[005] Monoclonal antibodies to FXII are known in the art and have been described, for example, in US Patent/Publication Nos. 4963657, 5500349, 8119137, 8715672, 9856326, 9856325, 9518127, 20130095108, 20140072572, 20140072600, and in WO2006066878, WO2013014092, EP1830924B1, EP27345522A1, and EP2623110A1.

[006] Fully human antibodies that specifically bind to (activated) FXII protein with high affinity and prevent thrombosis without increasing the risk of bleeding could be important in the prevention and treatment of various FXII-associated diseases (*e.g.*, thrombosis, embolism, edema).

BRIEF SUMMARY

[007] The present disclosure provides antibodies and antigen-binding fragments thereof that specifically bind the activated form of coagulation Factor XII protein (FXIIa). In certain embodiments, the antibodies also bind the zymogen form of Factor XII (FXII). In certain embodiments, the antibodies are fully human antibodies that bind to FXII and also to FXIIa ("dual FXII/FXIIa binders") with high affinity. The antibodies of the present disclosure are useful, *inter alia*, for inhibiting or neutralizing the activity of FXII protein. In certain embodiments, the antibodies are useful in preventing, treating or ameliorating at least one symptom or indication of a FXII-associated disease or disorder in a subject. In certain embodiments, the antibodies may be administered prophylactically or therapeutically to a subject having or at risk of having a FXII-associated disease or disorder. In certain preferred embodiments. In specific embodiments, the antibodies prevent thrombosis without increasing bleeding risk in a subject. Such antibodies can be used as anti-coagulation therapy without increasing risk of bleeding when administered to a subject in need thereof, along with less frequent dosing in a subject with a FXII-associated disease or disorder.

[008] The antibodies of the disclosure can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.*, to increase persistence in the host or to eliminate residual effector functions (Reddy *et al*., 2000, J. Immunol. 164:1925-1933). In certain embodiments, the antibodies may be bispecific.

[009] In a first example, the present disclosure provides isolated recombinant monoclonal antibodies or antigen-binding fragments thereof that bind specifically to Factor XII (FXII) and/or activated Factor XII (FXIIa). In some embodiments, the antibodies are fully human monoclonal antibodies. In certain embodiments, the antibodies are "dual binders," being able to bind FXII and FXIIa.

[010] Exemplary anti-FXII/FXIIa antibodies of the present disclosure are listed in Tables 1 and 2 herein. Table 1 sets forth the amino acid sequence identifiers of the heavy chain

variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDRs) (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDRs) (LCDR1, LCDR2 and LCDR3) of exemplary antibodies. Table 2 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary antibodies.

[011] The present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[012] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[013] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain examples, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-FXII/FXIIa antibodies listed in Table 1. In certain examples, the HCVR/LCVR amino acid sequence pair is selected from one of SEQ ID NOs: 2/22 (*e.g.*, REGN9533) or 22/30 (*e.g.*, REGN9534).

[014] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said HCVR comprising an amino acid sequence listed in Table 1 having no more than twelve amino acid substitutions, and/or said LCVR comprising an amino acid sequence listed in Table 1 having no more than ten amino acid substitutions. For example, the present disclosure provides antibodies or antigen-binding fragments thereof comprising a HCVR and a LCVR, said HCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22, said amino acid sequence having one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve amino acid substitutions. In another example, the present disclosure provides antibodies or antigen-binding fragments thereof comprising a HCVR and a LCVR, said LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10 and 30, said amino acid sequence having one, two, three, four, five, six, seven, eight, nine or ten amino acid substitutions. In one embodiment, the present disclosure provides anti-FXII/FXIIa antibodies or antigen-binding fragments thereof comprising a HCVR and a LCVR, said HCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22, said amino acid sequence having at least one amino acid substitution, and/or said

LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 10 and 30, said amino acid sequence having at least one amino acid substitution.

[015] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[016] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[017] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[018] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[019] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[020] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[021] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino acid sequences listed in Table 1. According to certain examples, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-FXII

antibodies listed in Table 1. In certain examples, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 2/22 (*e.g.*, REGN9533) or 22/30 (*e.g.*, REGN9534).

