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; or, 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.

5. The dsRNA agent of any one of claims 1-4, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

6. The dsRNA of any one of claims 1-5, wherein the dsRNA agent comprises at least one modified nucleotide; optionally, wherein all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

7. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation factor XI (FXI) is provided, wherein the dsRNA agent is represented by II, III or IV;
the dsRNA agent II 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):

$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$ 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;
the dsRNA agent III 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):

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

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;
the dsRNA agent IV 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: $5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$

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

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.

8. The dsRNA agent of claims 6 or 7, 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’-methoyxyethyl 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 mopholino 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;

preferably, the dsRNA agent comprises an E-vinylphosphonate nucleotide at the 5′ end of the guide strand;

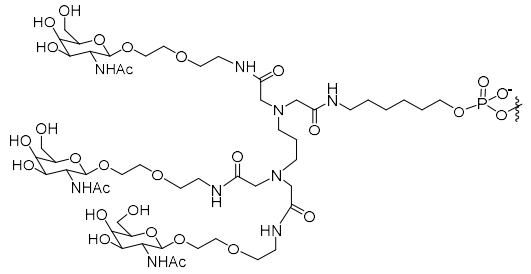
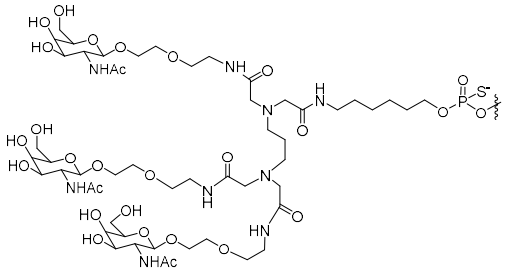
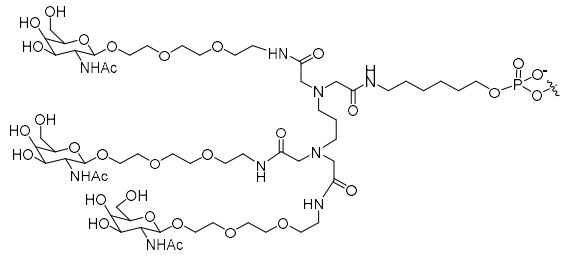
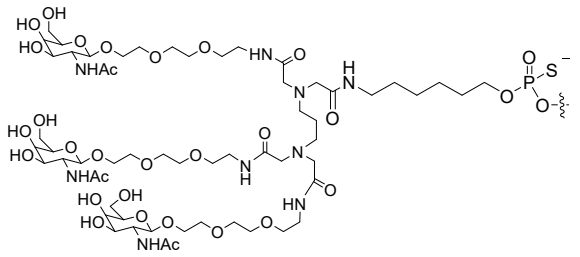
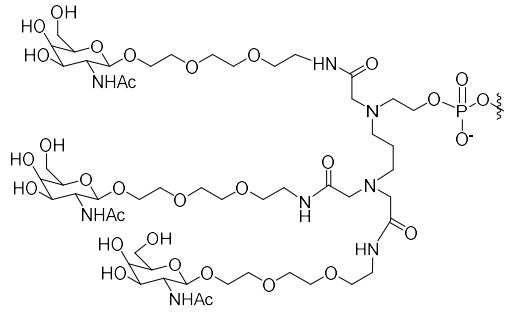
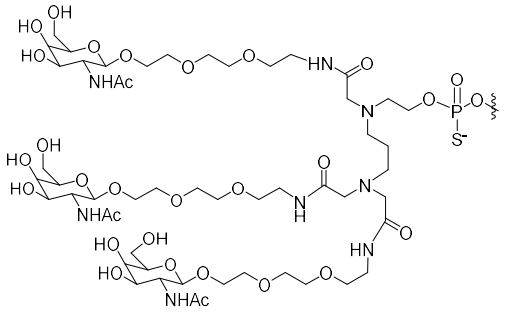
optionally, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage; and optionally, wherein the sense strand comprises at least one phosphorothioate internucleoside linkage, and/or, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage, preferably, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages, preferably, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages; or

