targeting agent that may be useful according to some embodiments of methods of the invention is an agent that directs a FXI dsRNA agent of the invention to and/or into a

cell to be treated. A targeting agent of choice will depend upon such elements as: the nature of the FXI-associated disease or condition, and on the cell type being targeted. In a non-limiting example, in some embodiments of the invention it may be desirable to target a FXI dsRNA agent to and/or into a liver cell. It will be understood that in some embodiments of methods of the invention, a therapeutic agent comprises a FXI dsRNA agent with only a delivery agent, such as a delivery agent comprising N-Acetylgalactosamine (GalNAc), without any additional attached elements. For example, in some aspects of the invention a FXI dsRNA agent may be attached to a delivery compound comprising GalNAc and included in a composition comprising a pharmaceutically acceptable carrier and administered to a cell or subject without any detectable labels, or targeting agents, etc. attached to the FXI dsRNA agent.

In cases where a FXI dsRNA agent of the invention is administered with and/or attached to one or more delivery agents, targeting agents, labeling agents, etc. a skilled artisan will be aware of and able to select and use suitable agents for use in methods of the invention. Labeling agents may be used in certain methods of the invention to determine the location of a FXI dsRNA agent in cells and tissues and may be used to determine a cell, tissue, or organ location of a treatment composition comprising a FXI dsRNA agent that has been administered in methods of the invention. Procedures for attaching and utilizing labeling agents such as enzymatic labels, dyes, radiolabels, etc. are well known in the art. It will be understood that in some embodiments of compositions and methods of the invention, a labeling agent is attached to one or both of a sense polynucleotide and an antisense polynucleotide included in a FXI dsRNA agent.

Delivery of FXI dsRNA agents and FXI antisense polynucleotide agents

Certain embodiments of methods of the invention, includes delivery of a FXI dsRNA agent into a cell. As used herein the term, “delivery” means facilitating or effecting uptake or absorption into the cell. Absorption or uptake of a FXI dsRNA agent can occur through unaided diffusive or active cellular processes, or by use of delivery agents, targeting agents, etc. that may be associated with a FXI dsRNA agent of the invention. Delivery means that are suitable for use in methods of the invention include, but are not limited to: *in vivo* delivery, in which a FXI dsRNA agent is injected into a tissue site or administered systemically. In some embodiments of the invention, a FXI dsRNA agent is attached to a delivery agent.

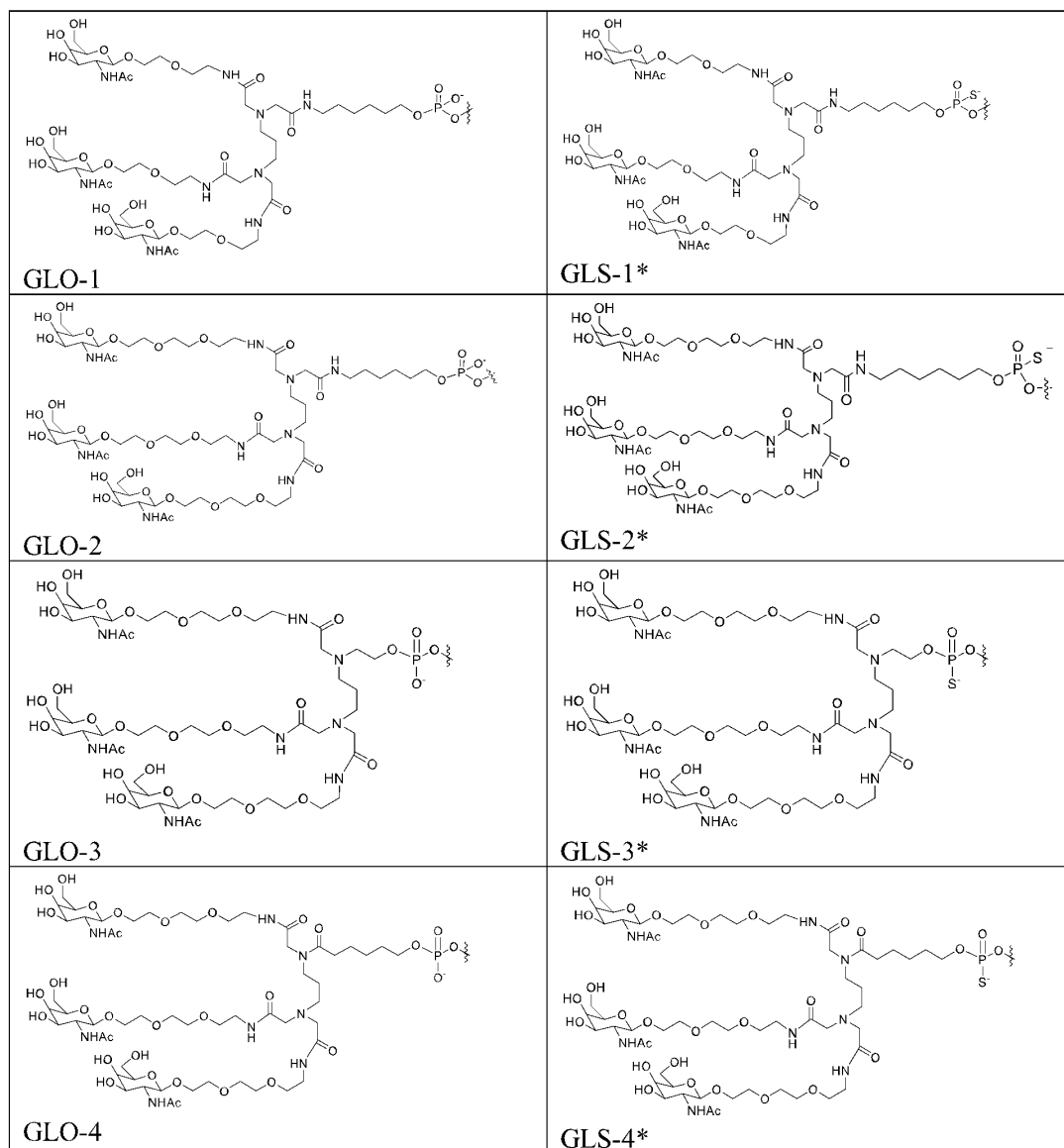
Non-limiting examples of methods that can be used to deliver FXI dsRNA agents to cells, tissues and/or subjects include: FXI dsRNA-GalNAc conjugates, SAMiRNA technology, LNP-based delivery methods, and naked RNA delivery. These and other delivery methods have been used successfully in the art to deliver therapeutic RNAi agents for treatment of various diseases and conditions, such as but

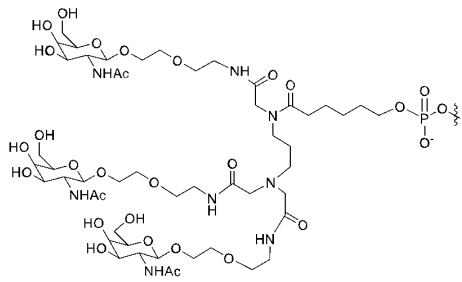
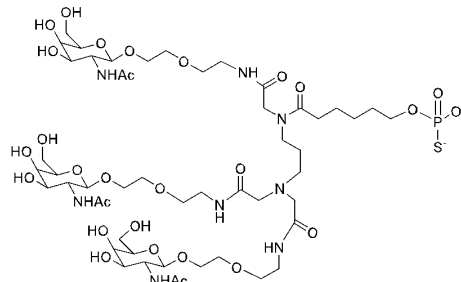
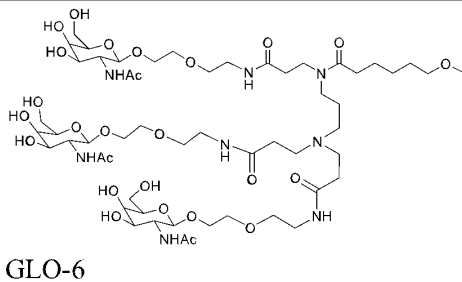
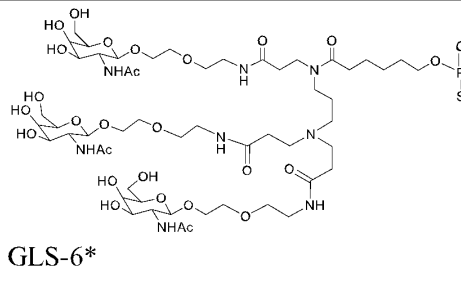
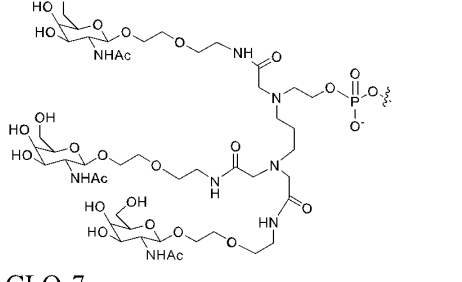
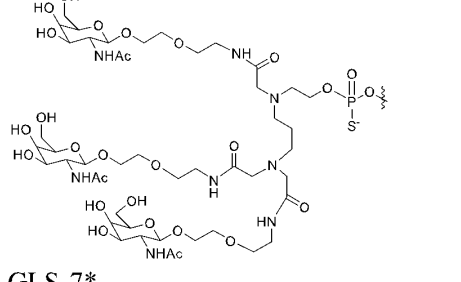
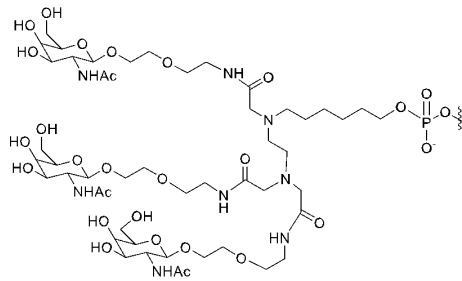
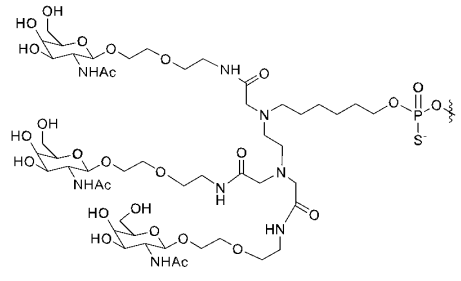
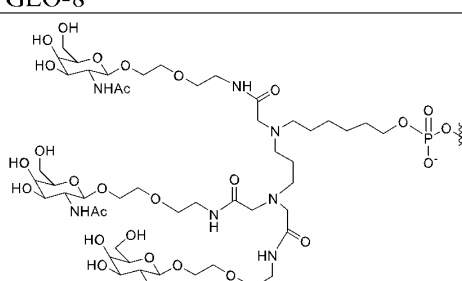
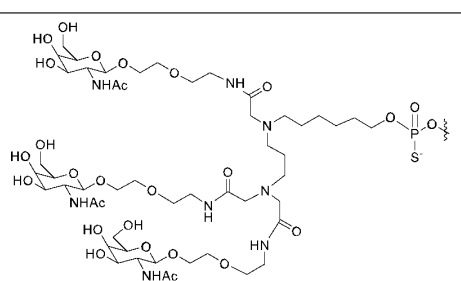
not limited to: liver diseases, acute intermittent porphyria (AIP), hemophilia, pulmonary fibrosis, etc. Details of various delivery means are found in publications such as: Nikam, R.R. & K. R. Gore (2018) *Nucleic Acid Ther*, 28 (4), 209-224 Aug 2018; Springer A.D. & S.F. Dowdy (2018) *Nucleic Acid Ther*. Jun 1; 28(3): 109–118; Lee, K. et al., (2018) *Arch Pharm Res*, 41(9), 867-874; and Nair, J.K. et al., (2014) *J. Am. Chem. Soc.* 136:16958-16961, the content each of which is incorporated by reference herein.

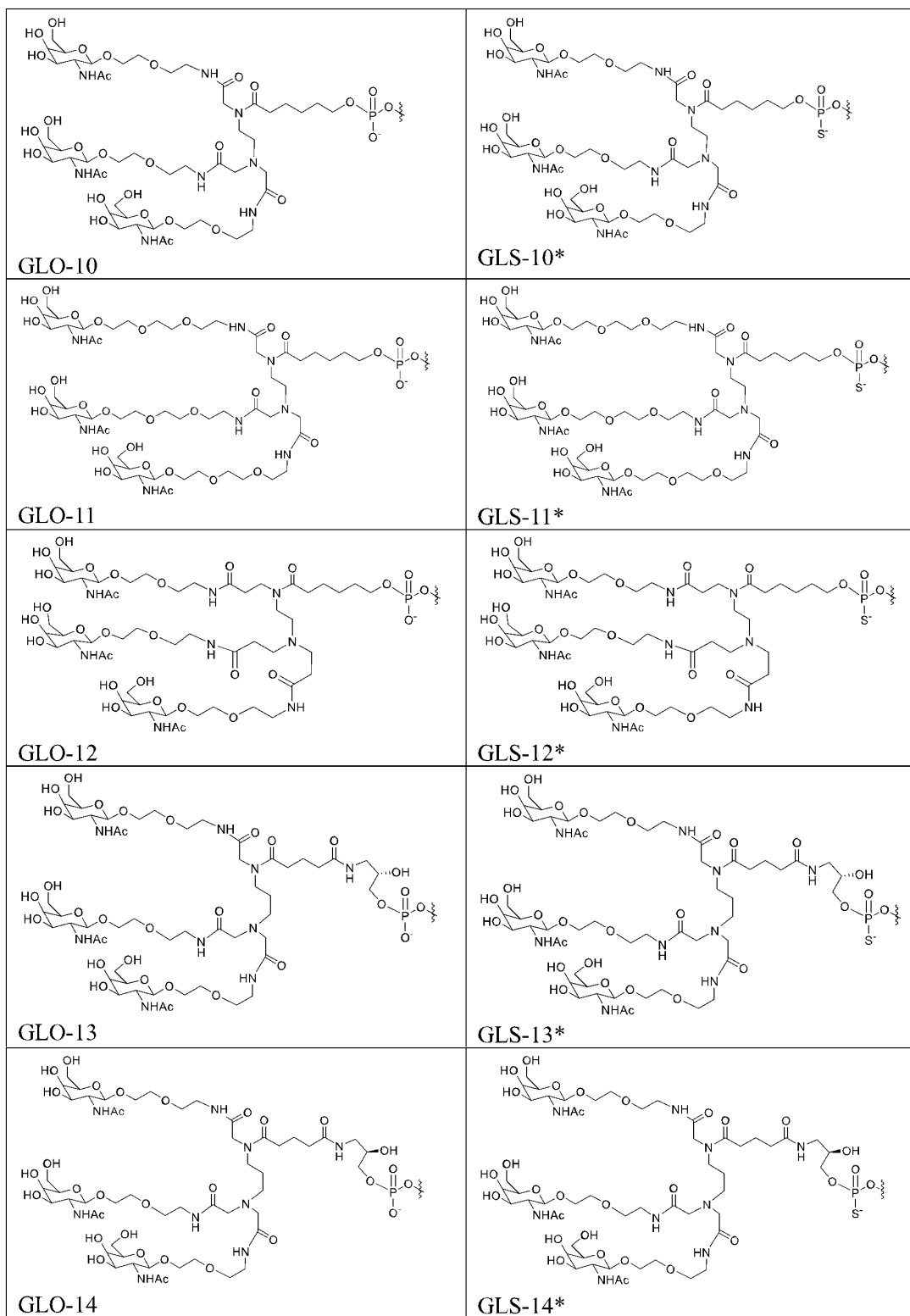
Some embodiments of the invention comprise use of lipid nanoparticles (LNPs) to deliver a FXI dsRNA agent of the invention to a cell, tissue, and/or subject. LNPs are routinely used for *in vivo* delivery of FXI dsRNA agents, including therapeutic FXI dsRNA agents. One benefit of using an LNP or other delivery agent is an increased stability of the FXI RNA agent when it is delivered to a subject using the LNP or other delivery agent. In some embodiments of the invention an LNP comprises a cationic LNP that is loaded with one or more FXI RNAi molecules of the invention. The LNP comprising the FXI RNAi molecule(s) is administered to a subject, the LNPs and their attached FXI RNAi molecules are taken up by cells via endocytosis, their presence results in release of RNAi trigger molecules, which mediate RNAi.

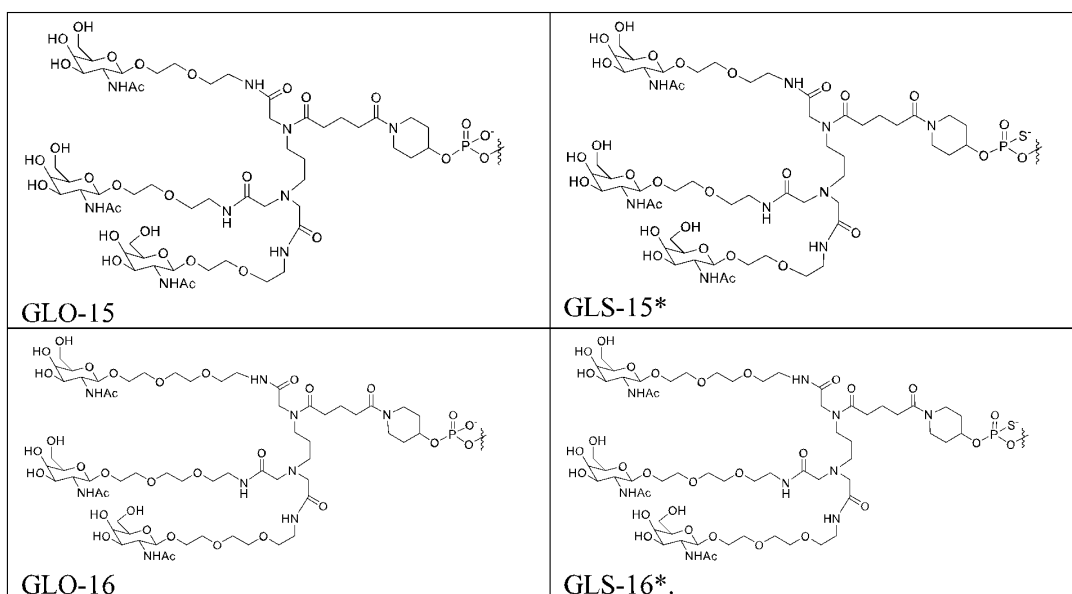
Another non-limiting example of a delivery agent that may be used in embodiments of the invention to delivery a FXI dsRNA agent of the invention to a cell, tissue and/or subject is an agent comprising GalNAc that is attached to a FXI dsRNA agent of the invention and delivers the FXI dsRNA agent to a cell, tissue, and/or subject. Examples of certain additional delivery agents comprising GalNAc that can be used in certain embodiments of methods and composition of the invention are disclosed in PCT Application: WO2020191183A1, WO2023/045995A1 (incorporated herein in its entirety). A non-limiting example of a GalNAc targeting ligand that can be used in compositions and methods of the invention to deliver a FXI dsRNA agent to a cell is a targeting ligand cluster. Examples of targeting ligand clusters that are presented herein are referred to as: GalNAc Ligand with phosphodiester link (GLO) and GalNAc Ligand with phosphorothioate link (GLS *). The term “GLX-n” may be used herein to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is shown below, with the below with location of attachment of the GalNAc-targeting ligand to an RNAi agent of the invention at far right of each (shown with “}”). It will be understood that any RNAi and dsRNA molecule of the invention can be attached to the GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*,

GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, GLO-1 through GLO-16 and GLS-1* through GLS-16* structures are shown below.