[022] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said HCVR comprising HCDR1 comprising an amino acid sequence differing from an amino acid sequence listed in Table 1 by 1 amino acid, HCDR2 comprising an amino acid sequence differing from an amino acid sequence listed in Table 1 by 1 amino acid, and HCDR3 comprising an amino acid sequence differing from an amino acid sequence listed in Table 1 by 1 amino acid. In certain examples, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said LCVR comprising LCDR1 comprising an amino acid sequence differing from an amino acid sequence listed in Table 1 by 1 amino acid, LCDR2 comprising an amino acid sequence differing from an amino acid sequence listed in Table 1 by 1 amino acid, and LCDR3 comprising an amino acid sequence differing from an amino acid sequence listed in Table 1 by 1 amino acid. For example, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said HCVR comprising HCDR1 comprising an amino acid sequence of SEQ ID NO: 4 or an amino acid sequence differing from SEQ ID NO: 4 by 1 amino acid, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6 or an amino acid sequence differing from SEQ ID NO: 6 by 1 amino acid, and HCDR3 comprising an amino acid sequence of SEQ ID NO: 8 or an amino acid sequence differing from SEQ ID NO: 8 by 1 amino acid. In example, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said LCVR comprising LCDR1 comprising an amino acid sequence of SEQ ID NO : 12 or an amino acid sequence differing from SEQ ID NO: 12 by 1 amino acid, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14 or an amino acid sequence differing from SEQ ID NO: 14 by 1 amino acid, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16 or an amino acid sequence differing from SEQ ID NO: 16 by 1 amino acid.

[023] As another example, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said HCVR comprising HCDR1 comprising an amino acid sequence of SEQ ID NO: 24 or an amino acid sequence differing from SEQ ID NO: 24 by 1 amino acid, HCDR2 comprising an amino acid sequence of SEQ ID NO: 26 or an amino acid sequence differing from SEQ ID NO: 26 by 1 amino acid, and HCDR3 comprising an amino acid sequence of SEQ ID NO: 28 or an amino acid sequence differing from SEQ ID NO: 28 by 1 amino acid. In another example, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a HCVR and a LCVR, said LCVR comprising LCDR1 comprising an amino acid sequence of SEQ ID NO: 32 or an amino acid sequence differing from SEQ ID NO: 32 by 1 amino acid, LCDR2 comprising an

amino acid sequence of SEQ ID NO: 14 or an amino acid sequence differing from SEQ ID NO: 14 by 1 amino acid, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 34 or an amino acid sequence differing from SEQ ID NO: 34 by 1 amino acid.

[024] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary antibodies listed in Table 1. In certain examples, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is selected from the group consisting of SEQ ID NOs: 4-6-8-12-14-16 (*e.g.*,REGN9533), or 24-26-28-32-14-34 (*e.g.*, REGN9534).

[025] In a related example, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary antibodies listed in Table 1. For example, the present disclosure includes antibodies, or antigen-binding fragments thereof, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10 (*e.g.*, REGN9533) or 10/30 (*e.g.*, REGN9534). Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[026] In certain examples, the present disclosure includes an antibody or antigen-binding fragment thereof that binds specifically to FXII and/or FXIIa, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein the HCVR comprises: (i) the amino acid sequence

selected from the group consisting of SEQ ID NOs: 2 and 22, (ii) an amino acid sequence having at least 90% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22, (iii) an amino acid sequence having at least 95% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22; or (iv) the amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22 having no more than 12 amino acid substitutions; and the LCVR comprises: (i) the amino acid sequence selected from the group consisting of SEQ ID NOs: 10 and 30, (ii) an amino acid sequence having at least 90% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 10 and 30, (iii) an amino acid sequence having at least 95% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 10 and 30; or (iv) the amino acid sequence selected from the group consisting of SEQ ID NOs: 10 and 30 having no more than 10 amino acid substitutions.

[026a] In one aspect, there is provided an antibody, or antigen-binding fragment thereof, that binds to human Factor XII (FXII) and/or activated FXII (FXIIa), wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain complementarity determining region (HCDR)1, HCDR2 and HCDR3 contained within a heavy chain variable region (HCVR) and a light chain complementarity determining region (LCDR)1, LCDR2 and LCDR3 contained within a light chain variable region (LCVR), (a) wherein the HCVR comprises an amino acid sequence set forth as SEQ ID NO: 2; and wherein the LCVR comprises an amino acid sequence set forth as SEQ ID NO: 10; or (b) wherein the HCVR comprises an amino acid sequence set forth as SEQ ID NO: 22; and wherein the LCVR comprises an amino acid sequence set forth as SEQ ID NO: 30.