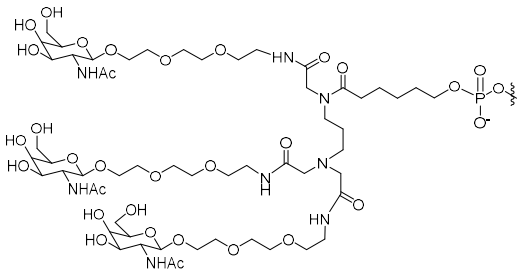
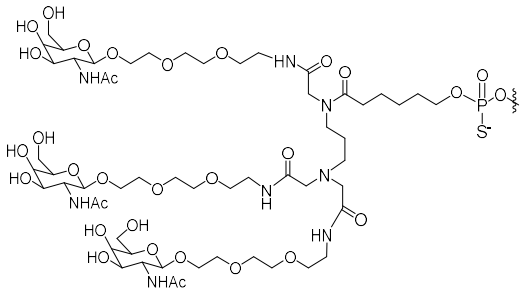
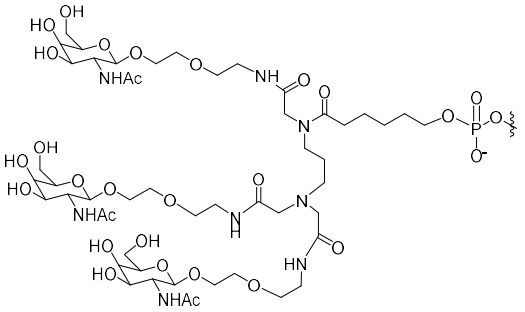
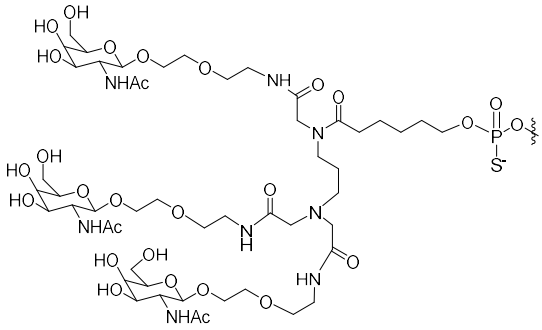
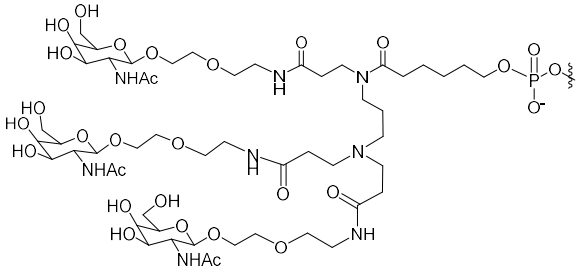
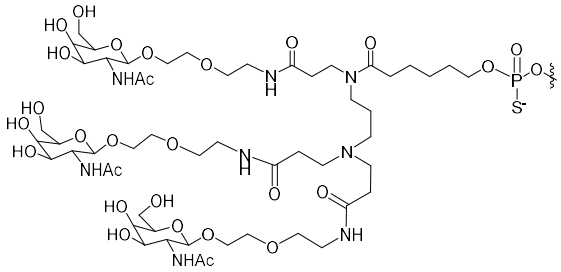
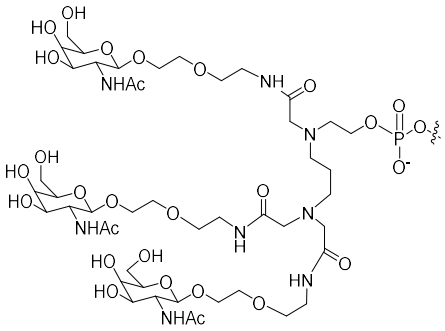
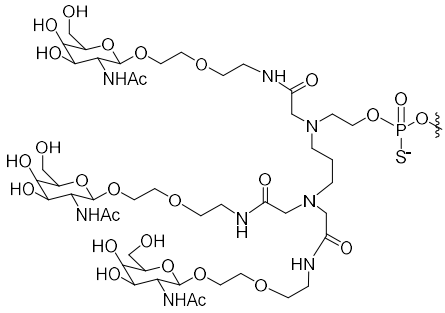
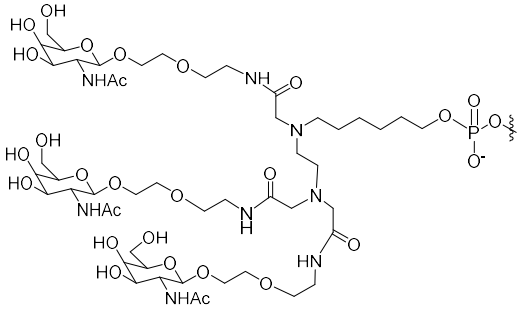
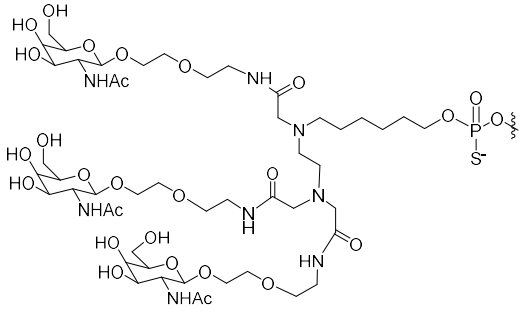
wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3, and optionally, wherein the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.