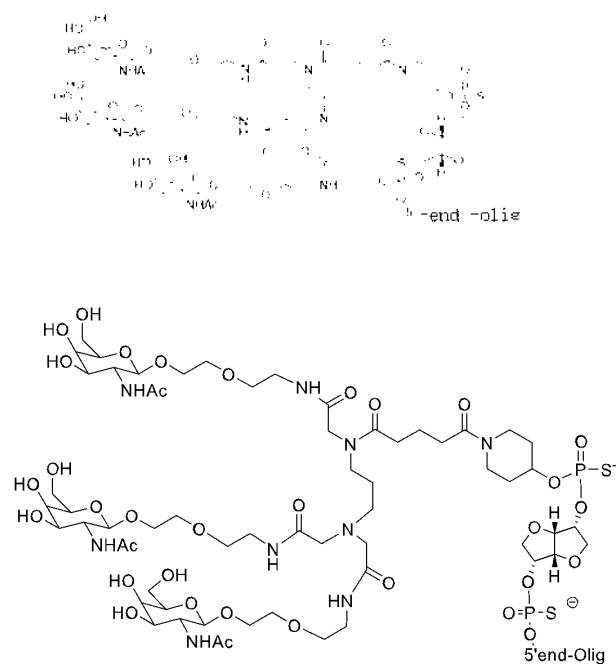


 GLO-5	 GLS-5*
 GLO-6	 GLS-6*
 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*





In certain embodiments, the aforesaid isomannide nucleotides may further conjugate to one or more GalNAc targeting ligands. Specific examples of isomannide nucleotides conjugated to a GalNAc targeting ligand include, but are not limited to:



In some embodiments of the invention, in vivo delivery can also be by a beta-glucan delivery system, such as those described in U.S. Pat. Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. In vitro introduction of a FXI RNAi agent into a cell may also be done using art-known methods such as electroporation and

lipofection. In certain embodiments of methods of the invention, a FXI dsRNA is delivered without a targeting agent. These RNAs may be delivered as “naked” RNA molecules. As a non-limiting example, a FXI dsRNA of the invention may be administered to a subject to treat a FXI-associated disease or condition in the subject, such as a liver disease, in a pharmaceutical composition comprising the RNAi agent, but not including a targeting agent such as a GalNAc targeting compound.

In addition to certain delivery means described herein, it will be understood that RNAi delivery means, such as but not limited to those described herein and those used in the art, can be used in conjunction with embodiments of FXI RNAi agents and treatment methods described herein.

FXI dsRNA agents of the invention may be administered to a subject in an amount and manner effective to reduce a level and activity of FXI polypeptide in a cell and/or subject. In some embodiments of methods of the invention one or more FXI dsRNA agents are administered to a cell and/or subject to treat a disease or condition associated with FXI expression and activity. Methods of the invention, in some embodiments, include administering one or more FXI dsRNA agents to a subject in need of such treatment to reduce a disease or condition associated with FXI expression in the subject. FXI dsRNA agents or FXI antisense polynucleotide agents of the invention can be administered to reduce FXI expression and/or activity in one more of *in vitro*, *ex vivo*, and *in vivo* cells.

In some embodiments of the invention, a level, and thus an activity, of FXI polypeptide in a cell is reduced by delivering (e.g. introducing) a FXI dsRNA agent or FXI antisense polynucleotide agent into a cell. Targeting agents and methods may be used to aid in delivery of a FXI dsRNA agent or FXI antisense polynucleotide agent to a specific cell type, cell subtype, organ, spatial region within a subject, and/or to a sub-cellular region within a cell. A FXI dsRNA agent can be administered in certain methods of the invention singly or in combination with one or more additional FXI dsRNA agents. In some embodiments, 2, 3, 4, or more independently selected FXI dsRNA agents are administered to a subject.

In certain embodiments of the invention, a FXI dsRNA agent is administered to a subject to treat a FXI-associated disease or condition in conjunction with one or more additional therapeutic regimens for treating the FXI-associated disease or condition. Non-limiting examples of additional therapeutic regimens are: administering one or more FXI antisense polynucleotides of the invention, administering a non-FXI dsRNA therapeutic agent, and a behavioral modification. An additional therapeutic regimen may be administered at a time that is one or more of: prior to, simultaneous with, and following administration of a FXI dsRNA agent of the invention. It will be understood that simultaneous with as used herein, within five minutes of time zero, within 10 minutes of time zero, within 30 minutes of time zero, within 45 minutes of time zero, and within 60 minutes of time zero, with “time zero” the time of administration of the FXI dsRNA agent of the invention to the subject.

Non-limiting examples of non-FXI dsRNA therapeutic agents are: NSAID/Cyclooxygenase inhibitors, such as, aspirin; adenosine diphosphate (ADP) receptor inhibitors, such as, clopidogrel (PLAVIX) and ticlopidine (TICLID).; phosphodiesterase inhibitors, such as, cilostazol (PLETAL); glycoprotein IIB/IIIa inhibitors, such as, abciximab (REOPRO), eptifibatide (INTEGRILIN), tirofiban (AGGRASTAT), and defibrotide; adenosine reuptake inhibitors, such as, dipyridamole (PERSANTINE); warfarin (and related coumarins), heparin; direct thrombin inhibitors, such as lepirudin, bivalirudin, apixaban, LOVENOX (enoxaparin); and small molecular compounds that interfere directly with the enzymatic action of particular coagulation factors (e.g. rivaroxaban, which interferes with Factor Xa). These and other therapeutic agents and behavior modifications are known in the art and used to treat a FXI disease or condition in a subject and may be administered to a subject in combination with the administration of one or more FXI dsRNA agents of the invention to treat the FXI disease or condition. A FXI dsRNA agent of the invention administered to a cell or subject to treat a FXI-associated disease or condition may act in a synergistic manner with one or more other therapeutic agents or activities and increase the effectiveness of the one or more therapeutic agents or activities and/or to increase the effectiveness of the FXI dsRNA agent at treating the FXI-associated disease or condition.

Treatment methods of the invention that include administration of a FXI dsRNA agent can be used prior to the onset of a FXI-associated disease or condition and/or when a FXI-associated disease or condition is present, including at an early stage, mid-stage, and late stage of the disease or condition and all times before and after any of these stages. Methods of the invention may also be to treat subjects who have previously been treated for a FXI-associated disease or condition with one or more other therapeutic agents and/or therapeutic activities that were not successful, were minimally successful, and/or are no longer successful at treating the FXI-associated disease or condition in the subject.

Vector Encoded dsRNAs

In certain embodiments of the invention, a FXI dsRNA agent can be delivered into a cell using a vector. FXI dsRNA agent transcription units can be included in a DNA or RNA vector. Prepare and use of such vectors encoding transgenes for delivering sequences into a cell and or subject are well known in the art. Vectors can be used in methods of the invention that result in transient expression of FXI dsRNA, for example for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more weeks. The length of the transient expression can be determined using routine methods based on elements such as, but not limited to the specific vector construct selected and the target cell and/or tissue. Such transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed

to permit it to be inherited as an extrachromosomal plasmid (Gassmann, et al., Proc. Natl. Acad. Sci. USA (1995) 92:1292).

An individual strand or strands of a FXI dsRNA agent can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced to a cell using means such as transfection or infection. In certain embodiments each individual strand of a FXI dsRNA agent of the invention can be transcribed by promoters that are both included on the same expression vector. In certain embodiments of the invention a FXI dsRNA agent is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the FXI dsRNA agent has a stem and loop structure.

Non-limiting examples of RNA expression vectors are DNA plasmids or viral vectors. Expression vectors useful in embodiments of the invention can be compatible with eukaryotic cells. Eukaryotic cell expression vectors are routinely used in the art and are available from a number of commercial sources. Delivery of FXI dsRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that allows for introduction into a desired target cell.

Viral vector systems that may be included in an embodiment of a method of the include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, etc.; (c) adeno-associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, e.g., vaccinia virus vectors or avipox, e.g. canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Constructs for the recombinant expression of a FXI dsRNA agent may include regulatory elements, such as promoters, enhancers, etc., which may be selected to provide constitutive or regulated/inducible expression. Viral vector systems, and the use of promoters and enhancers, etc. are routine in the art and can be used in conjunction with methods and compositions described herein.

Certain embodiments of the invention include use of viral vectors for delivery of FXI dsRNA agents into cells. Numerous adenovirus-based delivery systems are routinely used in the art for delivery to, for example, lung, liver, the central nervous system, endothelial cells, and muscle. Non-limiting examples of viral vectors that may be used in methods of the invention are: AAV vectors, a pox virus such as a vaccinia virus, a Modified Virus Ankara (MVA), NYVAC, an avipox such as fowl pox or canary pox.

Certain embodiments of the invention include methods of delivering FXI dsRNA agents into cells using a vector and such vectors may be in a pharmaceutically acceptable carrier that may, but need not, include a slow release matrix in which the gene delivery vehicle is imbedded. In some embodiments, a vector for delivering a FXI dsRNA can be produced from a recombinant cell, and a pharmaceutical composition of the invention may include one or more cells that produced the FXI dsRNA delivery system.

Pharmaceutical Compositions Containing FXI dsRNA or ssRNA agents

Certain embodiments of the invention include use of pharmaceutical compositions containing a FXI dsRNA agent or FXI antisense polynucleotide agent and a pharmaceutically acceptable carrier. The pharmaceutical composition containing the FXI dsRNA agent or FXI antisense polynucleotide agent can be used in methods of the invention to reduce FXI gene expression and FXI activity in a cell and is useful to treat a FXI-associated disease or condition. Such pharmaceutical compositions can be formulated based on the mode of delivery. Non-limiting examples of formulations for modes of delivery are: a composition formulated for subcutaneous delivery, a composition formulated for systemic administration via parenteral delivery, a composition formulated for intravenous (IV) delivery, a composition formulated for intrathecal delivery, a composition formulated for direct delivery into brain, etc. Administration of a pharmaceutic composition of the invention to deliver a FXI dsRNA agent or FXI antisense polynucleotide agent into a cell may be done using one or more means such as: topical (e.g., by a transdermal patch), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, e.g., via an implanted device; or intracranial, e.g., by intraparenchymal, intrathecal or intraventricular, administration. A FXI dsRNA agent or FXI antisense polynucleotide agent can also be delivered directly to a target tissue, for example directly into the liver, directly into a kidney, etc. It will be understood that “delivering a FXI dsRNA agent” or “delivering a FXI antisense polynucleotide agent” into a cell encompasses delivering a FXI dsRNA agent or FXI antisense polynucleotide agent, respectively, directly as well as expressing a FXI dsRNA agent in a cell from an encoding vector that is delivered into a cell, or by any suitable means with which the FXI dsRNA or FXI antisense polynucleotide agent becomes present in a cell. Preparation and use of formulations and means for delivering inhibitory RNAs are well known and routinely used in the art.

As used herein, a “pharmaceutical composition” comprises a pharmacologically effective amount of a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention and a

pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

As used herein terms such as: “pharmacologically effective amount,” “therapeutically effective amount” and “effective amount” refers to that amount of a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 10% reduction in that parameter. For example, a therapeutically effective amount of a FXI dsRNA agent or FXI antisense polynucleotide agent can reduce FXI polypeptide levels by at least 10%.

Effective amounts

Methods of the invention, in some aspects comprise contacting a cell with a FXI dsRNA agent or FXI antisense polynucleotide agent in an effective amount to reduce FXI gene expression in the contacted cell. Certain embodiments of methods of the invention comprise administering a FXI dsRNA agent or a FXI antisense polynucleotide agent to a subject in an amount effective to reduce FXI gene expression and treat a FXI-associated disease or condition in the subject. An “effective amount” used in terms of reducing expression of FXI and/or for treating a FXI-associated disease or condition, is an amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of a FXI dsRNA agent or FXI antisense polynucleotide agent to treat a FXI-associated disease or condition could be that amount necessary to (i) slow or halt progression of the disease or condition; or (ii) reverse, reduce, or eliminate one or more symptoms of the disease or condition. In some aspects of the invention, an effective amount is that amount of a FXI dsRNA agent or FXI antisense polynucleotide agent that when administered to a subject in need of a treatment of a

FXI-associated disease or condition, results in a therapeutic response that prevents and/or treats the disease or condition. According to some aspects of the invention, an effective amount is that amount of a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention that when combined or co-administered with another therapeutic treatment for a FXI-associated disease or condition, results in a therapeutic response that prevents and/or treats the disease or condition. In some embodiments of the invention, a biologic effect of treating a subject with a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention may be the amelioration and or absolute elimination of symptoms resulting from the FXI-associated disease or condition. In some embodiments of the invention, a biologic effect is the complete abrogation of the FXI-associated disease or condition, as evidenced for example, by a diagnostic test that indicates the subject is free of the FXI-associated disease or condition. A non-limiting example of a physiological symptom that may be detected includes a reduction in FXI level in liver of a subject following administration of an agent of the invention. Additional art-known means of assessing the status of a FXI-associated disease or condition can be used to determine an effect of an agent and/or methods of the invention on a FXI-associated disease or condition.

Typically an effective amount of a FXI dsRNA agent or FXI antisense polynucleotide agent to decrease FXI polypeptide activity to a level to treat a FXI-associated disease or condition will be determined in clinical trials, establishing an effective dose for a test population versus a control population in a blind study. In some embodiments, an effective amount will be that results in a desired response, e.g., an amount that diminishes a FXI-associated disease or condition in cells, tissues, and/or subjects with the disease or condition. Thus, an effective amount of a FXI dsRNA agent or FXI antisense polynucleotide agent to treat a FXI-associated disease or condition that can be treated by reducing FXI polypeptide activity may be the amount that when administered decreases the amount of FXI polypeptide activity in the subject to an amount that is less than the amount that would be present in the cell, tissue, and/or subject without the administration of the FXI dsRNA agent or FXI antisense polynucleotide agent. In certain aspects of the invention the level of FXI polypeptide activity, and/or FXI gene expression present in a cell, tissue, and/or subject that has not been contacted with or administered a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention is referred to as a "control" amount. In some embodiments of methods of the invention a control amount for a subject is a pre-treatment amount for the subject, in other words, a level in a subject before administration of a FXI agent can be a control level for that subject and compared to a level of FXI polypeptide activity and/or FXI gene expression in the subject following siRNA administered to the subject. In the case of treating a FXI-associated disease or condition the desired response may be reducing or eliminating one or more symptoms of the disease or condition in the cell, tissue, and/or subject. The reduction or

elimination may be temporary or may be permanent. It will be understood that the status of a FXI-associated disease or condition can be monitored using methods of determining FXI polypeptide activity, FXI gene expression, symptom evaluation, clinical testing, etc. In some aspects of the invention, a desired response to treatment of a FXI-associated disease or condition is delaying the onset or even preventing the onset of the disease or condition.

An effective amount of a compound that decreases FXI polypeptide activity may also be determined by assessing physiological effects of administration of a FXI dsRNA agent or FXI antisense polynucleotide agent on a cell or subject, such as a decrease of a FXI-associated disease or condition following administration. Assays and/or symptomatic monitoring of a subject can be used to determine efficacy of a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention, which may be administered in a pharmaceutical compound of the invention, and to determine the presence or absence of a response to the treatment. A non-limiting example, is that one or more art-known tests of activated partial thromboplastin time (aPTT), prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a blood sample of the animal. Another non-limiting example, is that one or more art-known tests of liver function can be used to determine the status of the FXI-associated liver disease or condition in a subject before and after treatment of the subject with a FXI dsRNA agent of the invention.

Some embodiments of the invention include methods of determining an efficacy of an dsRNA agent or FXI antisense polynucleotide agent of the invention administered to a subject, to treat a FXI-associated disease or condition by assessing and/or monitoring one or more “physiological characteristics” of the FXI-associated disease or condition in the subject. Non-limiting examples of physiological characteristics of a FXI-associated disease or condition are the FXI mRNA level, the FXI protein level, or activated partial thromboplastin time (aPTT), prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a plasma, or a tissue sample, and/or accumulation of fat and/or expansion of lipid droplets in the liver, etc. Standard means of determining such physiological characteristic are known in the art and include, but are not limited to, blood tests, imaging studies, physical examination, etc.

It will be understood that the amount of a FXI dsRNA agent or FXI antisense polynucleotide agent administered to a subject can be modified based, at least in part, on such determinations of disease and/or condition status and/or physiological characteristics determined for a subject. The amount of a treatment may be varied for example by increasing or decreasing the amount of a FXI-dsRNA agent or FXI antisense polynucleotide agent, by changing the composition in which the FXI dsRNA agent or FXI antisense polynucleotide agent, respectively, is administered, by changing the route of administration, by changing the dosage timing and so on. The effective amount of a FXI

dsRNA agent or FXI antisense polynucleotide agent will vary with the particular condition being treated, the age and physical condition of the subject being treated; the severity of the condition, the duration of the treatment, the nature of the concurrent therapy (if any), the specific route of administration, and additional factors within the knowledge and expertise of the health practitioner. For example, an effective amount may depend upon the desired level of FXI polypeptide activity and or FXI gene expression that is effective to treat the FXI-associated disease or condition. A skilled artisan can empirically determine an effective amount of a particular FXI dsRNA agent or FXI antisense polynucleotide agent of the invention for use in methods of the invention without necessitating undue experimentation. Combined with the teachings provided herein, by selecting from among various FXI dsRNA agents or FXI antisense polynucleotide agents of the invention, and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned that is effective to treat the particular subject. As used in embodiments of the invention, an effective amount of a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention can be that amount that when contacted with a cell results in a desired biological effect in the cell.

It will be recognized that FXI gene silencing may be determined in any cell expressing FXI, either constitutively or by genomic engineering, and by any appropriate assay. In some embodiments of the invention, FXI gene expression is reduced by at least 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% by administration of a FXI dsRNA agent of the invention. In some embodiments of the invention, FXI gene expression is reduced by at between 5% and 10%, 5% and 25%, 10% and 50%, 10% and 75%, 25% and 75%, 25% and 100%, or 50% and 100% by administration of a FXI dsRNA agent of the invention.