[027] The present disclosure provides anti-FXII/FXIIa antibodies, or antigen-binding fragments thereof, comprising a heavy chain (HC) and a light chain (LC), wherein the heavy chain comprises a sequence having at least 90% sequence identity to SEQ ID NO: 18, and the light chain comprises a sequence having at least 90% sequence identity to SEQ ID NO: 20. In another example, the heavy chain comprises a sequence having at least 90% sequence identity to SEQ ID NO: 36, and the light chain comprises a sequence having at least 90% sequence identity to SEQ ID NO: 38. In some examples, the heavy chain comprises a sequence having at least 90% sequence identity to SEQ ID NO: 40, and the light chain comprises a sequence having at least 90% sequence identity to SEQ ID NO: 20.

[028] In certain examples, the present disclosure provides anti-FXII/FXIIa antibodies, or antigen-binding fragments thereof, comprising an Fc domain comprising one or more mutations that alter Fc region function. In some examples, the Fc domain comprises a mutation in the C_H2 or a C_H3 region that increase FcγR binding activity. In some examples, the Fc domain comprises at least one mutation in one or

more amino acids selected from the group consisting of amino acids at positions 248, 250, 252, 254, 256. 257, 307, 311, 376, 380, 428, 433 and 434. In some examples, the Fc domain comprises at least one mutation in one or more amino acids at positions 252, 254 and 256. In some examples, the at least one mutation in the Fc domain comprises mutating position 252 to Y, mutating position 254 to T; and/or mutating position 256 to E. In some examples, the at least one mutation in the Fc domain increases the half-life of the antibody, or antigen-binding fragment thereof, in blood plasma compared to an antibody, or an antigen-binding fragment thereof, without the mutation. In some examples, the half-life is increased by at least 1.2-fold, preferably at least 1.5-fold, compared to an antibody, or an antigen-binding fragment thereof, without the mutation.

[029] The present disclosure includes anti-FXII/FXIIa antibodies having a modified glycosylation pattern. In some examples, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al*. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).
[030] In certain examples, the present disclosure provides antibodies and antigen-binding fragments thereof that exhibit pH-dependent binding to FXII. For example, the present disclosure includes antibodies and antigen-binding fragment thereof that bind FXII with higher affinity at neutral pH than at acidic pH (*i.e.*, reduced binding at acidic pH).
[031] The present disclosure also provides for antibodies and antigen-binding fragments thereof that compete for specific binding to FXII or to FXIIa with an antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.
[032] The present disclosure also provides antibodies and antigen-binding fragments thereof that cross-compete for binding to FXII/FXIIa with a reference antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.
[033] The present disclosure also provides antibodies and antigen-binding fragments thereof that bind to the same epitope as a reference antibody or antigen-binding fragment thereof comprising three CDRs of a HCVR and three CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.
[034] In some examples, the antibody or antigen binding fragment thereof may bind specifically to FXII and/or FXIIa in an agonist manner, i.e., it may enhance or stimulate FXII/FXIIa binding and/or activity; in other examples, the antibody may bind specifically to FXII and/or FXIIa in an antagonist manner, i.e., it may block FXII binding and/or activity.
[035] The present disclosure also provides isolated antibodies and antigen-binding fragments thereof that block FXIIa binding to FXI. In some examples, the antibody or antigen-binding fragment thereof that blocks FXIIa binding to FXI may bind to the same epitope on FXIIa as FXI or may bind to a different epitope on FXIIa as FXI.
[036] In certain examples, the antibodies or antigen-binding fragments of the present disclosure are bispecific comprising a first binding specificity to a first epitope of FXII/FXIIa

and a second binding specificity to a second epitope of FXII/FXIIa wherein the first and second epitopes are distinct and non-overlapping.