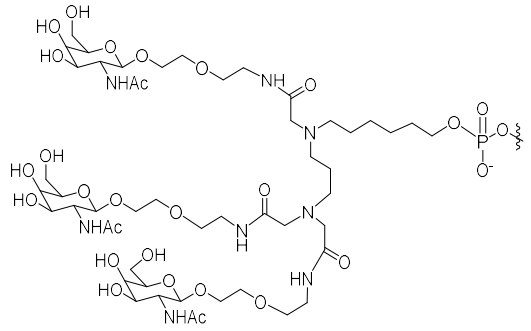
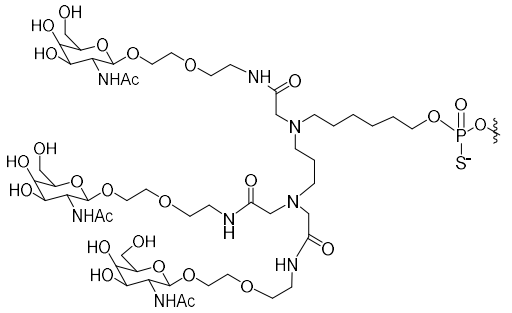
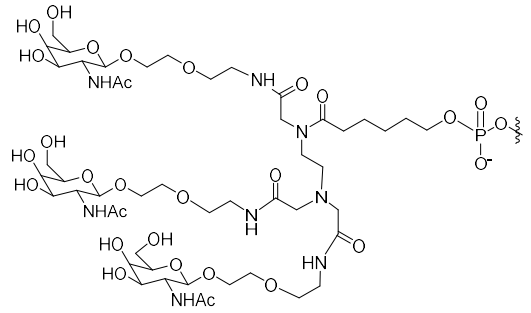
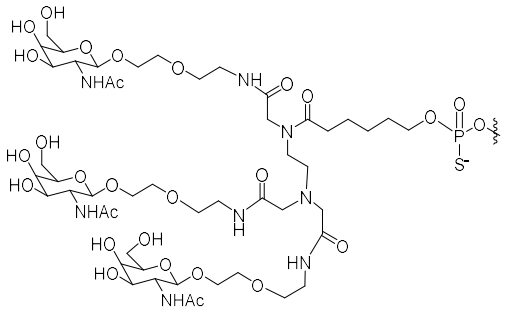
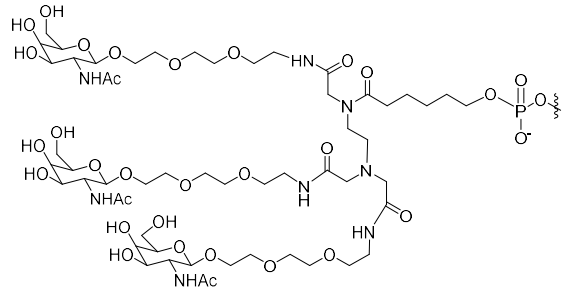
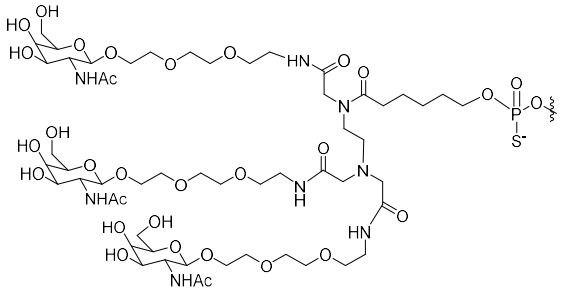
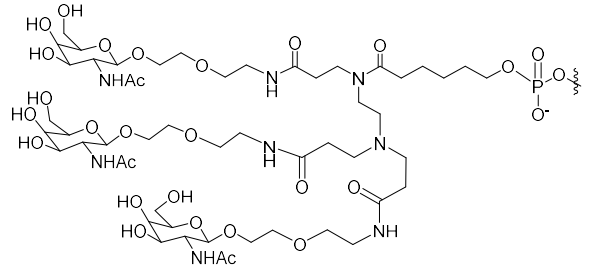