Dosing

FXI dsRNA agents and FXI antisense polynucleotide agents are delivered in pharmaceutical compositions in dosages sufficient to inhibit expression of FXI genes. In certain embodiments of the invention, a dose of FXI dsRNA agent or FXI antisense polynucleotide agent is in a range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of 1 to 50 mg per kilogram body weight, 5 to 40 mg/kg body weight, 10 to 30 mg/kg body weight, 1 to 20 mg/kg body weight, 1 to 10 mg/kg body weight, 4 to 15 mg/kg body weight per day, inclusive. For example, the FXI dsRNA agent or FXI antisense polynucleotide agent can be administered in an amount that is from about 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 1 mg/kg,

1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4 mg/kg, 4.1 mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, 5 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8 mg/kg, 5.9 mg/kg, 6 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 9 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33mg/kg, 34 mg/kg, 35 mg/kg, 36 mg/kg, 37 mg/kg, 38 mg/kg, 39 mg/kg, 40 mg/kg, 41 mg/kg, 42 mg/kg, 43mg/kg, 44 mg/kg, 45 mg/kg, 46 mg/kg, 47 mg/kg, 48 mg/kg, 49 mg/kg, through 50 mg/kg body per single dose.

Various factors may be considered in the determination of dosage and timing of delivery of a FXI dsRNA agent of the invention. The absolute amount of a FXI dsRNA agent or FXI antisense polynucleotide agent delivered will depend upon a variety of factors including a concurrent treatment, the number of doses and the individual subject parameters including age, physical condition, size and weight. These are factors well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. In some embodiments, a maximum dose can be used, that is, the highest safe dose according to sound medical judgment.

Methods of the invention may in some embodiments include administering to a subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more doses of a FXI dsRNA agent or FXI antisense polynucleotide agent. In some instances, a pharmaceutical compound, (e.g., comprising a FXI dsRNA agent or comprising a FXI antisense polynucleotide agent) can be administered to a subject at least daily, every other day, weekly, every other week, monthly, etc. Doses may be administered once per day or more than once per day, for example, 2, 3, 4, 5, or more times in one 24 hour period. A pharmaceutical composition of the invention may be administered once daily, or the FXI dsRNA agent or FXI antisense polynucleotide agent may be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In some embodiments of methods of the invention, a pharmaceutical composition of the invention is administered to a subject one or more times per day, one or more times per week, one or more times per month, or one or more times per year.

Methods of the invention, in some aspects, include administration of a pharmaceutical compound alone, in combination with one or more other FXI dsRNA agents or FXI antisense polynucleotide agents, and/or in combination with other drug therapies or treatment activities or regimens that are administered to subjects with a FXI-associated disease or condition. Pharmaceutical compounds may be administered in pharmaceutical compositions. Pharmaceutical compositions used in methods of the invention may be sterile and contain an amount of a FXI dsRNA agent or FXI antisense polynucleotide agent that will reduce activity of a FXI polypeptide to a level sufficient to produce the desired response in a unit of weight or volume suitable for administration to a subject. A dose administered to a subject of a pharmaceutical composition that includes a FXI dsRNA agent or FXI antisense polynucleotide agent to reduce FXI protein activity can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

Treatment

FXI-associated diseases and conditions in which a decrease in a level and/or activity of FXI polypeptide is effective to treat the disease or condition, can be treated using methods and FXI dsRNA agents of the invention to inhibit FXI expression. Examples of diseases and conditions that may be treated with a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention and a treatment method of the invention, include, but are not limited to thromboembolic condition, the thromboembolic condition is deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, stroke, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), including thrombosis associated with dialysis, or other procoagulant condition. Also provided are methods useful treating, preventing, or ameliorating a thromboembolic condition without increasing bleeding risk in an individual. In certain embodiments, the individual is at risk for a thromboembolic condition, including, but not limited to infarct, thrombosis, embolism, thromboembolism such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a thromboembolic condition include immobility, surgery (particularly orthopedic surgery), dialysis, malignancy, pregnancy, older age, use of oral contraceptives, atrial fibrillation, previous thromboembolic condition, chronic inflammatory disease, inherited or acquired prothrombotic clotting disorders and thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD). Certain outcomes associated with development of a thromboembolic condition include decreased blood flow through an affected vessel, death of tissue,

and death. Such diseases and conditions may be referred to herein as “FXI-associated diseases and conditions” and “diseases and conditions caused and/or modulated by FXI.”

In certain aspects of the invention, a subject may be administered a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention at a time that is one or more of before or after diagnosis of a FXI-associated disease or condition. In some aspects of the invention, a subject is at risk of having or developing a FXI-associated disease or condition. A subject at risk of developing a FXI-associated disease or condition is one who has an increased probability of developing the FXI-associated disease or condition, compared to a control risk of developing the FXI-associated disease or condition. In some embodiments of the invention, a level of risk may be statistically significant compared to a control level of risk. A subject at risk may include, for instance, a subject who is, or will be, a subject who has a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to a FXI-associated disease or condition than a control subject without the preexisting disease or genetic abnormality; a subject having a family and/or personal medical history of the FXI-associated disease or condition; and a subject who has previously been treated for a FXI-associated disease or condition. It will be understood that a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to a FXI-associated disease or condition, may be a disease or genetic abnormality that when present has been previously identified as having a correlative relation to a higher likelihood of developing a FXI-associated disease or condition.

It will be understood that a FXI dsRNA agent or FXI antisense polynucleotide agent may be administered to a subject based on a medical status of the individual subject. For example, a healthcare provider for a subject may assess a FXI level measured in a sample obtained from a subject and determine it is desirable to reduce the subject's FXI level, by administration of a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention. In this example, the FXI level may be considered to be a physiological characteristic of a FXI-associated condition, even if the subject is not diagnosed as having a FXI-associated disease such as one disclosed herein. A healthcare provider may monitor changes in the subject's FXI level, as a measure of efficacy of the administered FXI dsRNA agent or FXI antisense polynucleotide agent of the invention. In a non-limiting example, a biological sample, such as a blood or serum sample may be obtained from a subject and a FXI level for the subject determined in the sample. A FXI dsRNA agent or FXI antisense polynucleotide agent is administered to the subject and a blood or liver sample is obtained from the subject following the administration and the FXI level determined using the sample and the results compared to the results determined in the subject's pre-administration (prior) sample. A reduction in the subject's FXI level in the later sample compared to the pre-administration level indicates the administered FXI dsRNA agent or FXI antisense polynucleotide agent efficacy in reducing the lipid level in the subject.

Certain embodiments of methods of the invention include adjusting a treatment that includes administering a dsRNA agent or a FXI antisense polynucleotide agent of the invention to a subject based at least in part on assessment of a change in one or more of the subject's physiological characteristics of a FXI-associated disease or condition resulting from the treatment. For example, in some embodiments of the invention, an effect of an administered dsRNA agent or FXI antisense polynucleotide agent of the invention may be determined for a subject and used to assist in adjusting an amount of a dsRNA agent or FXI antisense polynucleotide agent of the invention subsequently administered to the subject. In a non-limiting example, a subject is administered a dsRNA agent or FXI antisense polynucleotide agent of the invention, the subject's FXI level is determined after the administration, and based at least in part on the determined level, a greater amount of the dsRNA agent or FXI antisense polynucleotide agent is determined to be desirable in order to increase the physiological effect of the administered agent, for example to reduce or further reduce the subject's FXI level. In another non-limiting example, a subject is administered a dsRNA agent or FXI antisense polynucleotide agent of the invention, the subject's FXI level is determined after the administration and based at least in part on the determined level, a lower amount of the dsRNA agent or FXI antisense polynucleotide agent is desirable to administer to the subject.

Thus, some embodiments of the invention include assessing a change in one or more physiological characteristics of resulting from a subject's previous treatment to adjust an amount of a dsRNA agent or FXI antisense polynucleotide agent of the invention subsequently administered to the subject. Some embodiments of methods of the invention include 1, 2, 3, 4, 5, 6, or more determinations of a physiological characteristic of a FXI-associated disease or condition to assess and/or monitor the efficacy of an administered FXI dsRNA agent or FXI antisense polynucleotide agent of the invention, and optionally using the determinations to adjust one or more of: a dose, administration regimen, and or administration frequency of a dsRNA agent or FXI antisense polynucleotide agent of the invention to treat a FXI-associated disease or condition in a subject. In some embodiments of methods of the invention, a desired result of administering an effective amount of a dsRNA agent or FXI antisense polynucleotide agent of the invention to a subject is a reduction of the subject's the FXI mRNA level, the FXI protein level in the subject, or activated partial thromboplastin time (aPTT), prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a plasma, or a tissue sample, and/or accumulation of fat and/or expansion of lipid droplets in the liver, etc., as compared to a prior level determined for the subject, or to a control level.

As used herein, the terms "treat", "treated", or "treating" when used with respect to a FXI-associated disease or condition may refer to a prophylactic treatment that decreases the likelihood of a

subject developing the FXI-associated disease or condition, and also may refer to a treatment after the subject has developed a FXI-associated disease or condition in order to eliminate or reduce the level of the FXI-associated disease or condition, prevent the FXI-associated disease or condition from becoming more advanced (e.g., more severe), and/or slow the progression of the FXI-associated disease or condition in a subject compared to the subject in the absence of the therapy to reduce activity in the subject of FXI polypeptide.

Certain embodiments of agents, compositions, and methods of the invention can be used to inhibit FXI gene expression. As used herein in reference to expression of a FXI gene, the terms “inhibit,” “silence,” “reduce,” “down-regulate,” and “knockdown” mean the expression of the FXI gene, as measured by one or more of: a level of RNA transcribed from the gene, a level of activity of FXI expressed, and a level of FXI polypeptide, protein or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the FXI gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is contacted with (e.g., treated with) a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention, compared to a control level of RNA transcribed from the FXI gene, a level of activity of expressed FXI, or a level of FXI translated from the MRNA, respectively. In some embodiments, a control level is a level in a cell, tissue, organ or subject that has not been contacted with (e.g. treated with) the FXI dsRNA agent or FXI antisense polynucleotide agent.

Administration methods

A variety of administration routes for a FXI dsRNA agent or FXI antisense polynucleotide agent are available for use in methods of the invention. The particular delivery mode selected will depend at least in part, upon the particular condition being treated and the dosage required for therapeutic efficacy. Methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of treatment of a FXI-associated disease or condition without causing clinically unacceptable adverse effects. In some embodiments of the invention, a FXI dsRNA agent or FXI antisense polynucleotide agent may be administered via an oral, enteral, mucosal, subcutaneous, and/or parenteral route. The term “parenteral” includes subcutaneous, intravenous, intrathecal, intramuscular, intraperitoneal, and intrasternal injection, or infusion techniques. Other routes include but are not limited to nasal (e.g., via a gastro-nasal tube), dermal, vaginal, rectal, sublingual, and inhalation. Delivery routes of the invention may include intrathecal, intraventricular, or intracranial. In some embodiments of the invention, a FXI dsRNA agent or FXI antisense polynucleotide agent may be placed within a slow release matrix and administered by placement of the matrix in the subject. In some aspects of the invention, a FXI dsRNA

agent or FXI antisense polynucleotide agent may be delivered to a subject cell using nanoparticles coated with a delivery agent that targets a specific cell or organelle. Various delivery means, methods, agents are known in the art. Non-limiting examples of delivery methods and delivery agents are additionally provided elsewhere herein. In some aspects of the invention, the term “delivering” in reference to a FXI dsRNA agent or FXI antisense polynucleotide agent may mean administration to a cell or subject of one or more “naked” FXI dsRNA agent or FXI antisense polynucleotide agent sequences and in certain aspects of the invention “delivering” means administration to a cell or subject via transfection means, delivering a cell comprising a FXI dsRNA agent or FXI antisense polynucleotide agent to a subject, delivering a vector encoding a FXI dsRNA agent or FXI antisense polynucleotide agent into a cell and/or subject, etc. Delivery of a FXI dsRNA agent or FXI antisense polynucleotide agent using a transfection means may include administration of a vector to a cell and/or subject.

In some methods of the invention one or more FXI dsRNA agents or FXI antisense polynucleotide agents may be administered in formulations, which may be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients. In some embodiments of the invention a FXI dsRNA agent or FXI antisense polynucleotide agent may be formulated with another therapeutic agent for simultaneous administration. According to methods of the invention, a FXI dsRNA agent or FXI antisense polynucleotide agent may be administered in a pharmaceutical composition. In general, a pharmaceutical composition comprises a FXI dsRNA agent or FXI antisense polynucleotide agent and optionally, a pharmaceutically-acceptable carrier. Pharmaceutically-acceptable carriers are well-known to those of ordinary skill in the art. As used herein, a pharmaceutically-acceptable carrier means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients, e.g., the ability of the FXI dsRNA agent or FXI antisense polynucleotide agent to inhibit FXI gene expression in a cell or subject. Numerous methods to administer and deliver dsRNA agents or FXI antisense polynucleotide agents for therapeutic use are known in the art and may be utilized in methods of the invention.

Pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers and other materials that are well-known in the art. Exemplary pharmaceutically acceptable carriers are described in U.S. Pat. No. 5,211,657 and others are known by those skilled in the art. Such preparations may routinely contain salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to

prepare pharmaceutically-acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically-acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Some embodiments of methods of the invention include administering one or more FXI dsRNA agents or FXI antisense polynucleotide agents directly to a tissue. In some embodiments, the tissue to which the compound is administered is a tissue in which the FXI-associated disease or condition is present or is likely to arise, non-limiting examples of which are the liver or kidney. Direct tissue administration may be achieved by direct injection or other means. Many orally delivered compounds naturally travel to and through the liver and kidneys and some embodiments of treatment methods of the invention include oral administration of one or more FXI dsRNA agents to a subject. FXI dsRNA agents or FXI antisense polynucleotide agents, either alone or in conjunction with other therapeutic agents, may be administered once, or alternatively they may be administered in a plurality of administrations. If administered multiple times, the FXI dsRNA agent or FXI antisense polynucleotide agent may be administered via different routes. For example, though not intended to be limiting, a first (or first several) administrations may be made via subcutaneous means and one or more additional administrations may be oral and/or systemic administrations.

For embodiments of the invention in which it is desirable to administer a FXI dsRNA agent or FXI antisense polynucleotide agent systemically, the FXI dsRNA agent or FXI antisense polynucleotide agent may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with or without an added preservative. FXI dsRNA agent formulations (also referred to as pharmaceutical compositions) may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like.

Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Lower doses will result from other forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day may be used as needed to achieve appropriate systemic or local levels of one or more FXI dsRNA agents or FXI antisense polynucleotide agents and to achieve appropriate reduction in FXI protein activity.

In yet other embodiments, methods of the invention include use of a delivery vehicle such as biocompatible microparticle, nanoparticle, or implant suitable for implantation into a recipient, e.g., a subject. Exemplary bioerodible implants that may be useful in accordance with this method are described in PCT Publication No. WO 95/24929 (incorporated by reference herein), which describes a biocompatible, biodegradable polymeric matrix for containing a biological macromolecule.

Both non-biodegradable and biodegradable polymeric matrices can be used in methods of the invention to deliver one or more FXI dsRNA agents or FXI antisense polynucleotide agents to a subject. In some embodiments, a matrix may be biodegradable. Matrix polymers may be natural or synthetic polymers. A polymer can be selected based on the period of time over which release is desired, generally in the order of a few hours to a year or longer. Typically, release over a period ranging from between a few hours and three to twelve months can be used. The polymer optionally is in the form of a hydrogel that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multivalent ions or other polymers.

In general, FXI dsRNA agents or FXI antisense polynucleotide agents may be delivered in some embodiments of the invention using the bioerodible implant by way of diffusion, or by degradation of the polymeric matrix. Exemplary synthetic polymers for such use are well known in the art. Biodegradable polymers and non-biodegradable polymers can be used for delivery of FXI dsRNA agents or FXI antisense polynucleotide agents using art-known methods. Bioadhesive polymers such as bioerodible hydrogels (see H. S. Sawhney, C. P. Pathak and J. A. Hubbell in *Macromolecules*, 1993, 26, 581-587, the teachings of which are incorporated by reference herein) may also be used to deliver FXI dsRNA agents or FXI antisense polynucleotide agents for treatment of a FXI-associated disease or condition. Additional suitable delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of a FXI dsRNA agent or FXI antisense polynucleotide agent, increasing convenience to the subject and the medical care professional. Many types of release delivery systems are available and known to those of ordinary skill in the art. (See for example: U.S. Pat. Nos. 5,075,109; 4,452,775; 4,675,189; 5,736,152;

3,854,480; 5,133,974; and 5,407,686 (the teaching of each of which is incorporated herein by reference). In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be suitable for prophylactic treatment of subjects and for subjects at risk of developing a recurrent FXI-associated disease or condition. Long-term release, as used herein, means that the implant is constructed and arranged to deliver a therapeutic level of a FXI dsRNA agent or FXI antisense polynucleotide agent for at least up to 10 days, 20 days, 30 days, 60 days, 90 days, six months, a year, or longer. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

Therapeutic formulations of FXI dsRNA agents or FXI antisense polynucleotide agents may be prepared for storage by mixing the molecule or compound having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers [Remington's Pharmaceutical Sciences 21st edition, (2006)], in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG).

Cells, Subjects, and Controls

Methods of the invention may be used in conjunction with cells, tissues, organs and/or subjects. In some aspects of the invention a subject is a human or vertebrate mammal including but not limited to a dog, cat, horse, cow, goat, mouse, rat, and primate, e.g., monkey. Thus, the invention can be used to treat FXI-associated diseases or conditions in human and non-human subjects. In some aspects of the invention a subject may be a farm animal, a zoo animal, a domesticated animal or non-domesticated animal and methods of the invention can be used in veterinary prevention and treatment regimens. In

some embodiments of the invention, the subject is a human and methods of the invention can be used in human prevention and treatment regimens.

Non-limiting examples of subjects to which the present invention can be applied are subjects who are diagnosed with, suspected of having, or at risk of having a disease or condition associated with a higher than desirable FXI expression and/or activity, also referred to as “elevated levels of FXI expression”. Non-limiting examples of diseases and conditions associated with a higher than desirable levels of FXI expression and/or activity are described elsewhere herein. Methods of the invention may be applied to a subject who, at the time of treatment, has been diagnosed as having the disease or condition associated with a higher than desirable FXI expression and/or activity, or a subject who is considered to be at risk for having or developing a disease or condition associated with a higher than desirable FXI expression and/or activity. In some aspects of the invention a disease or condition associated with a higher than desirable FXI level of expression and/or activity is an acute disease or condition, and in certain aspects of the invention a disease or condition associated with a higher than desirable FXI level of expression and/or activity is a chronic disease or condition.

In a non-limiting example, a FXI dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, statin resistant hypercholesterolemia, which is a disease in which it is desirable to reduce FXI expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

In another non-limiting example, a FXI dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, hyperlipidemia, which is a disease in which it is desirable to reduce FXI expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

A cell to which methods of the invention may be applied include cells that are *in vitro*, *in vivo*, *ex vivo* cells. Cells may be in a subject, in culture, and/or in suspension, or in any other suitable state or condition. A cell to which a method of the invention may be applied can be a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, kidney cell or other type of vertebrate cell, including human and non-human mammalian cells. In certain aspects of the invention, a cell to which methods of the invention may be applied is a healthy, normal cell that is not known to be a disease cell. In certain embodiments of the invention a cell to which methods and compositions of the invention are applied to a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, and/or a kidney cell. In certain aspects of the invention, a control cell is a normal cell, but it will be understood that a cell having a disease or condition may also serve as a control cell in particular circumstances for

example to compare results in a treated cell having a disease or condition versus an untreated cell having the disease or condition, etc.