[037] In certain examples, the present disclosure provides an isolated antibody or antigen-binding fragment thereof that has one or more of the following characteristics: (a) is a fully human monoclonal antibody; (b) binds to activated Factor XII (FXIIa); (c) binds to FXII with a dissociation constant (K_D) of less than 1.5 nM at 25°C, as measured in a surface plasmon resonance assay; (d) binds to FXII with a K_D of less than 17nM at 37°C, as measured in a surface plasmon resonance assay; (e) binds to FXIIa with a K_D of less than 5nM, preferably less than 0.9 nM, at 25°C as measured in a surface plasmon resonance assay; (f) binds to FXIIa with a K_D of less than 6.5nM, preferably less than 2.5nM, at 37°C as measured in a surface plasmon resonance assay; (g) blocks thrombin generation by intrinsic pathway at a concentration of less than 250nM, as measured by functional plasma assays; and/or (h) blocks thrombin generation by intrinsic pathway without blocking thrombin generation by extrinsic pathway, as measured by functional plasma assays.

[038] In another example, the present disclosure provides nucleic acid molecules encoding anti-FXII/FXIIa antibodies or portions thereof. For example, the present disclosure provides nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[039] The present disclosure also provides nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[040] The present disclosure also provides nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[041] The present disclosure also provides nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[042] The present disclosure also provides nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[043] The present disclosure also provides nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[044] The present disclosure also provides nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[045] The present disclosure also provides nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[046] The present disclosure also provides nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary antibodies listed in Table 1.

[047] The present disclosure also provides nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary antibodies listed in Table 1.

[048] The present disclosure also provides nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain examples, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid

sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain examples according to this aspect of the disclosure, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-FXII antibody listed in Table 1.

[048a] Thus, in one aspect, there is provided an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR as defined herein; a polynucleotide sequence that encodes an LCVR as defined herein; or a polynucleotide sequence that encodes an HCVR and an LCVR as defined herein.

[049] In a related example, the present disclosure provides recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an antibody. For example, the present disclosure includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 2. In certain examples, the present disclosure provides expression vectors comprising: (a) a nucleic acid molecule comprising a nucleic acid sequence encoding a HCVR of an antibody that binds FXII/FXIIa, wherein the HCVR comprises an amino acid sequence selected from the group consisting of sequences listed in Table 1; and/or (b) a nucleic acid molecule comprising a nucleic acid sequence encoding a LCVR of an antibody that binds FXII/FXIIa, wherein the LCVR comprises an amino acid sequence selected from the group consisting of sequences listed in Table 1. Also included within the scope of the present disclosure are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced. In certain examples, the host cells comprise a mammalian cell or a prokaryotic cell. In certain examples, the host cell is a Chinese Hamster Ovary (CHO) cell or an *Escherichia coli* (*E. coli*) cell. In certain examples, the present disclosure provides methods of producing an antibody or antigen-binding fragment thereof of the disclosure, the methods comprising introducing into a host cell an expression vector comprising a nucleic acid sequence encoding a HCVR and/or LCVR of an antibody or antigen-binding fragment thereof operably linked to a promoter; culturing the host cell under conditions favorable for expression of the nucleic acid sequence; and isolating the antibody or antigen-binding fragment thereof from the culture medium and/or host cell. The isolated antibody or antigen-binding fragment thereof may purified using any of the methods known in prior art.

[049a] Hence, in one aspect, there is provided a vector comprising the polynucleotide as defined herein. In another aspect, there is provided a cell expressing the vector as defined

herein.

[050] In another example, the disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of at least one recombinant monoclonal antibody or antigen-binding fragment thereof which specifically binds FXII/FXIIa and a pharmaceutically acceptable carrier. In a related example, the disclosure features a composition which is a combination of an anti-FXII/FXIIa antibody and a second therapeutic agent. In one

example, the second therapeutic agent is any agent that is advantageously combined with an anti-FXII/FXIIa antibody. Exemplary agents that may be advantageously combined with an anti-FXII/FXIIa antibody include, without limitation, other agents that bind and/or inhibit FXII activity (including other antibodies or antigen-binding fragments thereof, etc.) and/or agents which do not directly bind FXII but nonetheless treat or ameliorate at least one symptom or indication of a FXII-associated disease or disorder. Additional combination therapies and co-formulations involving the anti-FXII antibodies of the present disclosure are disclosed elsewhere herein.

[050a] Accordingly, in one aspect, there is provided a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof as defined herein and a pharmaceutically acceptable carrier or diluent.