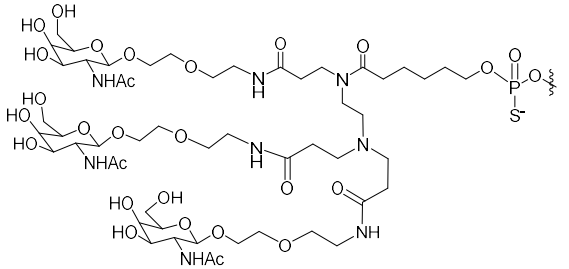
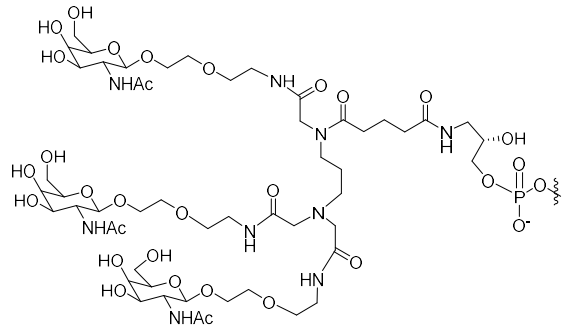
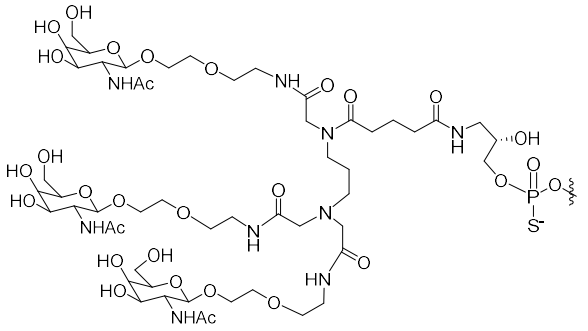
9. The dsRNA agent of any one of claims 1-8, wherein the sense strand is complementary or substantially complementary to the antisense strand for a region of 16-23 or 19-21 nucleotides in length.