A level of FXI polypeptide activity can be determined and compared to control level of FXI polypeptide activity, according to methods of the invention. A control may be a predetermined value, which can take a variety of forms. It can be a single cut-off value, such as a median or mean. It can be established based upon comparative groups, such as in groups having normal levels of FXI polypeptide and/or FXI polypeptide activity and groups having increased levels of FXI polypeptide and/or FXI polypeptide activity. Another non-limiting example of comparative groups may be groups having one or more symptoms of or a diagnosis of a FXI-associated disease or condition; groups without having one or more symptoms of or a diagnosis of the disease or condition; groups of subjects to whom an siRNA treatment of the invention has been administered; groups of subjects to whom an siRNA treatment of the invention has not been administered. Typically, a control may be based on apparently healthy normal individuals in an appropriate age bracket or apparently healthy cells. It will be understood that controls according to the invention may be, in addition to predetermined values, samples of materials tested in parallel with the experimental materials. Examples include samples from control populations or control samples generated through manufacture to be tested in parallel with the experimental samples. In some embodiments of the invention, a control may include a cell or subject not contacted or treated with a FXI dsRNA agent of the invention and in such instances, a control level of FXI polypeptide and/or FXI polypeptide activity can be compared to a level of FXI polypeptide and/or FXI polypeptide activity in a cell or subject contacted with a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention.

In some embodiments of the invention a level of FXI polypeptide determined for a subject can be a control level against which a level of FXI polypeptide determined for the same subject at a different time is compared. In a non-limiting example, a level of FXI is determined in a biological sample obtained from a subject who has not been administered a FXI treatment of the invention. In some embodiments, the biological sample is a serum sample. In some embodiments, the biological sample is a liver sample. The level of FXI polypeptide determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of a FXI dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and the level of FXI polypeptide in the subsequent sample or samples can be compared to the control/baseline level for the subject. Such comparisons can be used to assess onset, progression, or recession of a FXI associated disease or condition in the subject. For example, a level of FXI polypeptide in the baseline sample obtained from the subject that is higher than a level obtained from the same subject after the subject has been administered a FXI dsRNA agent or FXI

antisense polynucleotide agent of the invention indicates regression of the FXI-associated disease or condition and indicates efficacy of the administered FXI dsRNA agent of the invention for treatment of the FXI-associated disease or condition.

In some aspects of the invention, values of one or more of a level of FXI polypeptide and/or FXI polypeptide activity determined for a subject may serve as control values for later comparison of levels of FXI polypeptide and/or FXI activity, in that same subject, thus permitting assessment of changes from a “baseline” FXI polypeptide activity in a subject. Thus, an initial FXI polypeptide level and/or initial FXI polypeptide activity level may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of FXI polypeptide and/or FXI polypeptide activity in the subject, with the initial level serving as a control level for that subject.

Using methods of the invention, FXI dsRNA agents and/or FXI antisense polynucleotide agents of the invention may be administered to a subject. Efficacy of the administration and treatment of the invention can be assessed when a level of FXI polypeptide in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration level of FXI polypeptide in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example a level of FXI polypeptide in a control serum sample. It will be understood that a level of FXI polypeptide and a level of FXI polypeptide activity both correlate with a level of FXI gene expression. Certain embodiments of methods of the invention comprise administering a FXI dsRNA and/or FXI antisense agent of the invention to a subject in an amount effective to inhibit FXI gene expression and thereby reduce a level of FXI polypeptide and reduce a level of FXI polypeptide activity in the subject.

Some embodiments of the invention, include determining presence, absence, and/or an amount (also referred to herein as a level) of FXI polypeptide in one or more biological samples obtained from one or more subjects. The determination can be used to assess efficacy of a treatment method of the invention. For example, methods and compositions of the invention can be used to determine a level of FXI polypeptide in a biological sample obtained from a subject previously treated with administration of a FXI dsRNA agent and/or a FXI antisense agent of the invention. A level of FXI polypeptide determined in a serum sample obtained from the treated subject that is lower by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pretreatment level of FXI polypeptide determined for the subject, or compared to a non-contacted control biological sample level, indicates a level of efficacy of the treatment administered to the subject.

In some embodiments of the invention a physiological characteristic of a FXI-associated disease or condition determined for a subject can be a control determination against which a determination of the physiological characteristic in the same subject at a different time is compared. In a non-limiting

example, a physiological characteristic such as the FXI mRNA level, the FXI protein level in the subject, or activated partial thromboplastin time (aPTT), prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a blood sample of the animal. The FXI mRNA level (and/or other physiological characteristic of a FXI disease or condition) determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of a FXI dsRNA agent to the subject in a treatment method of the invention, one or more additional liver or serum samples can be obtained from the subject and FXI mRNA level and/or FXI protein level in the subsequent sample or samples are compared to the control/baseline level and/or ratio, respectively, for the subject. Such comparisons can be used to assess onset, progression, or recession of a FXI associated disease or condition in the subject. For example, FXI mRNA level in the baseline sample obtained from the subject that is higher than FXI mRNA level determined in a sample obtained from the same subject after the subject has been administered a FXI dsRNA agent or FXI antisense polynucleotide agent of the invention indicates regression of the FXI-associated disease or condition and indicates efficacy of the administered FXI dsRNA agent of the invention for treatment of the FXI-associated disease or condition.

In some aspects of the invention, values of one or more of a physiological characteristic of a FXI-associated disease or condition determined for a subject may serve as control values for later comparison of the physiological characteristics in that same subject, thus permitting assessment of changes from a “baseline” physiological characteristic in a subject. Thus, an initial physiological characteristic may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of FXI polypeptide and/or FXI polypeptide activity in the subject, with the initial physiological characteristic determination serving as a control for that subject.

Using methods of the invention, FXI dsRNA agents and/or FXI antisense polynucleotide agents of the invention may be administered to a subject in an effective amount to treat a FXI disease or condition. Efficacy of the administration and treatment of the invention can be assessed by determining a change in one or more physiological characteristics of the FXI disease or condition. In a non-limiting example, a FXI mRNA level in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration lipid in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example FXI mRNA level in a control serum sample. It will be understood that the FXI mRNA level, the FXI protein level in the subject, or activated partial thromboplastin time (aPTT), prothrombin time (PT) test, thrombin time (TCT), bleeding time, or presence of D-dimer in a blood each correlates with a level of FXI gene expression. Certain embodiments of methods of the invention comprise administering a FXI dsRNA and/or FXI antisense

agent of the invention to a subject in an amount effective to inhibit FXI gene expression and thereby reduce the FXI mRNA level, the FXI protein level in the subject, or otherwise positively impact a physiological characteristic of a FXI-associated disease or condition in the subject.

Some embodiments of the invention, include determining presence, absence, and/or a change in a physiological characteristic of a FXI-associated disease or condition using methods such as but not limited to: (1) assessing one or more biological samples obtained from one or more subjects for the physiological characteristic; (2) imaging a subject (for example but not limited to obtaining a liver image); and (3) or physical examination of the subject. The determination can be used to assess efficacy of a treatment method of the invention.

Kits

Also within the scope of the invention are kits that comprise one or more FXI dsRNA agents and/or FXI antisense polynucleotide agents and instructions for its use in methods of the invention. Kits of the invention may include one or more of a FXI dsRNA agent, FXI sense polynucleotide, and FXI antisense polynucleotide agent that may be used to treat a FXI-associated disease or condition. Kits containing one or more FXI dsRNA agents, FXI sense polynucleotides, and FXI antisense polynucleotide agents can be prepared for use in treatment methods of the invention. Components of kits of the invention may be packaged either in aqueous medium or in lyophilized form. A kit of the invention may comprise a carrier being compartmentalized to receive in close confinement therein one or more container means or series of container means such as test tubes, vials, flasks, bottles, syringes, or the like. A first container means or series of container means may contain one or more compounds such as a FXI dsRNA agent and/or FXI sense or antisense polynucleotide agent. A second container means or series of container means may contain a targeting agent, a labelling agent, a delivery agent, etc. that may be included as a portion of a FXI dsRNA agent and/or FXI antisense polynucleotide to be administered in an embodiment of a treatment method of the invention.

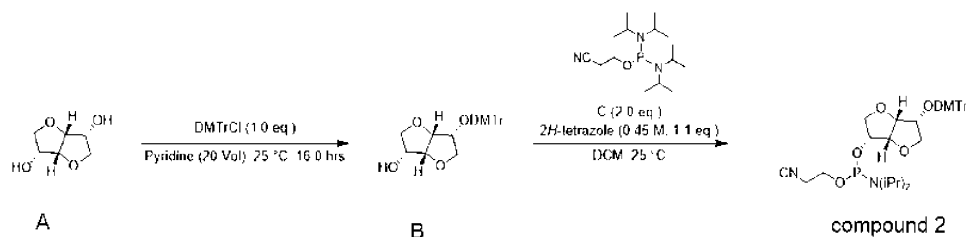
A kit of the invention may also include instructions. Instructions typically will be in written form and will provide guidance for carrying-out a treatment embodied by the kit and for making a determination based upon that treatment.

The following examples are provided to illustrate specific instances of the practice of the present invention and are not intended to limit the scope of the invention. As will be apparent to one of ordinary skill in the art, the present invention will find application in a variety of compositions and methods.

Examples

Example 1.

Phosphoramidite Compound 2



DMTrCl (232 g, 684 mmol, 1.0 *eq*) in pyridine (400 mL) was added to the solution of isomannidite compound **A** (100 g, 684 mmol, 1.0 *eq*) in pyridine (600 mL), and the mixture was stirred at 25 °C for 12 hrs. LC-MS showed compound **A** was consumed completely and one main peak with desired mass was detected. The resulting reaction mixture was diluted with water (500 mL), extracted with DCM (500 mL *2), and the combined organic phases were washed with brine (500 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue. The residue was purified by column chromatography (DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound **B** (150 g, 48.9% yield) a yellow solid.

¹H NMR: EC4783-404-P1B1_C (400 MHz, DMSO-*d*₆)

δ ppm 7.46 (br d, *J*=7.63 Hz, 2 H) 7.28 - 7.37 (m, 6 H) 7.19 - 7.25 (m, 1 H) 6.90 (br d, *J*=7.88 Hz, 4 H) 4.70 (d, *J*=6.50 Hz, 1 H) 3.99 - 4.09 (m, 6 H) 3.88 - 3.96 (m, 2 H) 3.83 (br dd, *J*=7.82, 6.94 Hz, 1 H) 3.74 (s, 6 H) 3.41 (br t, *J*=8.13 Hz, 1 H) 3.05 (t, *J*=8.44 Hz, 1 H) 2.85 (br t, *J*=7.50 Hz, 1 H).

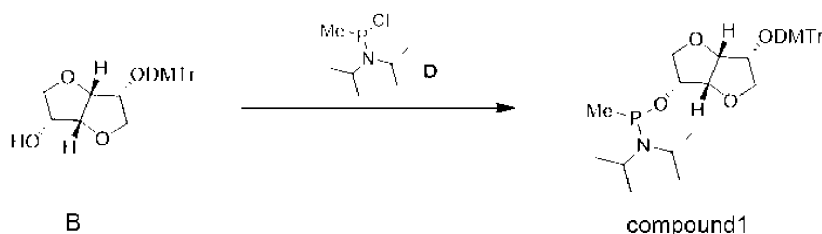
To a solution of compound **B** (80.0 g, 178 mmol, 1.0 *eq*) in DCM (800 mL) at 25 °C under N₂ atmosphere was added dropwise 2H-tetrazole (0.45 M, 436 mL, 1.1 *eq*), then compound **C** (80.6 g, 267 mmol, 85.0 mL, 1.5 *eq*) in DCM (200 mL) was added dropwise to the mixture. The reaction mixture was stirred at 25 °C under for 1.0 hr. LC-MS showed compound **B** was consumed completely and one main peak with desired mass was detected. The resulting reaction mixture was cooled to -20 °C and poured into ice cold sat. NaHCO₃ (500 mL), extracted with DCM (500 mL *3), the combined organic layers were washed with sat. NaHCO₃/brine=1:1 (300 mL/300 mL), dried over Na₂SO₄ and concentrated in vacuum (35 °C) to get the residue (100 mL). The residue was purified by column chromatography (Al₂O₃, DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound2 (77 g, 119 mmol, 66.5% yield) as a white solid.

¹H NMR: EC4783-423-P1B1_C (400 MHz, DMSO-*d*₆)

δ ppm 7.22 (br d, *J*=7.50 Hz, 2 H) 7.05 - 7.14 (m, 6 H) 6.96 - 7.02 (m, 1 H) 6.67 (br dd, *J*=8.82, 1.81 Hz, 4 H) 3.95 - 4.07 (m, 2 H) 3.73 - 3.83 (m, 1 H) 3.62 - 3.72 (m, 2 H) 3.48 - 3.53 (m, 6 H) 3.27 -

3.37 (m, 3 H) 3.11 (s, 6 H) 2.82 (td, $J=8.54$, 2.31 Hz, 1 H) 2.47 - 2.63 (m, 3 H) 2.28 (br d, $J=1.63$ Hz, 3 H) 0.82 - 1.00 (m, 13 H).

Phosphoramidite Compound 1



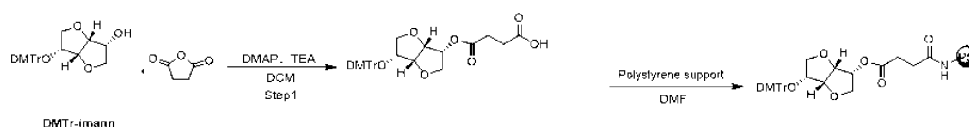
To a solution of compound **B** (500 mg, 1.11 mmol, 1.0 eq) in DCM (5.0 mL) was added compound **D** (607 mg, 3.34 mmol, 3.0 eq) and DIEA (432 mg, 3.34 mmol, 582 μ L, 3.0 eq) under N_2 atmosphere at 0-5 $^{\circ}\text{C}$, the mixture was stirred at 25 $^{\circ}\text{C}$ for 1.0 hrs. LC-MS showed Compound **B** was consumed completely, several new peaks were shown on LC-MS and $\sim 70.9\%$ of desired compound was detected. The resulting reaction mixture was cooled to -20 $^{\circ}\text{C}$ and poured into cold (0-5 $^{\circ}\text{C}$) sat. NaHCO_3 (5.0 mL) solution, extracted with DCM (5.0 mL $\times 2$), the combined organic layers were washed with cold (0-5 $^{\circ}\text{C}$) sat. NaHCO_3 /brine = 1:1 (5.0 mL/5.0 mL), dried over Na_2SO_4 and concentrated in vacuum to get the residue (~ 5 mL). The residue was purified by column chromatography (alkaline Al_2O_3 , Petroleum ether/Ethyl acetate = 10/1 to 5/1, 0.1% Et_3N) to give compound **1** (280 mg, 471 μ mol, 42.3% yield) was obtained as a white solid.

^1H NMR: EC10615-49-P1N (400 MHz, $\text{DMSO}-d_6$)

δ ppm 7.44 (br d, $J=7.63$ Hz, 2 H), 7.31 (br t, $J=7.94$ Hz, 6 H), 7.18 - 7.26 (m, 1 H), 6.89 (brd, $J=8.00$ Hz, 4 H), 4.08 - 4.13 (m, 1 H), 3.95 - 4.03 (m, 1 H), 3.84 - 3.93 (m, 1 H), 3.77 - 3.83 (m, 1 H), 3.74 (s, 6 H), 3.43 - 3.53 (m, 3 H), 3.38 (br d, $J=6.75$ Hz, 1 H), 2.94 - 3.04 (m, 1 H), 2.70 - 2.85 (m, 1 H), 1.09 - 1.15 (m, 12 H), 1.07 (br s, 3 H).

Other phosphoramidites may be prepared according to procedures described herein and/or prior arts such as, but are not limited to, US426,220 and WO02/36743.

Example2. Preparation of a solid support comprising phosphoramidites monomers of the present invention



represents amine methyl polyethylene macroporous resin carrier part

Dichloromethane (19.50kg) was added to the 50 L glass kettle under the protection of nitrogen and started stirring. The temperature was controlled at 20~30 °C, and DMTr imann (1.47 kg), triethylamine (1.50 kg), 4-dimethylaminopyridine (0.164 kg) and succinic anhydride (1.34 kg) was added to the glass kettle. The system was kept at 20~30 °C for 18h, samples were taken and the reaction was ended. Saturated sodium bicarbonate solution (22.50 kg) was added into the reaction system, stirred for 10-20 min, and allowed to separate into layers. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane, and the organic phase was combined and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to get the residue forming a gray to off-white solid of 1.83 kg.

N, N-dimethylformamide (23.50 kg) was added into a 100L glass kettle and stirred. The temperature was controlled at 20~30 °C. Under the protection of nitrogen, the products of the previous step, O-benzotriazole tetramethylurea hexafluorophosphate (0.33 kg) and N, N-diisopropylethylamine (0.13 kg) were added into the aforesaid 100L glass kettle through the solid feeding funnel and stirred for 10~30 minutes and were discharged into a 50 L zinc barrel for use. Macroporous amine methyl resin (3.25 kg) (purchased from Tianjin Nankai Hecheng Science and Technology Co., Ltd., batch number HA2X1209, load capacity 0.48 mmol/g) were added into the aforesaid 100 L solid phase synthesis reactor through the solid feeding funnel, the temperature was controlled at 20~30 °C, N, N-dimethylformamide (21.00 kg+21.00 kg) and the reaction solution in the zinc barrel of the previous step were add into the solid phase synthesis reactor. The system was subject to thermal insulation reaction, and the solid load was tracked to $\geq 250\mu\text{mol/g}$, and the load detection method was UV. The system was filtered under the pressure of nitrogen, the filter cake was washed with N, N-dimethylformamide for three times (26.00kg+26.10kg+26.00kg), and the filter cake was left in the kettle. CAP.A (50% acetonitrile and 50% acetic anhydride, 4.40kg+4.42kg+4.30kg) and CAP.B (20% pyridine and 30% N-methylimidazole and 50% acetonitrile, 4.40kg+4.40kg+4.47kg) were added into the 80L glass kettle, and stirred for 3~8min before use. This operation was repeated for three times to cap, and acetonitrile (18.00 kg+18.00 kg+18.00 kg+17.50 kg+17.50 kg) was added into the solid phase synthesis kettle. Filter-pressed after nitrogen bubbling for 10~30 min. This operation was repeated for four times, the filter cake was purged in the solid phase synthesis kettle with nitrogen for 2-4 h, and then was transferred to a 50 L filter press tank. The temperature was controlled at 15~30 °C, continued

drying, and obtained yellow to white solid product after drying, weight: 3.516 kg.