[051] In another example, the disclosure provides therapeutic methods for treating a disease or disorder associated with FXII in a subject using an anti-FXII/FXIIa antibody or antigen-binding portion of an antibody of the disclosure, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the disclosure to the subject in need thereof. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by inhibition of FXII activity. In certain examples, the disclosure provides methods to prevent, or treat a FXII-associated disease or disorder comprising administering a therapeutically effective amount of an anti-FXII/FXIIa antibody or antigen-binding fragment thereof of the disclosure to a subject in need thereof. In some examples, the antibody or antigen-binding fragment thereof may be administered prophylactically or therapeutically to a subject having or at risk of having a FXII-associated disease or disorder. In certain examples, the antibody or antigen-binding fragment thereof the disclosure is administered in combination with a second therapeutic agent to the subject in need thereof. The second therapeutic agent may be selected from the group consisting of an anti-coagulant, a direct thrombin inhibitor, a thrombolytic drug, a fibrinolytic drug, an anti-platelet drug, an anti-inflammatory drug, an anti-hypertensive drug, a second anti-FXII antibody, a lipid-lowering drug, mechanical clot retrieval, catheter-guided thrombolysis, compression stockings, surgery and any other drug or therapy known in the art. In certain examples, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with an antibody or antigen-binding fragment thereof of the disclosure, if such side effect(s) should occur. The antibody or fragment thereof may be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, or intramuscularly. The antibody or fragment thereof may be administered at a dose of about 0.1 mg/kg of body weight to about 100 mg/kg of body weight of the subject. In certain examples, an antibody of the present disclosure may be administered at one or more doses comprising between 10mg to 600mg.

[052] The present disclosure also includes use of an anti-FXII/FXIIa antibody or antigen-

binding fragment thereof of the disclosure in the manufacture of a medicament for the treatment of a disease or disorder that would benefit from the blockade of FXII/FXIIa binding and/or activity.

[052a] Thus, in one aspect, there is provided use of the pharmaceutical composition as defined herein in the manufacture of a medicament for preventing the formation of a thrombus in a subject or treating a subject at risk of thrombus formation, optionally wherein the subject has a disease, a disorder or a condition selected from the group consisting of venous thrombosis, arterial thrombosis, device thrombosis, thromboembolism, hereditary angioedema, stroke, thrombophilia, cardiac ischemia, atherosclerotic plaque rupture, use of mechanical valve prostheses, use of blood-contacting medical devices, use of blood-contacting extracorporeal circuits, venous thromboembolism, pulmonary embolism, deep vein thrombosis, portal vein thrombosis, Budd-Chiari syndrome, Paget-Schroetter disease, renal vein thrombosis, cerebral venous sinus thrombosis, jugular vein thrombosis, cavernous sinus thrombosis, hepatic artery thrombosis, limb ischemia and myocardial infarction.

[052b] In another aspect, there is provided an *in vitro* method of diagnosing or detecting a FXII-associated-disease or disorder, the method comprising contacting a sample of a subject with one or more antibodies or antigen-binding fragment thereof as defined herein, wherein the antibody or antigen-binding fragment thereof is detectably labeled.

[053] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[054] FIG. 1A shows the time course of mAb concentrations and hFXII/FXIIa concentrations measured for each individual mouse dosed with a single dose of 10 mg/kg of anti-hFXII/FXIIa parental antibody (REGN9533). **FIG. 1B** shows the time course of mAb concentrations and hFXII/FXIIa concentrations measured for each individual mouse dosed with a single dose of 10 mg/kg of anti-hFXII/FXIIa YTE-variant antibody (REGN17653). **FIG. 1C** shows the time course of mAb concentrations and hFXII/FXIIa concentrations measured for each individual mouse dosed with a single dose of 10 mg/kg of anti-Fel D1 control antibody (REGN1945).

DETAILED DESCRIPTION

[055] Before the present methods are described, it is to be understood that this disclosure is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[056] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Definitions

[057] The term “FXII”, also called “Factor XII” refers to coagulation Factor XII, also known as Hageman Factor. The 596-amino acid FXII protein is the zymogen form of Factor XIIa, a beta-globulin plasma serine protease composed of an amino-terminal heavy chain and a carboxy-terminal light chain. Its heavy chain contains two fibronectin-type domains (type I and II), two epidermal growth factor-like domains, a Kringle domain, and a proline-rich region, and its light chain contains the protease domain. Exposure of blood to negatively charged substances or artificial surfaces triggers thrombin generation and fibrin formation via