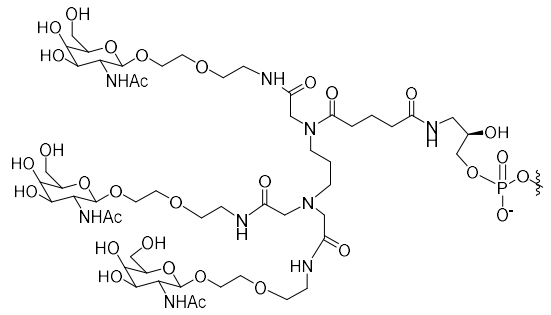
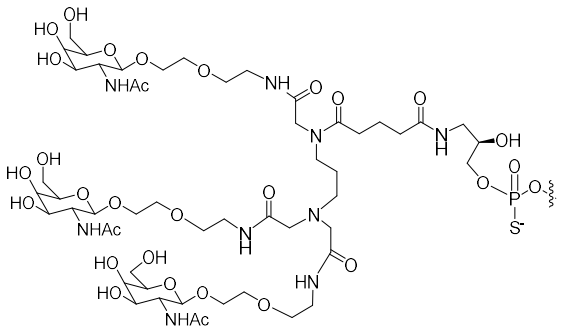
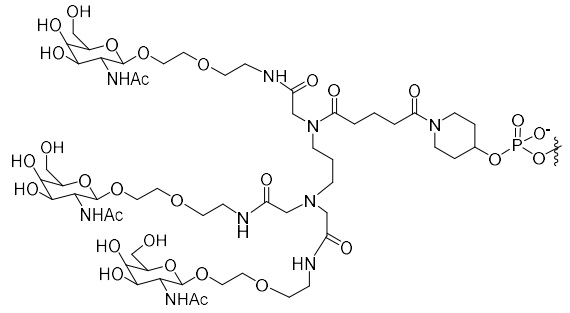
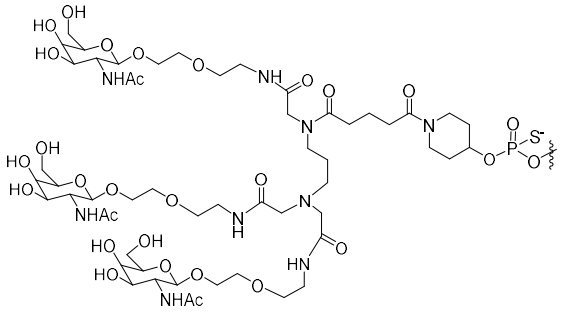
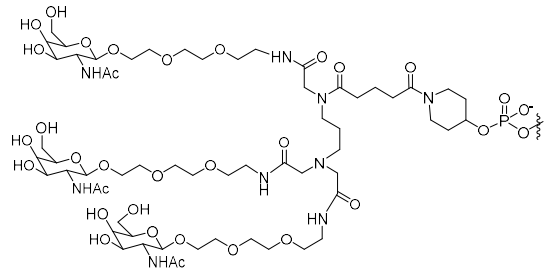
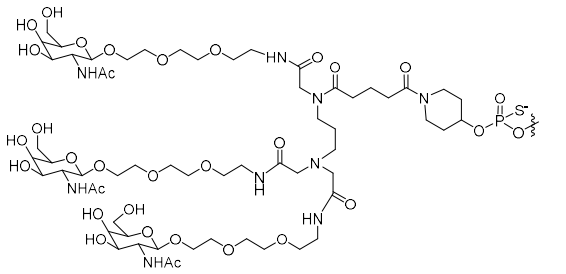
10. The dsRNA agent of any one of claims 1-9, wherein each strand is no more than 30, 25 or 23 nucleotides in length.