Example 3. Synthesis of FXI RNAi Agents.

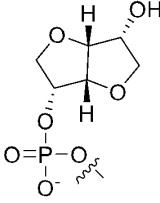
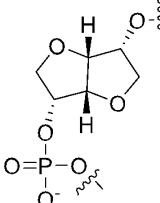
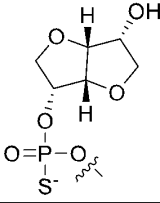
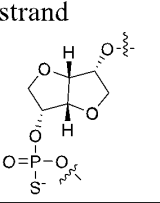
FXI RNAi agent duplexes shown in Table 2-3, above, were synthesized in accordance with the following general procedures:

Sense and antisense strand sequences of siRNA were synthesized on oligonucleotide synthesizers using a well-established solid phase synthesis method based on phosphoramidite chemistry. Oligonucleotide chain propagation is achieved through 4-step cycles: a deprotection, a condensation, a capping and an oxidation or a sulfurization step for addition of each nucleotide. Syntheses were performed on a solid support made of controlled pore glass (CPG, 1000 Å). Monomer phosphoramidites may be purchased from commercial sources or may be the phosphoramidite compounds in example 3. The phosphoramidite compounds herein may be attached to the 3'-end as a monomeric phosphoramidite, and further be attached to the CPG solid support. In the case of attachment at the 5'-end, the phosphoramidite compounds may be used for the final coupling reaction, and can be further conjugated to target ligands if necessary.. For siRNAs used for *in vitro* screening (Table 2), syntheses were carried out at 2 µmol scale, and for siRNAs used for *in vivo* testing (Table 3), syntheses were carried out at scale of 5 µmol or larger. In the case where the GalNAc ligand (GLO-0 as a non-limiting example) is attached at 3'-end of sense strand, GalNAc ligand attached CPG solid support was used. In the case where the GalNAc ligand (GLS-5* or GLS-15* as non-limiting example, GLS-5* or GLS-15* Phosphoramidites with GalNAc ligand cluster were public in WO2023/045995A1 (incorporated herein in its entirety)) is attached at 5'-end of sense strand, a GalNAc phosphoramidite was used for the last coupling reaction. Trichloroacetic acid (TCA) 3% in dichloromethane was used for deprotection of 4,4'-dimethoxytrityl protecting group (DMT). 5-Ethylthio-1H-tetrazole was used as an activator. I₂ in THF/Py/H₂O and phenylacetyl disulfide (PADS) in pyridine/MeCN was used for oxidation and sulfurization reactions, respectively. After the final solid phase synthesis step, solid support bound oligomer was cleaved and protecting groups were removed by treating with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution. For the synthesis of siRNAs used for *in vitro* screening, crude mixture was concentrated. The remaining solid was dissolved in 1.0 M NaOAc, and ice cold EtOH was added to precipitate out the single strand product as the sodium salt, which was used for annealing without further purification. For the synthesis of siRNAs used for *in vivo* testing, crude single strand product was further purified by ion pairing reversed phase HPLC (IP-RP-HPLC). Purified single strand oligonucleotide product from IP-RP-HPLC was converted to sodium salt by dissolving in 1.0 M NaOAc and precipitation by addition of ice cold EtOH. Annealing of equimolar complementary sense

stand and antisense strand oligonucleotide in water was performed to form the double strand siRNA product, which was lyophilized to afford a fluffy white solid.

Table 4: Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds, and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position of the parent nucleotide (i.e., it is a 2'-deoxy-2'- fluoronucleotide). It will also be understood that the abbreviations correspond to nucleotides which omit the 3'-phosphate when found at the 3'-terminal position (i.e., they are 3'-OH). A skilled artisan will understand that these abbreviations are just identification symbols and are able to determine the linking modes of the nucleotide sequences containing these abbreviations.

Abbreviations	Nucleotide(s)
A	adenosine-3'-phosphate
C	cytidine-3'-phosphate
G	guanosine-3'-phosphate
T	5-methyluridine-3'-phosphate
U	uridine-3'-phosphate
a	2'-O-methyladenosine-3'-phosphate
c	2'-O-methylcytidine-3'-phosphate
g	2'-O-methylguanosine-3'-phosphate
t	2'-O-methyl-5-methyluridine-3'-phosphate
u	2'-O-methyluridine-3'-phosphate
Af	2'-fluoroadenosine-3'-phosphate
Cf	2'-fluorocytidine-3'-phosphate
Gf	2'-fluoroguanosine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Af*	2'-fluoroadenosine-3'-phosphorothioate
Cf*	2'-fluorocytidine-3'-phosphorothioate
Gf*	2'-fluoroguanosine-3'-phosphorothioate
Tf*	2'-fluoro-5-methyluridine-3'-phosphorothioate
Uf*	2'-fluorouridine-3'-phosphorothioate
a*	2'-O-methyladenosine-3'-phosphorothioate
c*	2'-O-methylcytidine-3'-phosphorothioate
g*	2'-O-methylguanosine-3'-phosphorothioate
t*	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u*	2'-O-methyluridine-3'-phosphorothioate
aUNA	2', 3'-seco-adenosine-3'-phosphate
cUNA	2', 3'-seco-cytidine-3'-phosphate
gUNA	2', 3'-seco-guanosine-3'-phosphate

tUNA	2', 3'-seco-5-methyluridine-3'-phosphate	
uUNA	2', 3'-seco- uridine-3'-phosphate	
Vp	Vinyl-phosphate	
phos	5' - Phosphate	
invab	inverted abasic-5'-phosphate. linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strand; linked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand, It will also be understood that the abbreviations correspond to invab which omit the 5'-phosphate when found at the 3'-terminal position (i.e., they are 5'-OH)	
invab*	inverted abasic-5'-phosphorothioate. linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strandlinked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand, It will also be understood that the abbreviations correspond to invab* which omit the 5'- phosphorothioate when found at the 3'-terminal position (i.e., they are 5'-OH);	
imann	imann when at the end of each strand	imann when in the middle of each strand
		
imann*	isomannide residue- phosphorothioate	
	imann* when at the end of each strand	imann* when in the middle of each strand
		

Example 4. *In Vitro* Screening of FXI siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of psiCHECK(TM)-2 Vector plasmid and Lipofectamine 2000 (Invitrogen-11668-019) and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax (Invitrogen -13778-150) at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at two concentrations (1 nM and 0.1 nM) in triplicate.

Day 1, psiCHECK(TM)-2 Vector transfection (one plate)

(1) Transfer 2.5µg psiCHECK(TM)-2 Vector plasmid into an RNASE free Eppendorf tube (solution mix#1)

(2) Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to $1 \times 10^5/\text{ml}$

(3) Transfer 7.5 μL Lipofectamine 2000 (Invitrogen-11668-019) into solution mix#1 tube, mix.

(4) Add solution in Step 3 into cell suspension, mix, and dispense suspension into the 96 well plate (100 $\mu\text{L}/\text{well}$)

Day 2, siRNAs transfection

(1) Dilute Lipofectamine®RNAiMAX Reagent with Opti-MEM® Medium.

(2) Dilute the siRNA with RNA-free water to make 12 $\times$ stock.

(3) Mix equal volume of diluted RNAiMax and siRNA. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Add 45 μL /well compound Lipofectamine® RNAiMAX(Opti-MEM) mix into 225 μL /well DMEM fresh medium, and discard the supernatants in assay plate, add 120 μL /well compound mix into 96 well plates.

(5) No compound control well was defined as cells transfected with psiCHECK(TM)-2 Vector and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

(1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.

(2) Transfer 100 μL cell lysates into a plate, then measure the firefly luminescence.

(3) Add 50 μL of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.

(4) Calculate the relative expression

Data analysis

Ratio of sample well= (sample Renilla luminescence-background blank)/ (sample Fireflyluminescence-background blank)

Ratio of no compound control well= (control Renilla luminescence-background blank)/ (control sample Fireflyluminescence-background blank)

% inhibition= $100 - (\text{Ratio of sample well} / \text{the average Ratio of no compound control}) \times 100\%$.

Table 5 provides experimental results of *in vitro* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean $\pm$ SD)		Duplex AV#	Average Inhibition % (Mean $\pm$ SD)	
	1 nM	0.1 nM		1nM	0.1nM
AV01117	0.26 $\pm$ 2.95	-11.90 $\pm$ 8.49	AV01167	24.66 $\pm$ 12.25	25.74 $\pm$ 0.42
AV01118	1.08 $\pm$ 1.05	22.01 $\pm$ 1.15	AV01168	49.35 $\pm$ 0.88	5.23 $\pm$ 7.85

AV01119	4.59±7.36	-7.30±7.40	AV01169	13.28±16.64	-15.92±16.77
AV01120	-2.77±11.32	1.56±6.52	AV01170	5.02±13.96	-11.70±8.90
AV01121	24.47±5.03	-3.01±6.29	AV01171	37.00±11.60	3.39±6.49
AV01122	81.75±6.08	39.09±11.84	AV01172	1.30±5.01	-22.90±7.17
AV01123	81.77±2.84	43.00±9.33	AV01173	22.82±5.54	-1.87±5.86
AV01124	56.74±4.37	19.87±9.34	AV01174	8.08±11.70	-2.71±8.17
AV01126	52.24±8.28	11.22±16.81	AV01175	43.69±9.15	9.57±15.70
AV01127	44.23±9.36	3.10±21.98	AV01176	12.74±16.21	-6.71±2.45
AV01128	30.80±16.34	1.74±11.10	AV01177	13.81±3.68	-13.37±8.36
AV01129	25.21±8.40	-12.48±11.16	AV01178	-11.01±8.68	2.61±8.10
AV01130	28.50±15.20	7.35±10.77	AV01179	7.36±18.41	-18.22±5.66
AV01131	15.59±15.26	21.76±23.89	AV01181	44.57±11.06	2.91±8.10
AV01132	21.75±8.82	14.96±8.32	AV01182	24.01±11.76	4.74±14.48
AV01133	22.80±13.62	13.92±9.18	AV01183	22.76±10.95	11.46±11.69
AV01134	5.47±10.44	16.80±12.49	AV01184	8.07±6.11	-3.87±15.94
AV01135	27.84±7.52	14.05±15.30	AV01185	14.19±12.67	-11.91±13.99
AV01136	18.96±28.28	4.22±8.31	AV01186	25.59±13.43	1.91±5.41
AV01137	33.34±14.65	26.26±10.32	AV01187	-3.14±2.19	-9.44±9.09
AV01138	48.10±5.22	21.30±11.12	AV01188	-1.45±4.31	-8.54±8.93
AV01139	40.60±28.81	3.65±7.32	AV01189	33.69±31.77	-4.88±20.57
AV01141	52.94±15.68	19.49±13.32	AV01190	-2.06±9.93	1.43±2.31
AV01142	68.60±7.56	26.69±9.29	AV01191	20.30±17.54	15.39±20.78
AV01143	55.74±8.85	3.10±6.00	AV01192	23.78±4.83	4.27±6.34
AV01145	26.81±10.58	-6.48±27.31	AV01193	19.68±12.52	-2.98±18.96
AV01146	52.62±2.67	24.54±6.62	AV01194	8.96±13.33	-4.94±7.13
AV01147	12.00±18.31	0.45±15.35	AV01195	27.54±3.63	2.43±9.09
AV01148	6.03±19.71	2.61±31.65	AV01196	18.36±34.34	-0.24±11.74
AV01149	-1.83±5.11	7.56±34.29	AV01197	14.00±23.45	3.70±7.81
AV01150	28.99±14.10	0.51±23.46	AV01198	26.48±0.79	-3.38±12.06
AV01151	26.05±8.99	-5.17±21.34	AV01199	23.16±7.33	10.76±4.88
AV01152	37.58±14.06	11.18±12.60	AV01200	59.22±2.97	27.28±5.00
AV01154	54.59±5.67	8.66±22.94	AV01201	38.67±6.89	14.47±4.39
AV01155	25.69±2.05	5.46±13.79	AV01203	45.91±8.65	17.58±10.08
AV01156	26.78±2.43	13.48±12.05	AV01204	64.97±3.26	45.64±6.65
AV01157	34.36±16.61	12.24±16.79	AV01205	66.01±0.60	33.58±2.13
AV01158	36.92±4.19	17.75±5.61	AV01206	13.09±14.51	5.19±28.38
AV01159	23.11±21.81	22.31±7.81	AV01207	13.23±2.65	11.98±6.41
AV01160	31.63±11.96	1.69±34.12	AV01208	31.62±8.88	9.33±3.28
AV01161	54.85±4.87	6.96±13.14	AV01209	34.67±21.61	8.92±3.25
AV01162	29.77±11.39	16.24±13.39	AV01210	9.20±11.38	12.36±2.26
AV01163	30.94±8.92	16.35±10.82	AV01211	-1.01±6.57	4.72±14.97
AV01164	18.08±15.04	6.41±4.09	AV01212	8.02±12.30	8.51±10.80
AV01165	13.00±4.04	1.55±19.80	AV01213	1.81±9.11	1.12±0.69
AV01166	27.13±3.91	24.17±17.81	/	/	/

Example 5 *In Vivo* testing of FXI siRNA Duplexes

At day 1, female C57BL/6J mice (4-6weeks, 4 in each group) were infected by intravenous administration of a solution of adeno-associated virus (AAV-GFP) vector encoding Human Factor XI and luciferase gene. At day 8, mice were subcutaneously administered a single 3 mg/kg of FXI siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 15, and

day 22. Plasma samples were isolated and serum samples were collected for quantification protein level through ELISA protocol. The results are shown in Tables 6-8.

Table 6 provides experimental results of in vivo studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)
AD00764	1.00 $\pm$ 0.10	0.82 $\pm$ 0.11
AD00766	0.79 $\pm$ 0.12	0.62 $\pm$ 0.05
AD00767	0.91 $\pm$ 0.13	0.73 $\pm$ 0.19
AD00769	0.66 $\pm$ 0.10	0.61 $\pm$ 0.10
AD00770	0.59 $\pm$ 0.14	0.61 $\pm$ 0.03
AD00771	0.78 $\pm$ 0.07	1.02 $\pm$ 0.11
AD00772	0.74 $\pm$ 0.06	0.60 $\pm$ 0.08
AD00774	0.93 $\pm$ 0.14	0.72 $\pm$ 0.12
AD00775	0.80 $\pm$ 0.09	0.56 $\pm$ 0.02

Table 7 provides experimental results of in vivo studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)
AD00776	0.24 $\pm$ 0.05	0.28 $\pm$ 0.04
AD00988	0.4 $\pm$ 0.03	0.46 $\pm$ 0.06
AD00989	0.47 $\pm$ 0.06	0.41 $\pm$ 0.08
AD00990	0.18 $\pm$ 0.05	0.12 $\pm$ 0.06
AD00991	0.18 $\pm$ 0.03	0.21 $\pm$ 0.02
AD00992	0.78 $\pm$ 0.05	0.6 $\pm$ 0.08
AD00993	0.46 $\pm$ 0.03	0.43 $\pm$ 0.1
AD00994	0.97 $\pm$ 0.19	0.8 $\pm$ 0.11
AD00995	0.51 $\pm$ 0.21	0.49 $\pm$ 0.17
AD00996	0.25 $\pm$ 0.04	0.25 $\pm$ 0.04
AD00997	0.22 $\pm$ 0.04	0.14 $\pm$ 0.03
AD00998	0.15 $\pm$ 0.03	0.14 $\pm$ 0.03
AD00999	0.23 $\pm$ 0.07	0.21 $\pm$ 0.03
AD01000	0.25 $\pm$ 0.06	0.24 $\pm$ 0.09
AD01001	0.71 $\pm$ 0.04	0.66 $\pm$ 0.07
AD01002	0.15 $\pm$ 0.01	0.13 $\pm$ 0.02
AD01003	0.34 $\pm$ 0.04	0.41 $\pm$ 0.1
AD01004	0.57 $\pm$ 0.16	0.75 $\pm$ 0.19
AD01005	0.46 $\pm$ 0.05	0.57 $\pm$ 0.05
AD01006	0.55 $\pm$ 0.09	0.92 $\pm$ 0.14
AD01007	0.49 $\pm$ 0.06	0.63 $\pm$ 0.02
AD01008	0.52 $\pm$ 0.06	0.71 $\pm$ 0.09
AD01009	0.32 $\pm$ 0.04	0.28 $\pm$ 0.06
AD01010	0.22 $\pm$ 0.06	0.29 $\pm$ 0.04

AD01011	0.46±0.1	0.66±0.14
AD01012	0.34±0.05	0.49±0.05
AD01013	0.7±0.23	0.95±0.17
AD01014	0.23±0.07	0.3±0.12
AD01015	0.22±0.05	0.33±0.04
AD01016	0.11±0.03	0.27±0.06
AD01018	0.2±0.03	0.32±0.01
AD01019	0.2±0.1	0.32±0.07
AD01020	0.29±0.06	0.36±0.03

Table 8 provides experimental results of *in vivo* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean ±SD)	D22 remaining percent relative to D8 (Mean ±SD)
AD01484	0.35±0.05	0.32±0.04
AD01485	0.46±0.06	0.44±0.05
AD01486	0.41±0.02	0.28±0.04

Example 6. *In Vitro* Screening of FXI siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of psiCHECK(TM)-2 Vector plasmid and Lipofectamine 2000 and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at five concentrations (10nM, 3nM, 1 nM 0.1 nM and 0.03 nM) in triplicate. Dual-Glo® Luciferase analysis. The results are shown in Tables 9.

Table 9 provides experimental results of *in vitro* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Inhibition%				
	10nM	3nM	1nM	0.1nM	0.05nM
	MEAN±SD				
AV01214	82.79±2.35	71.95±3.97	55.13±2.49	17.63±7.45	4.90±9.04
AV01215	86.18±0.55	86.34±1.35	82.71±1.09	44.66±3.34	28.52±7.19
AV01216	85.72±0.65	83.45±0.83	77.35±3.58	38.95±5.65	19.59±2.29
AV01217	83.19±2.46	80.36±1.21	72.82±3.67	39.09±3.08	23.22±4.10
AV01218	87.00±4.36	88.18±2.63	78.66±2.89	18.96±9.62	9.57±5.89
AV01219	51.57±9.36	49.46±4.88	43.98±5.84	12.31±4.44	2.96±5.12

Example 7. *In Vitro* Screening of FXI siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of psiCHECK(TM)-2 Vector plasmid and Lipofectamine 2000 and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax (Invitrogen -13778-150) at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at two concentrations (1 nM and 0.1 nM) in triplicate.