CLAIMS

What is claimed is:

1. An antibody, or antigen-binding fragment thereof, that binds to human Factor XII (FXII) and/or activated FXII (FXIIa), wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain complementarity determining region (HCDR)1, HCDR2 and HCDR3 contained within a heavy chain variable region (HCVR) and a light chain complementarity determining region (LCDR)1, LCDR2 and LCDR3 contained within a light chain variable region (LCVR),

(a) wherein the HCVR comprises an amino acid sequence set forth as SEQ ID NO: 2; and wherein the LCVR comprises an amino acid sequence set forth as SEQ ID NO: 10; or

(b) wherein the HCVR comprises an amino acid sequence set forth as SEQ ID NO: 22; and wherein the LCVR comprises an amino acid sequence set forth as SEQ ID NO: 30.

2. The antibody, or antigen-binding fragment thereof, of claim 1, wherein:

(i) the HCVR comprises an amino acid sequence set forth as SEQ ID NO: 2; and wherein the LCVR comprises an amino acid sequence set forth as SEQ ID NO: 10, and wherein

(a) the HCDR1 comprises an amino acid sequence as set forth as SEQ ID NO: 4;

(b) the HCDR2 comprises an amino acid sequence as set forth as SEQ ID NO: 6;

(c) the HCDR3 comprises an amino acid sequence as set forth as SEQ ID NO: 8;

(d) the LCDR1 comprises an amino acid sequence as set forth as SEQ ID NO: 12;

(e) the LCDR2 comprises an amino acid sequence AAS; and

(f) the LCDR3 comprises an amino acid sequence as set forth as SEQ ID NO: 16; or wherein:

(ii) the HCVR comprises an amino acid sequence set forth as SEQ ID NO: 22; and wherein the LCVR comprises an amino acid sequence set forth as SEQ ID NO: 30, and wherein

(a) the HCDR1 comprises an amino acid sequence as set forth as SEQ ID NO: 24;

(b) the HCDR2 comprises an amino acid sequence as set forth as SEQ ID NO: 26;

(c) the HCDR3 comprises an amino acid sequence as set forth as SEQ ID NO: 28;

(d) the LCDR1 comprises an amino acid sequence as set forth as SEQ ID NO: 32;

(e) the LCDR2 comprises an amino acid sequence AAS; and

(f) the LCDR3 comprises an amino acid sequence as set forth as SEQ ID NO: 34.

3. The antibody, or antigen-binding fragment thereof, of claims 1 or 2, comprising a heavy chain (HC) and a light chain (LC), wherein:

the heavy chain comprises a sequence of SEQ ID NO: 18 or SEQ ID NO: 40, and the light chain comprises a sequence of SEQ ID NO: 20; or

the heavy chain comprises a sequence of SEQ ID NO: 36, and the light chain comprises a sequence of SEQ ID NO: 38.

4. The antibody, or antigen-binding fragment thereof, of any one of the previous claims, comprising an Fc domain, wherein the Fc domain comprises at least one mutation that alters Fc region function, optionally wherein

the Fc domain comprises at least one mutation in a CH2 region or a CH3 region that increases FcγR binding activity; and/or

the Fc domain comprises at least one mutation which increases the half-life of the antibody, or antigen-binding fragment thereof, in blood plasma compared to an antibody, or an antigen-binding fragment thereof, without the mutation,

further optionally wherein

the Fc domain comprises at least one mutation in one or more amino acids selected from the group consisting of amino acids at positions 248, 250, 252, 254, 256, 257, 307, 311, 376, 380, 428, 433 and 434; or

the Fc domain comprises at least one mutation selected from the group consisting of mutating position 252 to Y, mutating position 254 to T, mutating position 256 to E, and combinations thereof.

5. The antibody, or antigen-binding fragment thereof, of any one of the previous claims, wherein the antibody or antigen-binding fragment thereof, is a monoclonal antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, or a multi-specific antibody or antigen-binding fragment thereof, optionally wherein

the multi-specific antibody or antigen-binding fragment thereof binds different epitopes of FXII and/or FXIIa; or

the multi-specific antibody or antigen-binding fragment thereof contains antigen-binding domains specific for FXII, FXIIa, and one or more additional target polypeptides .