11. The dsRNA agent of any one of claims 1-10, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;
optionally, wherein the one or more targeting groups or linking groups are conjugated to the sense strand;
preferably, wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc), wherein the targeting group has a structure:

 GLO-1	 GLS-1*
 GLO-2	 GLS-2*
 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*

 GLO-14	 GLS-14*
 GLO-15	 GLS-15*
 GLO-16	 GLS-16*

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12. The dsRNA agent of any one of claims 1-11, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand; or, wherein the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.

13. The dsRNA agent of any one of claims 1-12, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end; or, wherein the sense strand comprises one or two inverted abasic residues or imann residues at 3' or/and 5' terminal end;
preferably, wherein the dsRNA agent has two blunt ends; or
at least one strand comprises a 3' overhang of at least 1 or 2 nucleotides.

14. A composition comprising one, two, three, or more dsRNA agents of any one of claims 1-13;
preferably, the composition further comprising a pharmaceutically acceptable carrier;
preferably, the composition further comprising one or more additional therapeutic agents;

preferably, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial; preferably, wherein the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

15. A cell comprising a dsRNA agent of any one of claims 1-13, preferably, the cell is a mammalian cell, optionally a human cell.

16. Use of one or more double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-13 or a composition of claim 14 in the manufacture of a medicament for inhibiting the expression of a FXI gene in a cell, wherein:
(i) a cell or plurality of cells is prepared to comprise an effective amount of the one or more double-stranded ribonucleic acid (dsRNA) agents or the composition,
and optionally:
(ii) the cell or plurality of cells prepared in (i) is maintained 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,
and preferably, the cell or plurality of cells is in a subject and the dsRNA agent is to be 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;
preferably 2, 3, 4, or more dsRNA agents are to be administered to the subject or contacted with the cell or plurality of cells;
preferably, inhibition of the FXI gene in the subject is assessed, following the administration of the dsRNA agent(s) to the subject, wherein a means for the assessing comprises:
(a) determining one or more physiological characteristics of a FXI -associated disease or condition in the subject and
(b) 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, preferably, 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), or the physiological characteristic is determined in a biological sample obtained from the subject, preferably, the biological

sample comprises one or more of: a blood sample, a serum sample, a tissue sample, a cell sample, and a liver sample.

17. Use of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13 or a composition of claim 14 in the manufacture of a medicament for inhibiting expression of a FXI gene in a subject, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent or the composition is to be administered to the subject,
and optionally, the dsRNA agent is to be administered to the subject subcutaneously or by IV administration, and optionally, inhibition of the FXI gene is assessed, 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,
and preferably, 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).

18. Use of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13, or a composition of claim 14 in the manufacture of a medicament for treating a disease or condition associated with the presence of FXI protein, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent, or the composition is to be administered to a subject to inhibit FXI gene expression,
preferably, 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,
and optionally, an additional therapeutic regimen is to be administered to the subject, and preferably, the additional therapeutic regimen comprises: to the subject one or more FXI antisense polynucleotides of the invention is to be administered to the subject, administering to the subject a non-FXI dsRNA therapeutic agent is to be administered to the subject, and a behavioral modification is to be implemented in the subject,

preferably, 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),
preferably, wherein the dsRNA agent is to be administered to the subject subcutaneously or IV administration,
and optionally, an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent is determined in the subject.

19. Use of a double-stranded ribonucleic acid (dsRNA) agent of claims 1-13, or a composition of claim 14 in the manufacture of a medicament for decreasing a level of FXI protein in a subject compared to a baseline pre-treatment level of FXI protein in the subject, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent, or the composition is to be administered to the subject, wherein the medicament is capable of decreasing the level of FXI gene expression,
preferably, the dsRNA agent is to be administered to the subject subcutaneously or is to be administered to the subject by IV administration.

20. Use of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13, or a composition of claim 14 in the manufacture of a medicament for 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, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent, or the composition is to be administered to the subject, wherein the medicament is capable of altering the physiological characteristic of the FXI-associated disease or condition in the subject,
preferably, the dsRNA agent is to be administered to the subject subcutaneously or is to be administered to the subject by IV administration, preferably 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).