Day 1, psiCHECK(TM)-2 Vector transfection (one plate)

- (1) Transfer 2.5µg psiCHECK(TM)-2 Vector plasmid into an RNASE free Eppendorf tube (solution mix#1)
- (2) Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to $1 \times 10^5/\text{ml}$
- (3) Transfer 7.5µL Lipofectamine 2000 into solution mix#1 tube, mix.
- (4) Add solution in Step 3 into cell suspension, mix, and dispense suspension into the 96 well plate (100 µl/well)

Day 2, siRNAs transfection

- (1) Dilute Lipofectamine®RNAiMAX Reagent with Opti-MEM® Medium.
- (2) Dilute the siRNA with RNA-free water to make 12×stock.
- (3) Mix equal volume of diluted RNAiMax and siRNA. Incubate the mixture at RT for 15 min to allow complex formation.
- (4) Add 45µl /well compound Lipofectamine® RNAiMAX(Opti-MEM) mix into 225µl /well DMEM fresh medium, and discard the supernatants in assay plate, add 120µl /well compound mix into 96 well plates.
- (5) No compound control well was defined as cells transfected with psiCHECK(TM)-2 Vector and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

- (1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.
- (2) Transfer 100 µl cell lysates into a plate, then measure the firefly luminescence.
- (3) Add 50µl of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.
- (4) Calculate the relative expression

Data analysis, The results are shown in Tables 10, and table 11.

Table10 provides experimental results of *in vitro* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Inhibition%	
	1nM	0.1nM
	MEAN $\pm$ SD	
AV05205	79.08 $\pm$ 5.23	41.26 $\pm$ 2.29
AV05206	91.29 $\pm$ 0.58	66.85 $\pm$ 0.86
AV05207	79.35 $\pm$ 1.75	28.65 $\pm$ 4.11
AV05208	56.84 $\pm$ 4.79	8.90 $\pm$ 8.74
AV05209	87.16 $\pm$ 1.70	56.61 $\pm$ 2.06
AV05210	82.01 $\pm$ 1.31	45.25 $\pm$ 2.38
AV05211	30.19 $\pm$ 2.05	-3.98 $\pm$ 5.12
AV05213	39.61 $\pm$ 3.98	28.17 $\pm$ 8.62
AV05214	5.45 $\pm$ 5.88	-4.48 $\pm$ 3.22
AV05215	43.76 $\pm$ 4.51	13.99 $\pm$ 1.77
AV05216	8.87 $\pm$ 4.42	-2.27 $\pm$ 3.69
AV05217	60.01 $\pm$ 3.12	19.48 $\pm$ 5.84
AV05218	43.72 $\pm$ 2.01	0.03 $\pm$ 7.72
AV05219	3.17 $\pm$ 0.73	3.96 $\pm$ 4.96
AV05221	42.92 $\pm$ 0.11	8.74 $\pm$ 7.94
AV05222	69.28 $\pm$ 1.06	19.52 $\pm$ 2.39
AV05223	61.55 $\pm$ 3.49	11.99 $\pm$ 3.62
AV05224	74.87 $\pm$ 1.29	27.33 $\pm$ 2.75
AV05225	-0.64 $\pm$ 3.22	-16.23 $\pm$ 1.90
AV05226	61.86 $\pm$ 2.87	11.34 $\pm$ 6.13
AV05227	-0.52 $\pm$ 9.53	-8.22 $\pm$ 5.89
AV05229	-6.10 $\pm$ 5.40	-0.76 $\pm$ 2.82
AV05230	50.11 $\pm$ 2.12	0.40 $\pm$ 5.72
AV05231	70.19 $\pm$ 3.31	18.91 $\pm$ 4.33
AV05232	55.20 $\pm$ 0.89	3.69 $\pm$ 0.51
AV05233	76.46 $\pm$ 1.97	24.38 $\pm$ 3.78
AV05234	35.09 $\pm$ 5.64	-8.01 $\pm$ 9.45
AV05235	73.71 $\pm$ 1.43	35.06 $\pm$ 4.04
AV05237	57.59 $\pm$ 0.70	6.28 $\pm$ 3.00
AV05238	60.49 $\pm$ 5.68	6.94 $\pm$ 6.83
AV05239	-5.94 $\pm$ 4.40	-12.10 $\pm$ 2.20
AV05240	54.76 $\pm$ 0.65	3.25 $\pm$ 7.96
AV05241	46.85 $\pm$ 1.56	-4.89 $\pm$ 1.53
AV05242	20.87 $\pm$ 1.56	-1.35 $\pm$ 4.25
AV05243	33.47 $\pm$ 5.54	-10.40 $\pm$ 6.93

AV05245	57.35 $\pm$ 3.05	25.34 $\pm$ 12.07
AV05246	8.12 $\pm$ 5.07	-9.35 $\pm$ 5.97
AV05247	28.82 $\pm$ 7.40	-1.96 $\pm$ 3.85
AV05248	7.00 $\pm$ 9.93	-8.32 $\pm$ 5.48
AV05249	17.18 $\pm$ 4.84	-15.84 $\pm$ 2.11
AV05250	0.92 $\pm$ 6.78	0.96 $\pm$ 1.51
AV05251	58.67 $\pm$ 3.92	10.05 $\pm$ 4.33
AV05253	80.69 $\pm$ 3.39	32.48 $\pm$ 3.25
AV05254	-5.05 $\pm$ 14.10	-10.79 $\pm$ 4.76
AV05255	-9.88 $\pm$ 7.86	-17.31 $\pm$ 8.70
AV05256	27.08 $\pm$ 3.23	-9.97 $\pm$ 6.02
AV05257	53.62 $\pm$ 5.53	11.62 $\pm$ 6.03
AV05258	13.11 $\pm$ 2.42	-6.85 $\pm$ 10.64
AV01215	77.87 $\pm$ 2.50	47.38 $\pm$ 4.29
AV05212	67.36 $\pm$ 3.51	44.24 $\pm$ 12.76
AV05220	32.06 $\pm$ 1.13	3.84 $\pm$ 5.78
AV05228	55.09 $\pm$ 0.72	9.90 $\pm$ 3.40
AV05236	35.24 $\pm$ 1.57	-10.97 $\pm$ 6.51
AV05244	67.60 $\pm$ 2.38	14.12 $\pm$ 4.20
AV05252	12.91 $\pm$ 6.68	-22.66 $\pm$ 6.06
AV01219	26.76 $\pm$ 6.38	-1.25 $\pm$ 9.41

Table 11 provides experimental results of *in vitro* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Inhibition%	
	1nM	0.1nM
	MEAN $\pm$ SD	
AV05499	16.81 $\pm$ 3.10	-46.45 $\pm$ 9.63
AV05500	19.76 $\pm$ 17.17	52.58 $\pm$ 10.45
AV05501	-17.54 $\pm$ 1.65	-33.96 $\pm$ 9.99
AV05502	98.14 $\pm$ 0.23	86.47 $\pm$ 1.69
AV05503	74.46 $\pm$ 2.28	0.43 $\pm$ 4.04
AV05504	44.32 $\pm$ 4.94	-2.68 $\pm$ 9.07
AV05505	50.27 $\pm$ 0.91	6.65 $\pm$ 1.70
AV05507	61.92 $\pm$ 1.10	-7.92 $\pm$ 9.63
AV05508	71.09 $\pm$ 0.47	-6.98 $\pm$ 3.77
AV05509	-46.01 $\pm$ 6.65	-44.48 $\pm$ 4.58
AV05510	57.15 $\pm$ 1.94	-22.07 $\pm$ 6.00

AV05511	69.78±0.53	6.30±5.93
AV05512	76.56±0.42	32.35±1.55
AV05513	86.53±0.50	54.15±2.76
AV05515	68.01±0.62	25.37±2.93
AV05516	72.66±1.26	9.42±5.55
AV05517	61.89±0.97	8.12±5.15
AV05518	1.23±8.21	-14.40±4.47
AV05519	79.60±1.12	56.83±0.47
AV05520	16.90±3.04	-7.90±6.13
AV05521	1.19±9.66	-14.68±6.46
AV05523	17.20±4.36	-7.00±5.07
AV05524	-20.54±3.99	-24.28±7.87
AV05525	32.83±4.22	-12.59±4.56
AV05526	81.66±2.64	35.24±3.93
AV05527	0.51±5.39	-14.88±12.98
AV05528	23.56±0.67	-8.78±5.28
AV05529	38.26±1.62	11.94±3.56
AV05531	25.29±3.76	-21.26±7.13
AV05532	79.96±0.14	26.30±1.18
AV05533	41.86±0.60	-15.67±4.86
AV05534	27.49±0.37	-9.27±6.25
AV05535	66.68±0.94	41.37±6.31
AV05536	44.23±2.20	0.37±5.69
AV05537	44.60±3.79	1.71±2.37
AV05539	67.27±0.47	16.50±9.81
AV05540	39.71±3.01	-20.69±0.25
AV05541	12.49±2.50	-21.61±2.69
AV05542	77.36±0.43	32.15±3.86
AV05544	30.74±5.26	-8.35±10.91
AV05545	29.91±5.61	1.75±5.23
AV05547	21.33±4.35	-31.09±2.62
AV05548	33.89±10.18	-8.06±3.11
AV05549	29.00±8.42	-19.67±6.14
AV05550	25.19±0.13	-24.85±3.66
AV05551	17.15±1.90	-10.25±0.63
AV05552	43.57±2.38	1.44±2.66
AV05553	61.17±3.03	13.62±3.15
AV05555	75.59±0.99	11.43±8.58
AV05556	55.61±1.35	-10.31±5.81
AV05557	51.26±1.92	-16.26±10.43

AV05558	13.00±1.19	-32.22±2.91
AV05559	50.47±2.93	-14.17±9.83
AV05560	-14.87±1.03	-20.64±7.62
AV05561	66.63±1.91	14.95±3.95
AV05563	57.57±1.70	8.09±2.37
AV05564	40.29±4.22	-31.86±7.78
AV05565	12.18±2.62	-27.45±8.77
AV05566	65.80±3.05	15.15±5.49
AV05567	71.54±1.47	14.41±3.00
AV05568	83.41±0.37	22.03±3.94
AV05569	84.68±0.07	46.50±4.47
AV05506	65.48±1.53	-10.03±5.11
AV05514	42.67±2.09	-18.15±1.89
AV05522	10.68±3.31	-30.88±3.21
AV05530	-1.47±7.63	-31.54±5.14
AV05538	81.21±0.93	34.38±2.87
AV05546	5.58±5.00	-23.08±6.45
AV05554	83.96±0.64	50.15±1.74
AV05562	63.32±2.13	-1.08±4.57
AV05570	75.09±1.61	32.17±5.48
AV01215	81.20±0.46	44.87±0.80
AV01219	33.96±1.76	-13.89±6.12

Example 8 *In Vivo* testing of FXI siRNA Duplexes

At day 1, female C57BL/6J mice (4-6weeks, 4 in each group) were infected by intravenous administration of a solution of adeno-associated virus (AAV-GFP) vector encoding Human Factor XI and luciferase gene. At day 8, mice were subcutaneously administered a single 2 or 3 mg/kg of FXI siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 15, and day 22. Plasma samples were isolated and serum samples were collected for quantification protein level through ELISA protocol. The results are shown in Tables 12-14.

Table 12 provides experimental results of *in vivo* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	remaining percent relative to D8 (Mean ± SD)		Dosage mg/kg
	D15	D22	
AD01002	0.11±0.03	/	3
AD00997-1	0.22±0.07	/	3

AD01606	0.33±0.08	/	3
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Table 13 provides experimental results of in vivo studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	FXI remaining compared to day8 (Mean ±SEM)		Dose(mg/kg)
	Day15	Day22	
AD00990	0.14±0.02	0.12±0.02	3
AD00991	0.18±0.07	0.18±0.02	3
AD00997	0.17±0.02	0.19±0.07	3
AD001002	0.08±0.03	0.07±0.03	3
AD02349	1.18±0.13	1.02±0.13	3
AD02350	0.78±0.07	0.86±0.02	3
AD02351	0.4±0.01	0.33±0.01	3
AD02352	0.12±0.01	0.12±0.03	3
AD02353	0.2±0.03	0.23±0.03	3
AD02354	0.27±0.01	0.3±0.04	3
AD02355	0.52±0.07	0.39±0.06	3
AD02356	0.27±0.04	0.35±0.06	3
AD02357	0.3±0.02	0.23±0.02	3
AD02358	0.31±0.05	0.25±0.06	3
AD02359	0.18±0.06	0.22±0.04	3
AD02360	0.19±0.02	0.28±0.02	3
AD02361	0.26±0.05	0.28±0.06	3
AD02362	0.17±0.02	0.15±0.01	3
AD02363	0.36±0.05	0.38±0.03	3
AD02364	0.43±0.05	0.41±0.08	3
AD02365	0.3±0.03	0.23±0.03	3
AD02366	0.23±0.03	0.16±0.02	3

Table 14 provides experimental results of in vivo studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	FXI remaining compared to day8 (Mean ±SEM)		Dose(mg/kg)
	Day15	Day22	
AD00991	0.11±0.03	0.16±0.01	3
AD00997	0.11±0.01	0.11±0.03	3
AD02369	1.17±0.24	1.12±0.26	3

AD02370	1.01±0.18	1.11±0.2	3
AD02371	0.41±0.02	0.46±0.07	3
AD02372	0.13±0.03	0.15±0.02	3
AD02373	0.65±0.11	0.73±0.07	3
AD02374	0.55±0.06	0.54±0.1	3
AD02375	0.05±0	0.07±0.02	3
AD02376	0.26±0	0.25±0.03	3
AD02377	0.14±0.02	0.12±0.01	3
AD02378	0.75±0.11	0.53±0.09	3
AD02379	0.28±0.03	0.29±0.05	3
AD02380	0.18±0.03	0.2±0.06	3
AD02381	1.16±0.13	1.13±0.23	3
AD02382	0.35±0.05	0.28±0.06	3
AD02383	0.38±0.06	0.28±0.04	3
AD02384	0.44±0.05	0.4±0.03	3
AD02385	0.22±0.04	0.16±0.04	3
AD02386	0.47±0.05	0.37±0.03	3
AD02387	0.39±0.05	0.22±0.02	3
AD02388	0.72±0.2	0.57±0.26	3
AD02389	0.54±0.07	0.45±0.05	3
AD02390	0.91±0.01	0.91±0.05	3
AD02391	0.6±0.03	0.53±0.06	3
AD02392	0.25±0.07	0.21±0.06	3
AD02393	0.8±0.12	0.78±0.11	3
AD02394	0.28±0.01	0.2±0.02	3
AD02395	0.52±0.03	0.58±0.08	3
AD02396	0.46±0.03	0.45±0	3
AD02397	0.3±0.04	0.26±0.03	3
AD02398	0.4±0.04	0.28±0.07	3
AD02399	0.08±0	0.07±0	3
AD02400	0.53±0.01	0.39±0.03	3
AD02401	0.76±0.07	0.6±0.11	3
AD02402	0.26±0.06	0.16±0.04	3
AD02403	0.54±0.06	0.43±0.12	3
AD02404	0.19±0.01	0.14±0.01	3

At day 1, female C57BL/6J mice (4-6weeks, 4 in each group) were infected by intravenous administration of a solution of adeno-associated virus (AAV-GFP) vector encoding Human Factor XI and luciferase gene. At day 8, mice were subcutaneously administered a single 2 mg/kg of FXI siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 21, and day 28.

Plasma samples were isolated and serum samples were collected for quantification protein level through ELISA protocol. The results are shown in Tables 15.

Table 15 provides experimental results of in vivo studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	FXI remaining compared to day8 (Mean $\pm$ SEM)		Dose(mg/kg)
	Day21	Day28	
AD00990	0.15 $\pm$ 0.04	0.17 $\pm$ 0.05	2
AD00991	0.14 $\pm$ 0.01	0.22 $\pm$ 0.02	2
AD00997	0.16 $\pm$ 0.04	0.15 $\pm$ 0.05	2
AD02432	0.25 $\pm$ 0.01	0.4 $\pm$ 0.03	2
AD02433	0.4 $\pm$ 0.1	0.58 $\pm$ 0.05	2
AD02434	0.52 $\pm$ 0.08	0.63 $\pm$ 0.12	2
AD02435	1.16 $\pm$ 0.12	1.68 $\pm$ 0.16	2
AD02436	0.66 $\pm$ 0.11	0.67 $\pm$ 0.07	2
AD02437	0.42 $\pm$ 0.04	0.66 $\pm$ 0.06	2
AD02438	0.55 $\pm$ 0.09	0.65 $\pm$ 0.07	2
AD02439	0.24 $\pm$ 0.02	0.35 $\pm$ 0.06	2
AD02440	0.19 $\pm$ 0.02	0.21 $\pm$ 0.05	2
AD02441	0.24 $\pm$ 0.04	0.4 $\pm$ 0.14	2
AD02442	0.82 $\pm$ 0.12	0.98 $\pm$ 0.03	2
AD02443	0.15 $\pm$ 0.02	0.17 $\pm$ 0.03	2
AD02444	0.09 $\pm$ 0.02	0.05 $\pm$ 0.01	2
AD02445	0.15 $\pm$ 0.01	0.1 $\pm$ 0.03	2
AD02446	0.1 $\pm$ 0.02	0.09 $\pm$ 0.02	2
AD02447	0.05 $\pm$ 0.01	0.04 $\pm$ 0	2

Example 9. *In Vivo* testing of FXI siRNA Duplexes in NHP PD model

Cynomolgus monkeys (3-5 years old, 3~6 kg of weights, 3 monkeys in each group) were enrolled in the study. Each monkey was subcutaneously administered a single 4 mg/kg of FXI siRNA agents or PBS at day 1 (pre-dosing of siRNA). After overnight fast, Plasma were drawn at day -14 (pre-dose), day -7 (pre-dose), 1 (pre-dose), 8, 15, 22, 29, 43, 50 and 57; liver biopsy were drawn at day -7 (pre-dose), 29 and 57. FXI protein concentration in serum were measured by ELISA method (FXI ELISA kit, Abcam, 1002579-4), the result is shown in table 16. FXI mRNA level in liver were

measured by QPCR method, the result is shown in table 17 . FXI activity were also measured by automatic blood clotting analyzer(siemens) the result are shown in table18.