6. The antibody, or antigen-binding fragment thereof, of any one of the previous claims, comprising one or more of the following characteristics:

(a) is a fully human monoclonal antibody;

(b) binds to activated Factor XII (FXIIa, FXIIab);

(c) binds to FXII with a dissociation constant (KD) of less than 1.5nM at 25 ºC;

(d) binds to FXII with a KD of less than 17nM at 37 °C;

(e) binds to FXIIa with a KD of less than 5nM, preferably less than 0.9nM, at 25 °C;

(f) binds to FXIIa with a KD of less than 6.5nM, preferably less than 2.5nM, at 37 °C;

(g) binds to FXIIab with a KD of less than 5nM, preferably less than 0.7nM, at 25 °C;

(h) blocks thrombin generation by intrinsic pathway at a concentration of less than 250nM;

(I) blocks thrombin generation by intrinsic pathway without blocking thrombin generation by extrinsic pathway;

(j) is a humanized antibody or a chimeric antibody; and

(k) comprises a modified glycosylation pattern, wherein the modification increases antibody dependent cellular cytotoxicity (ADCC) function and/or alters complement dependent cytotoxicity (CDC) activity;

or any combinations thereof of (a)-(k).

7. The antibody, or the antigen binding fragment thereof, of any one of the previous claims, wherein the antibody, or the antigen binding fragment thereof is chemically or biologically conjugated to a therapeutic moiety, optionally wherein the therapeutic moiety comprises a radioactive agent, a cytokine, an interferon, a target or a reporter moiety, an enzyme, a second different antibody, a peptide or a protein, and a therapeutic agent.

8. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof according to any one of the previous claims and a pharmaceutically acceptable carrier or diluent.

9. An isolated polynucleotide molecule comprising

a polynucleotide sequence that encodes an HCVR of claim 1;

a polynucleotide sequence that encodes an LCVR of claim 1; or

a polynucleotide sequence that encodes an HCVR and an LCVR of claim 1.

10. A vector comprising the polynucleotide sequence of claim 9.

11. A cell expressing the vector of claim 10.

12. Use of the pharmaceutical composition of claim 8 in the manufacture of a medicament for preventing the formation of a thrombus in a subject or treating a subject at risk of thrombus formation, optionally wherein the subject has a disease, a disorder or a

condition selected from the group consisting of venous thrombosis, arterial thrombosis, device thrombosis, thromboembolism, hereditary angioedema, stroke, thrombophilia, cardiac ischemia, atherosclerotic plaque rupture, use of mechanical valve prostheses, use of blood-contacting medical devices, use of blood-contacting extracorporeal circuits, venous thromboembolism, pulmonary embolism, deep vein thrombosis, portal vein thrombosis, Budd-Chiari syndrome, Paget-Schroetter disease, renal vein thrombosis, cerebral venous sinus thrombosis, jugular vein thrombosis, cavernous sinus thrombosis, hepatic artery thrombosis, limb ischemia and myocardial infarction.

13. The use of claim 12, wherein one or more additional therapeutic agents is to be administered in combination with the medicament , optionally wherein the one or more therapeutic agents is selected from the group consisting of an anti-coagulant, a direct thrombin inhibitor, a thrombolytic drug, a fibrinolytic drug, an anti-platelet drug, an anti-inflammatory drug, an anti-hypertensive drug, a second anti-FXII antibody, a lipid-lowering drug, a cholesterol-lowering drug ,an immunosuppressive agent, mechanical clot retrieval, catheter-guided thrombolysis, compression stockings, and surgery.

14. The use of claim 12 or 13, wherein the pharmaceutical composition is to be administered subcutaneously, intravenously, intradermally, intraperitoneally, or intramuscularly;

the pharmaceutical composition is to be administered at a dose of about 0.1 mg/kg to about 100 mg/kg of body weight of the subject;

the pharmaceutical composition is to be administered at one or more doses comprising between about 10 mg to about 600 mg; and/or

the pharmaceutical composition is to be administered for more than one dose, wherein the subsequent doses are approximately the same amount or less than the amount of the initial dose, and wherein the subsequent dose are separated by at least 1 day to 3 days; at least one week, at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

15. An *in vitro* method of diagnosing or detecting a FXII-associated-disease or disorder, the method comprising contacting a sample of a subject with one or more antibodies or antigen-binding fragment thereof of any one of claims 1-7, wherein the antibody or antigen-binding fragment thereof is detectably labeled.