Table 16 The results of FXI protein concentration in serum were measured by ELISA method

Duplex AD#	FXI remaining compared to pre-dosing (%) (Mean $\pm$ SEM)								Dose(mg/kg)
	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	
AD00990	53.41 $\pm$ 3.31	36.31 $\pm$ 5.61	22.88 $\pm$ 3.47	21.06 $\pm$ 2.6	18.28 $\pm$ 3.11	19.6 $\pm$ 3.23	21.96 $\pm$ 3.58	23.54 $\pm$ 3.28	4
AD00991	51.14 $\pm$ 3.45	30.19 $\pm$ 2.1	24.18 $\pm$ 5.99	16.8 $\pm$ 2.38	21.7 $\pm$ 0.59	18.92 $\pm$ 0.71	22.87 $\pm$ 1.93	23.13 $\pm$ 3.04	4
AD00997	51.17 $\pm$ 0.64	27.64 $\pm$ 2.22	20.48 $\pm$ 1.76	12.76 $\pm$ 1.83	15.2 $\pm$ 1.74	16.04 $\pm$ 2.01	24.49 $\pm$ 2.97	21.21 $\pm$ 1.49	4
AD00999	55.43 $\pm$ 1.55	50.06 $\pm$ 6.84	39.88 $\pm$ 5.89	32.11 $\pm$ 5.57	32.94 $\pm$ 8.68	27.98 $\pm$ 7.69	38.45 $\pm$ 13.76	37.63 $\pm$ 9.47	4
AD00998	69.26 $\pm$ 1.14	51.84 $\pm$ 2.42	40.36 $\pm$ 2.34	26.97 $\pm$ 1.05	29.18 $\pm$ 2.61	32.98 $\pm$ 1.26	41.79 $\pm$ 2.96	41.49 $\pm$ 2.81	4
AD01002	51.89 $\pm$ 4.55	33.71 $\pm$ 5.67	26.52 $\pm$ 5.36	23.95 $\pm$ 4.66	24.36 $\pm$ 4.32	25.17 $\pm$ 7.02	29.96 $\pm$ 8.5	36.04 $\pm$ 5.18	4
AD01016	52.82 $\pm$ 3.14	36.16 $\pm$ 0.99	29.16 $\pm$ 0.91	27.77 $\pm$ 2.92	28.06 $\pm$ 1.77	26.81 $\pm$ 3.23	36.35 $\pm$ 3.96	35.78 $\pm$ 4.25	4
AD01606	59.18 $\pm$ 1.71	44.86 $\pm$ 2.79	36.93 $\pm$ 5.81	44.21 $\pm$ 8.24	42.59 $\pm$ 6.26	46.44 $\pm$ 5.53	53.87 $\pm$ 6.85	57.25 $\pm$ 6.59	4

Table 17 The results of FXI mRNA level in liver were measured by QPCR method.

Duplex AD#	F11 remaining relative to pre-dosing baseline (Mean $\pm$ SEM)	F11 remaining relative to pre-dosing baseline (Mean $\pm$ SEM)	Dosage mg/kg
	D29	D57	
AD00990	0.25 $\pm$ 0.05	0.22 $\pm$ 0.04	4
AD00991	0.17 $\pm$ 0.04	0.22 $\pm$ 0	4
AD00997	0.2 $\pm$ 0.03	0.22 $\pm$ 0.02	4
AD00999	0.24 $\pm$ 0.04	0.32 $\pm$ 0.09	4
AD00998	0.21 $\pm$ 0.03	0.3 $\pm$ 0.09	4
AD01002	0.2 $\pm$ 0.01	0.23 $\pm$ 0.06	4
AD01016	0.2 $\pm$ 0.02	0.27 $\pm$ 0.06	4
AD01606	0.38 $\pm$ 0.15	0.57 $\pm$ 0.15	4

Table 18 The results of FXI activity

Duplex AD#	FXI activity remaining compared to pre-dosing (%)(Mean $\pm$ SEM)							
	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
AD00990	40.12 $\pm$ 5.28	23.3 $\pm$ 5.19	14.72 $\pm$ 3.71	15.23 $\pm$ 3.92	21.6 $\pm$ 6.31	17.46 $\pm$ 4.59	24.87 $\pm$ 6.51	24.09 $\pm$ 6.51
AD00991	30.55 $\pm$ 1.56	15.47 $\pm$ 1.11	13.17 $\pm$ 0.67	11.91 $\pm$ 0.96	18.07 $\pm$ 1.51	13.25 $\pm$ 1.27	19.47 $\pm$ 2.08	17.57 $\pm$ 0.95
AD00997	34.18 $\pm$ 1.62	16.64 $\pm$ 0.26	12.1 $\pm$ 1.55	13.25 $\pm$ 1.28	16.67 $\pm$ 1.24	16.28 $\pm$ 3.1	23.01 $\pm$ 4.12	21.06 $\pm$ 3.99
AD00999	48.51 $\pm$ 5.04	25.61 $\pm$ 1.98	24.54 $\pm$ 1.56	24.76 $\pm$ 3.56	32.85 $\pm$ 7.92	37.58 $\pm$ 11.96	38.98 $\pm$ 12.72	36.38 $\pm$ 9.58
AD00998	50.7 $\pm$ 5.02	27.61 $\pm$ 6.33	26.17 $\pm$ 8.28	25.87 $\pm$ 7.87	28.65 $\pm$ 8.97	28.36 $\pm$ 9.19	38.29 $\pm$ 11.19	41.64 $\pm$ 12.94
AD01002	37.76 $\pm$ 3.41	20.59 $\pm$ 0.5	16.64 $\pm$ 1.22	17.39 $\pm$ 2.23	21.51 $\pm$ 0.51	21.05 $\pm$ 1.61	29.83 $\pm$ 3.48	31.94 $\pm$ 4.5
AD01016	40.68 $\pm$ 7.97	24.69 $\pm$ 6.09	21.24 $\pm$ 7.01	21.03 $\pm$ 5.78	30.17 $\pm$ 10.1	28.1 $\pm$ 8.71	39.88 $\pm$ 13.17	37.48 $\pm$ 12.76
AD01606	41.65 $\pm$ 2.36	23.39 $\pm$ 2.59	21.55 $\pm$ 3.47	27.11 $\pm$ 5.31	30.22 $\pm$ 6.3	33.89 $\pm$ 10.61	47.97 $\pm$ 12.23	60.26 $\pm$ 20.67

Example 10. *In Vivo* testing of FXI siRNA Duplexes in NHP PD model

Cynomolgus monkeys (3-5 years old, 3~6 kg of weights, 3 monkeys in each group) were enrolled in the study. Each monkey was subcutaneously administered a single 6 mg/kg of FXI siRNA agents or PBS at day 1 (pre-dosing of siRNA). After overnight fast, Plasma was drawn at day -14 (pre-dose), day -7 (pre-dose), 1 (pre-dose), 8, 15, 22, and 29; liver biopsy were drawn at day -7 (pre-dose), 29 and 57. FXI activity were also measured by automatic blood clotting analyzer (siemens). the result are shown in table 19.

Table 19. The results of FXI activity

Duplex AD#	FXI activity remaining compared to pre-dosing (%)(Mean $\pm$ SEM)				dosage
	Day8	Day15	Day22	Day29	
AD00990-2	45.66 $\pm$ 5.86	23 $\pm$ 5.13	12.54 $\pm$ 2.8	9.69 $\pm$ 2.6	6 mpk
AD00991	49.84 $\pm$ 7.32	23.09 $\pm$ 5.4	17 $\pm$ 6.19	15.85 $\pm$ 6.39	6 mpk
AD00997-2	34.38 $\pm$ 7	16.49 $\pm$ 4.34	8.03 $\pm$ 1.82	5.32 $\pm$ 1.05	6 mpk
AD02352	32.15 $\pm$ 3.25	17.58 $\pm$ 6.17	9.27 $\pm$ 2.26	7.96 $\pm$ 2.14	6 mpk
AD02362	40.95 $\pm$ 1.84	20.81 $\pm$ 3.48	11.19 $\pm$ 0.26	11.35 $\pm$ 0.59	6 mpk
AD02375-1	34.58 $\pm$ 3.39	13.16 $\pm$ 1.35	6.68 $\pm$ 1.32	6.04 $\pm$ 1.52	6 mpk
AD02399	38.11 $\pm$ 3.81	16.69 $\pm$ 4.67	11.01 $\pm$ 3.68	9.6 $\pm$ 3.73	6 mpk

AD02444	53.17 $\pm$ 1.32	30.61 $\pm$ 4.2	18.27 $\pm$ 3.46	14.76 $\pm$ 3.1	6 mpk
AD02445	57.14 $\pm$ 13.11	27.83 $\pm$ 8.31	19.93 $\pm$ 6.53	15.29 $\pm$ 5.09	6 mpk
AD02446	58.26 $\pm$ 6.77	24.03 $\pm$ 2.58	14.51 $\pm$ 1.39	12.91 $\pm$ 1.19	6 mpk
AD02447	43.24 $\pm$ 3.1	21.41 $\pm$ 4.34	14.99 $\pm$ 2.73	12.8 $\pm$ 2.18	6 mpk

Example 11. *In Vitro* Screening of FXI siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of psiCHECK(TM)-2 Vector plasmid and Lipofectamine 2000 and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax (Invitrogen -13778-150) at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at two concentrations (1 nM and 0.1 nM) in triplicate by Dual-Glo® Luciferase Assay. The results are shown in Tables 20.

Table20 provides experimental results of *in vitro* studies using various FXI RNAi agents to inhibit FXI expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Inhibition%	
	1nM	0.1nM
	MEAN $\pm$ SD	
AV06227	75.49 $\pm$ 1.35	30.45 $\pm$ 5.55
AV06228	77.41 $\pm$ 0.49	35.10 $\pm$ 2.74
AV06230	76.94 $\pm$ 1.64	36.96 $\pm$ 0.66
AV06231	65.75 $\pm$ 0.06	18.32 $\pm$ 2.69
AV06232	64.70 $\pm$ 1.25	17.66 $\pm$ 1.35
AV06233	84.42 $\pm$ 0.71	38.39 $\pm$ 3.03
AV06235	76.96 $\pm$ 0.69	28.80 $\pm$ 3.09
AV06236	71.58 $\pm$ 1.47	20.93 $\pm$ 6.90
AV06237	78.34 $\pm$ 0.95	38.08 $\pm$ 2.96
AV06238	67.44 $\pm$ 1.13	20.26 $\pm$ 0.84
AV06239	74.15 $\pm$ 1.42	32.56 $\pm$ 2.32
AV06240	43.19 $\pm$ 2.15	11.90 $\pm$ 5.32
AV06241	28.94 $\pm$ 3.22	5.57 $\pm$ 2.16
AV06234	72.02 $\pm$ 0.51	20.75 $\pm$ 2.98
AV01215	82.28 $\pm$ 0.69	43.50 $\pm$ 1.75
AV01219	32.13 $\pm$ 0.28	-5.74 $\pm$ 1.24

Equivalents

Although several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto; the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems, articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified, unless clearly indicated to the contrary.

All references, patents and patent applications and publications that are cited or referred to in this application are incorporated herein in their entirety herein by reference.

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent includes a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a FXI RNA transcript, wherein the region of complementarity includes at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand.
2. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 143-173, 150-180, 380-410, 384-414, 389-419, 402-432, 419-449, 536-566, 1141-1171, 1488-1518, 1561-1591, 2111-2141, 2112-2142, 2113-2143, 2115-2145, 2111-2145 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.
3. The dsRNA agent of claim 2, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 148-168, 155-175, 385-405, 389-409, 394-414, 407-427, 424-444, 541-561, 1146-1166, 1493-1513, 1566-1586, 2116-2136, 2117-2137, 2118-2138, 2120-2140, 2116-2140 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.
4. The dsRNA agent of any one of claims 1-3, wherein the antisense strand of dsRNA is substantially or fully complementary to any one of a target region of SEQ ID NO: 1, and preferably the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-3.
5. The dsRNA agent of any one of claims 1-4, wherein the sense strand sequence is at least substantially complementary to or fully complementary to the antisense strand sequence in the

dsRNA agent, preferably, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3.

6. The dsRNA agent of any one of claims 1-5, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

7. The dsRNA of any one of claims 1-6, wherein the dsRNA agent comprises at least one modified nucleotide.

8. The dsRNA agent of any one of claims 1-7, wherein all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

9. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to a FXI RNA transcript, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand sequence may be represented by formula (II):



wherein:

each N'_F represents a 2'-fluoro-modified nucleotide; each N'_{N1} and N'_{N2} independently represents a modified or unmodified nucleotide, N'_{N1} and N'_{N2} include only one 2'-fluorine modified nucleotides; each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' and n' are each independently an integer of 0 to 7.

10. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to a FXI RNA transcript, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand sequence may be represented by formula (III):



formula (III)

wherein:

each N_F represents a 2'-fluoro-modified nucleotide; each N_{M1} , N_{M2} , N_{M3} , N_{M4} , and N_{M5} independently represents a modified or unmodified nucleotide; N_{M1} , N_{M2} , N_{M3} , N_{M4} , and N_{M5} have only three 2'-fluoro-modified nucleotides; each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7.

11. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand is complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to an mRNA encoding FXI, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA duplex represented by formula (IV):

sense: 5'-(N'_L) $_n$ N'_L N'_L N'_L N'_L N'_F N'_L N'_F N'_L N'_{N1} N'_{N2} N'_L N'_L N'_L N'_L N'_L (N'_L) $_m$ -3'

antisense: 3'-(N_L) $_n$ N_{M1} N_L N_{M2} N_L N_F N_L N_{M3} N_L N_L N_L N_L N_{M4} N_L N_{M5} N_L N_L N_F N_L -5'

formula (IV)

wherein:

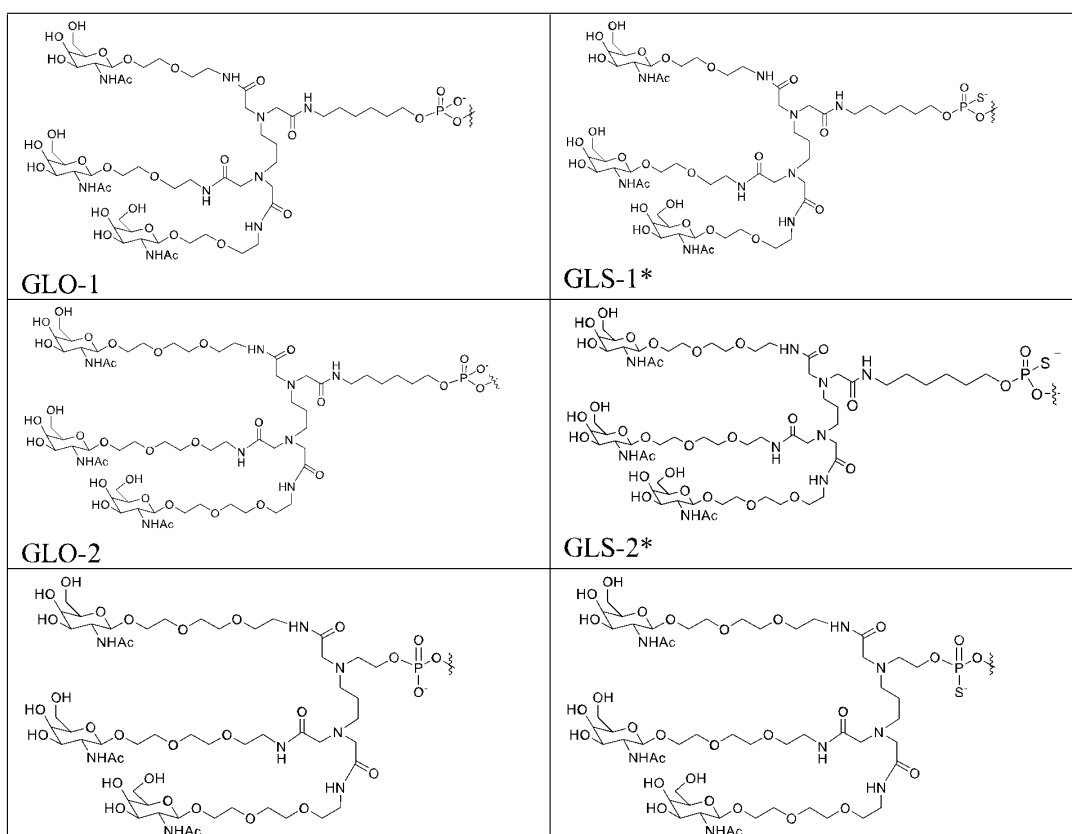
each strand is about 18 to about 30 nucleotides in length;

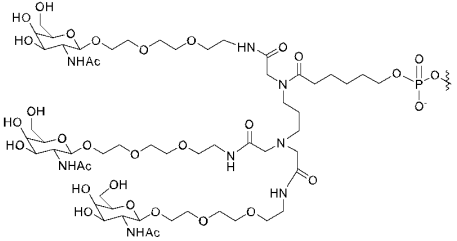
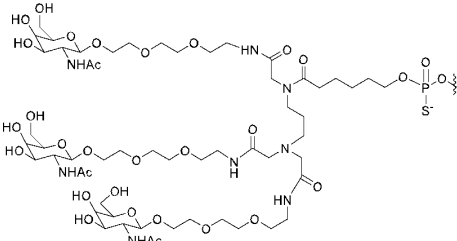
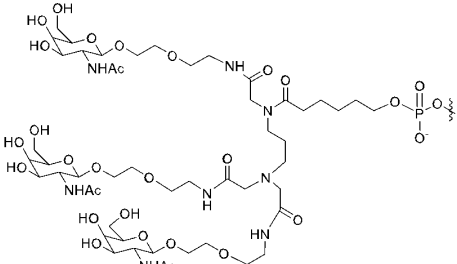
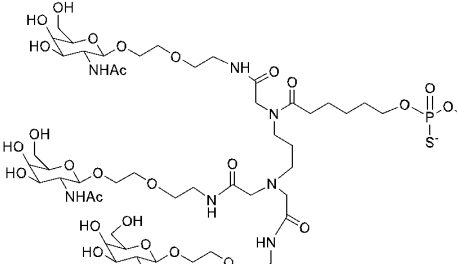
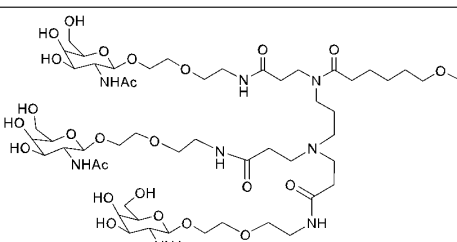
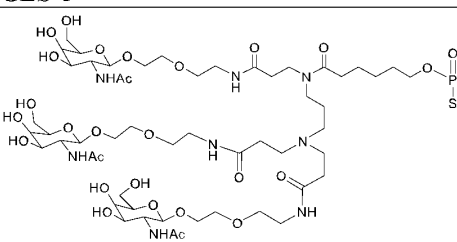
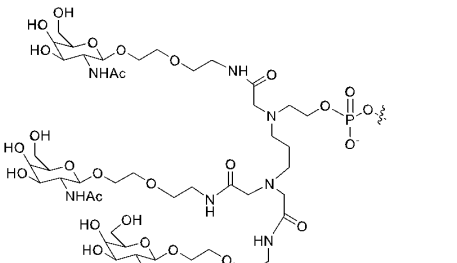
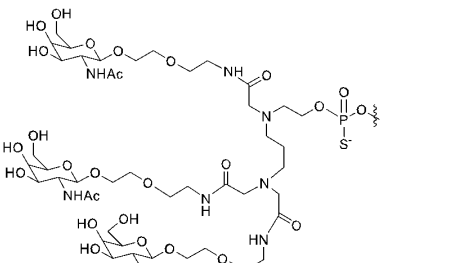
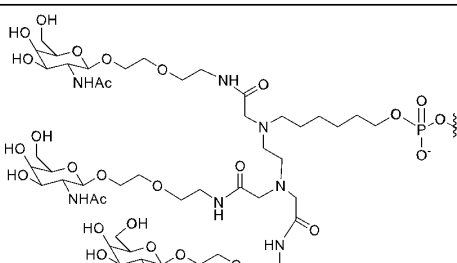
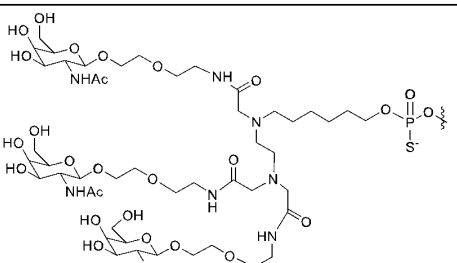
each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N'_{N1} , and N'_{N2} each independently represents a modified or unmodified nucleotide; N_{M1} , N_{M2} , N_{M3} , N_{M4} , and N_{M5} have only three 2'-fluoro-modified nucleotides; N'_{N1} and N'_{N2} include only one 2'-fluorine modified nucleotides; each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' , n' and n are each independently an integer of 0 to 7.

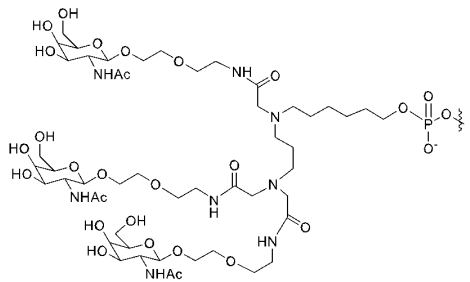
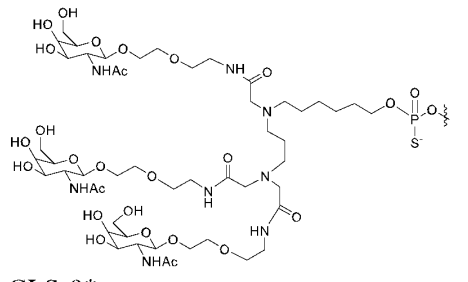
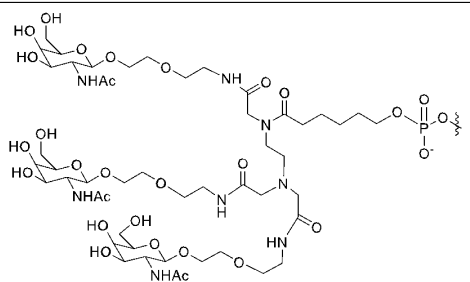
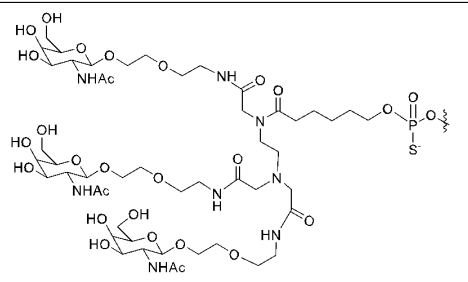
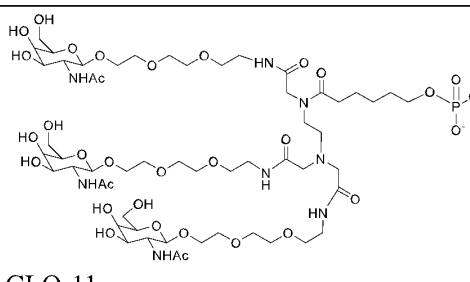
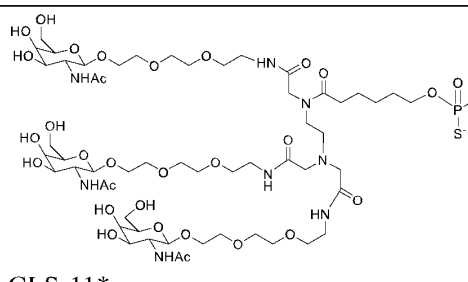
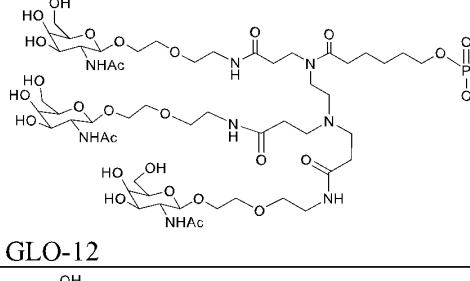
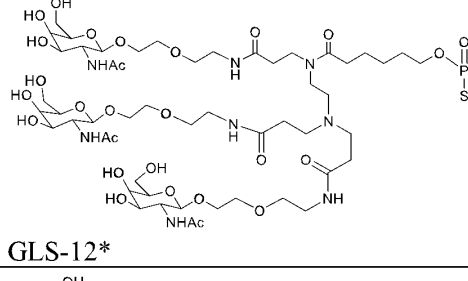
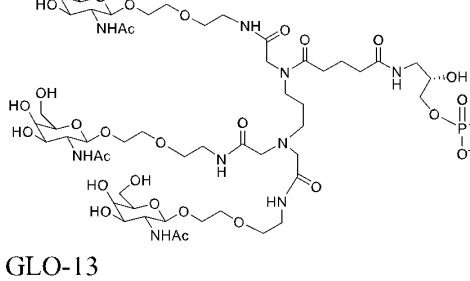
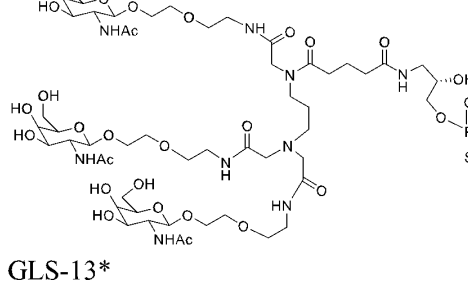
12. The dsRNA agent of any one of claims 7-11, wherein the one or more modified nucleotides are independently selected from the group consisting of: a 2'-O-methyl nucleotide, a 2'-Fluoro nucleotide, a 2'-deoxy nucleotide, a 2'3'-seco nucleotide mimic, a locked nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2'-F-Arabino nucleotide, a 2'-methoxyethyl nucleotide, an abasic nucleotide, an ribitol, inverted nucleotide, an inverted abasic nucleotide, an isomannide nucleotide, an inverted 2'-Ome nucleotide, an inverted 2'-deoxy nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

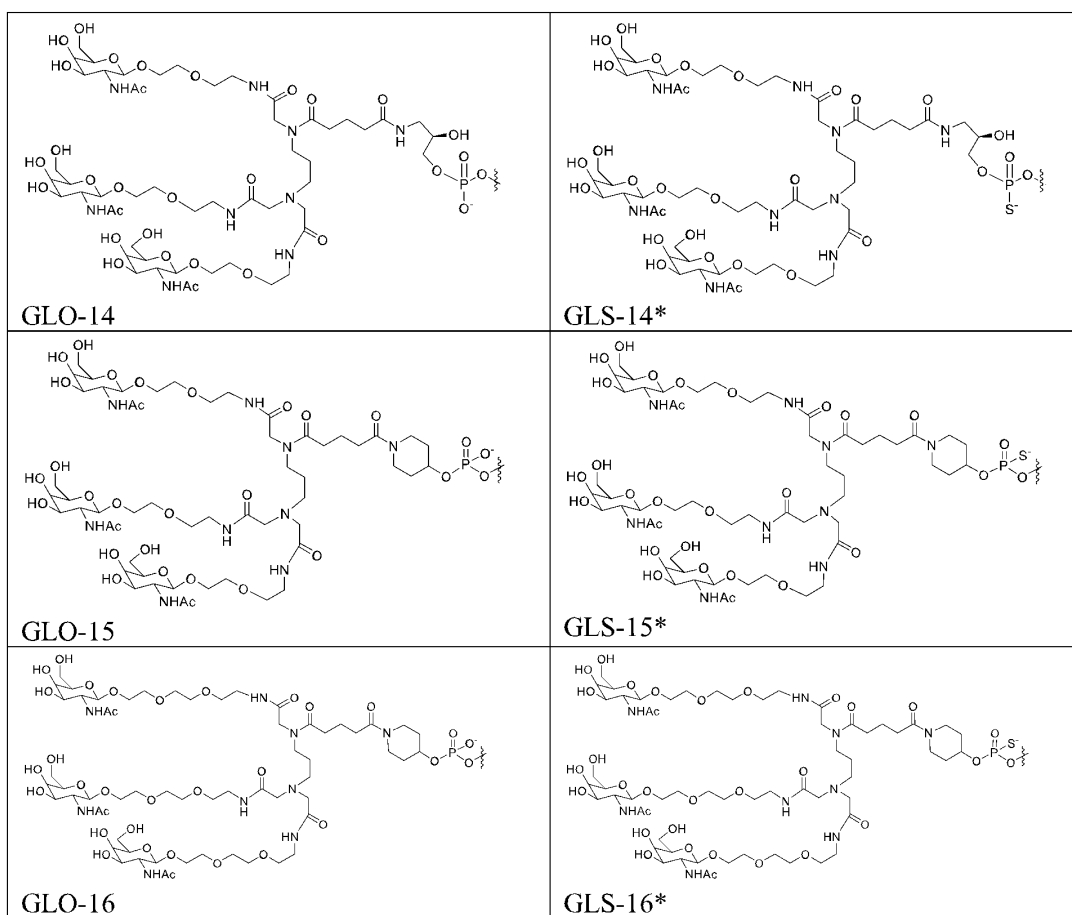
13. The dsRNA agent of any one of claims 1-12, comprises an E-vinylphosphonate nucleotide at the 5' end of the guide strand.
14. The dsRNA agent of any one of claims 1-13, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage.
15. The dsRNA agent of any one of claims 1-13, wherein the sense strand comprises at least one phosphorothioate internucleoside linkage.
16. The dsRNA agent of any one of claims 1-13, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage.
17. The dsRNA agent of any one of claims 1-13, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.
18. The dsRNA agent of any one of claims 1-13, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.
19. The dsRNA agent of any one of claims 1-18, wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3.
20. The dsRNA agent of any one of claims 1-18, wherein the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.
21. The dsRNA agent of any one of claims 1-20, wherein the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length.
22. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is 19-21 nucleotides in length.
23. The dsRNA agent of any one of claims 1-22, wherein each strand is no more than 30 nucleotides in length.

24. The dsRNA agent of any one of claims 1-22, wherein each strand is no more than 25 nucleotides in length.
25. The dsRNA agent of any one of claims 1-24, wherein each strand is no more than 23 nucleotides in length.
26. The dsRNA agent of any one of claims 1-25, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups.
27. The dsRNA agent of claim 26, wherein the one or more targeting groups or linking groups are conjugated to the sense strand.
28. The dsRNA agent of claim 26 or 27, wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc).
29. The dsRNA agent of claim 28 or 29, wherein the targeting group has a structure:



GLO-3 	GLS-3* 
GLO-4 	GLS-4* 
GLO-5 	GLS-5* 
GLO-6 	GLS-6* 
GLO-7 	GLS-7* 
GLO-8 	GLS-8* 

 GLO-9	 GLS-9*
 GLO-10	 GLS-10*
 GLO-11	 GLS-11*
 GLO-12	 GLS-12*
 GLO-13	 GLS-13*



30. The dsRNA agent of any one of claims 1-29, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand.

31. The dsRNA agent of any one of claims 1-29, wherein the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.

32. The dsRNA agent of any one of claims 1-29, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end.

33. The dsRNA agent of any one of claims 1-29, wherein the sense strand comprises one or two inverted abasic residues or imann residues at 3' or/and 5' terminal end.

34. The dsRNA agent of any one of claims 1-33, wherein the dsRNA agent has two blunt ends.

35. The dsRNA agent of any one of claims 1-33, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
36. The dsRNA agent of any one of claims 1-33, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.
37. The dsRNA agent of any one of claims 1-36 wherein the FXI RNA transcript is SEQ ID NO: 1.
38. A composition comprising one, two, three, or more dsRNA agents of any one of claims 1-37.
39. The composition of claim 38, further comprising a pharmaceutically acceptable carrier.
40. The composition of claim 39, further comprising one or more additional therapeutic agents.
41. The composition of claim 40, wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial.
42. The composition of claim 38, wherein the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.
43. A cell comprising a dsRNA agent of any one of claims 1-37.
44. The cell of claim 43, wherein the cell is a mammalian cell, optionally a human cell.
45. A method of inhibiting the expression of a FXI gene in a cell, the method comprising:
(i) preparing a cell or plurality of cells comprising an effective amount of one or more double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-37 or a composition of any one of claims 38-42.
46. The method of claim 45, further comprising:
(ii) maintaining the cell or plurality of cells prepared in claim 45(i) for a time sufficient to obtain degradation of the mRNA transcript of a FXI gene, thereby inhibiting expression of the FXI gene in the cell or plurality of cells and reducing a level of the FXI polypeptide in the cell or plurality of cells.

47. The method of claim 45 or 46, wherein the cell or plurality of cells is in a subject and the dsRNA agent is administered to the subject subcutaneously or by IV administration, or the cell or plurality of cells is outside a subject and is contacted with the dsRNA agent.

48. The method of any one of claims 45-47, wherein 2, 3, 4, or more dsRNA agents are administered to the subject or contacted with the cell or plurality of cells.

49. The method of any one of claims 45-48, further comprising assessing inhibition of the FXI gene in the subject, following the administration of the dsRNA agent(s) to the subject, wherein a means for the assessing comprises:

(i) determining one or more physiological characteristics of a FXI -associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-administration physiological characteristic of the FXI -associated disease or condition and/or to a control physiological characteristic of the FXI -associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the FXI gene in the subject.

50. The method of any one of claims 45-48, further comprising assessing inhibition of the FXI gene in the cell or plurality of cells, following contacting the dsRNA agent(s) to the cell or plurality of cells, wherein a means for the assessing comprises:

(i) determining one or more physiological characteristics of a FXI -associated disease or condition in the cell or plurality of cells and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-contact physiological characteristic of the FXI -associated disease or condition and/or to a control physiological characteristic of the FXI -associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the FXI gene in the cell or plurality of cells.

51. The method of claim 49 or 50, wherein the control physiological characteristic is the physiological characteristic in a subject with a FXI -associated disease or condition and not administered the dsRNA agent(s) or is the physiological characteristic in a cell with a FXI -associated disease or condition and not contacted with the dsRNA agent(s).

52. The method of any one of claims 49-51, wherein the determined physiological characteristic in the subject is one or more of: a level of plasma FXI mRNA level, the FXI protein level, or active form (FXIa) level, partial thromboplastin time (PTT) test, activated partial thromboplastin time test (aPTT or APTT).
53. The method of claim 49, wherein the physiological characteristic is determined in a biological sample obtained from the subject.
54. The method of claim 53, wherein the biological sample comprises one or more of: a blood sample, a serum sample, a tissue sample, a cell sample, and a liver sample.
55. The method of claim 49, wherein the determined physiological characteristic in the subject is abnormal compared to a control level of the physiological characteristic.
56. The method of claim 49 or 50, wherein the control physiological characteristic in the subject is the physiological characteristic in a subject with the FXI-associated disease or condition and not administered the anti- FXI dsRNA agent(s) and the control physiological characteristic in the cell or plurality of cells is the physiological characteristic in a cell with the FXI -associated disease or condition and not contacted with the anti- FXI dsRNA agent(s).
57. A method of inhibiting expression of a FXI gene in a subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-37 or a composition of any one of claims 38-42.
58. The method of claim 57, wherein the dsRNA agent is administered to the subject subcutaneously or by IV administration.
59. The method of any one of claims 57 or 58, further comprising assessing inhibition of the FXI gene, following the administration of the dsRNA agent, wherein a means for the assessing comprises:
- (i) determining one or more physiological characteristics of a FXI -associated disease or condition in the subject and
 - (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the FXI -associated disease or condition and/or to a control physiological characteristic of the FXI -associated disease or condition,

wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the FXI gene in the subject.

60. The method of claim 59, wherein the determined physiological characteristic is one or more of: the FXI mRNA level, the FXI protein level in the subject, or active form (FXIa) level, partial thromboplastin time (PTT) test, activated partial thromboplastin time test (aPTT or APTT).

61. A method of treating a disease or condition associated with the presence of FXI protein, the method comprising administering to a subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-37, or a composition of any one of claims 38-42, to inhibit FXI gene expression.

62. The method of claim 61, wherein the disease or condition is one or more of: thromboembolic condition, such as deep vein thrombosis, venous or arterial thrombosis, pulmonary embolism, myocardial infarction, thrombosis associated with chronic kidney disease or end-stage renal disease (ESRD), and stroke.

63. The method of claim 62, further comprising administering an additional therapeutic regimen to the subject.

64. The method of claim 63, wherein the additional therapeutic regimen comprises: administering to the subject one or more FXI antisense polynucleotides of the invention, administering to the subject a non-FXI dsRNA therapeutic agent, and a behavioral modification in the subject.

65. The method of claim 64, wherein the non-FXI dsRNA therapeutic agent is one of more of: NSAID/Cyclooxygenase inhibitors, such as, aspirin; adenosine diphosphate (ADP) receptor inhibitors, such as, clopidogrel (PLAVIX) and ticlopidine (TICLID); phosphodiesterase inhibitors, such as, cilostazol (PLETAL); glycoprotein IIB/IIIA inhibitors, such as, abciximab (REOPRO), eptifibatide (INTEGRILIN), tirofiban (AGGRASTAT), and defibrotide; adenosine reuptake inhibitors, such as, dipyridamole (PERSANTINE); warfarin (and related coumarins); heparin; direct thrombin inhibitors, such as, lepirudin, bivalirudin; apixaban, LOVENOX (enoxaparin); small molecular compounds that interfere directly with the enzymatic action of particular coagulation factors (e.g. rivaroxaban, which interferes with Factor Xa).

66. The method of any one of claims 61-65, wherein the dsRNA agent is administered to the subject subcutaneously or IV administration.

67. The method of any one of claims 61-65, further comprising determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject.

68. A method of decreasing a level of FXI protein in a subject compared to a baseline pre-treatment level of FXI protein in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of claims 1-37, or a composition of any one of claims 38-42, to decrease the level of FXI gene expression.

69. The method of claim 68, wherein the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

70. A method of altering a physiological characteristic of a FXI-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the FXI-associated disease or condition in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-37, or a composition of any one of claims 38-42, to alter the physiological characteristic of the FXI-associated disease or condition in the subject.

71. The method of claim 70, wherein the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

72. The method of any one of claims 70-71, wherein the physiological characteristic is one or more of: the FXI mRNA level, the FXI protein level in the subject, or active form (FXIa) level, partial thromboplastin time (PTT) test, activated partial thromboplastin time test (aPTT or APTT).