

(ASO) Phase II trial (Buller et al., N Engl J Med 2015, 372:232-240), FXI ASO produced significant reduction in venous thromboembolism (VTE), with a trend toward less bleeding, compared to enoxaparin, in patients undergoing total knee arthroplasty; (2) Human genetics and epidemiological studies (Duga et al., Semin Thromb Hemost 2013; Chen et al., Drug Discov Today 2014; Key, Hematology Am Soc Hematol Educ Program 2014, 2014:66-70) indicated that severe FXI deficiency (hemophilia C) confers reduced risk of ischemic stroke and deep vein thrombosis; conversely, increased levels of FXI are associated with a higher risk for VTE and ischemic stroke; and (3) Numerous lines of preclinical studies demonstrated that FXI(a) inhibition or loss-of-function mediate profound thromboprotection without compromising hemostasis (Chen et al. op. cit.). Of note, monoclonal antibodies 14E11 and 1A6 produced significant thrombus reduction in the baboon AV shunt thrombosis model (U.S. Patent No. 8,388,959; U.S. Patent No. US8,236,316; Tucker et al., Blood 2009, 113:936-944; Cheng et al., Blood 2010, 116:3981-3989). Moreover, 14E11 (as it cross-reacts with mouse FXI) provided protection in an experimental model of acute ischemic stroke in mice (Leung et al., Transl Stroke Res 2012, 3:381-389). Additional FXI-targeting mAbs have also been reported in preclinical models in validating FXI as an antithrombotic target with minimal bleeding risk (van Montfoort et al., Thromb Haemost 2013, 110; Takahashi et al., Thromb Res 2010, 125:464-470; van Montfoort, Ph.D. Thesis, University of Amsterdam, Amsterdam, Netherlands, 14 November 2014). Inhibition of FXI is thus a promising strategy for novel antithrombotic therapy with an improved benefit-risk profile compared to current standard-of-care anticoagulants.

There is currently a large unmet medical need for ant-thrombotic therapies for patients that have severe or end-stage renal disease (ESRD). Roughly 650,000 patients in the US have severe or ESRD and these patients suffer an extremely high incidence of thrombotic and thromboembolic complications (MI, stroke/TIA, peripheral artery disease (PAD), vascular access failure). ESRD patients also are more likely to have bleeding events than the general population. Since anticoagulation of any kind is not commonly prescribed in ESRD patients (due to bleeding risk and lack of data for non-vitamin K antagonist oral anti-coagulants (NOACs) in ESRD), there is a need for an anti-thrombotic therapy that has an acceptable benefit-risk profile in these patients.

BRIEF SUMMARY

The present disclosure provides human antibodies capable of selectively binding to coagulation Factor XI (anti-FXI antibodies) and inhibiting blood coagulation and associated

thrombosis, preferably without compromising hemostasis. Compositions include anti-coagulation Factor XI antibodies capable of binding to a defined epitope of the apple 3 (A3) domain of coagulation Factor XI. These antibodies exhibit neutralizing activity by inhibiting the conversion of the zymogen form FXI to its activated form, FXIa, under the action of FXIIa, and inhibiting FXIa-mediated activation of FIX. The antibodies are useful for FXI inhibition, which may confer a clinically relevant anti-thrombotic effect with a reduced risk of bleeding complications and hence an expanded therapeutic index compared to inhibition of more downstream clotting factors such as FXa and thrombin. Therefore, these antibodies provide a therapeutic approach for the prevention of thromboembolic complications, e.g., stroke prevention in atrial fibrillation (SPAF).

One unserved cohort at risk of vascular thrombosis that may benefit from FXI inhibition is the severe and end-stage renal disease (ESRD) population, in which non-vitamin K antagonist oral anti-coagulants (NOACs) are not typically used due to concerns regarding bleeding, which have led to a lack of clinical trial experience. The antibodies herein provide a novel anti-coagulant therapy for the prevention of thrombotic complications in ESRD patients. The antibodies herein may provide clinically relevant antithrombotic efficacy accompanied by an acceptable bleeding risk in ESRD patients.

Apart from ESRD and SPAF, FXI inhibition may also be indicated in additional patient segments that are at high risk for thrombosis. These include: 1) venous thromboembolism (VTE) prophylaxis in orthopedic surgery and/or secondary prevention of VTE; 2) reduction of revascularization and/or reduction of Major Adverse Limb Events (MALE) in PAD; 3) adjuvant therapy in ACS.

The present disclosure provides an antibody or antigen binding fragment comprising at least the six complementary determining regions (CDRs) of an anti-FXI antibody of the α FXI-18623p family, α FXI-18611p family, or α FXI-18611 family or at least the six complementary determining regions (CDRs) of an anti-FXI antibody of the α FXI-18623p family, α FXI-18611p family, or α FXI-18611 family wherein one or more of the six CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof, wherein an antibody of the α FXI-18623 family comprises a heavy chain (HC) variable region having the amino acid sequence shown in SEQ ID NO:28 or 29 and an LC variable region having the amino acid sequence shown in SEQ ID NO:30; an antibody of the α FXI-18611p family comprises an HC variable region having the amino acid sequence shown in SEQ ID NO:21 or 22 and a light chain (LC) variable region having the amino acid sequence shown in SEQ ID NO:25; and

antibody of the α FXI-18611 family comprises an HC variable region having the amino acid sequence shown in SEQ ID NO:23 or 24 and an LC variable region having the amino acid sequence shown in SEQ ID NO:25. In one aspect, there is provided an antibody or antigen binding fragment comprising: the six complementary determining regions (CDRs) of an anti-FXI antibody of the α FXI-18611p family, or α FXI-18611 family wherein the six CDRs comprise (a) CDR1, CDR2, and CDR3 of the heavy chain (HC) having the amino acid sequence shown in SEQ ID NO: 33; and (b) CDR1, CDR2, and CDR3 of the light chain (LC) having the amino acid sequence shown in SEQ ID NO: 26. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the six CDRs comprise or consist of CDR1, CDR2, and CDR3 of the HC of an anti-FXI antibody of the α FXI-18623p family, α FXI-18611p family, or α FXI-18611 family and CDR1, CDR2, and CDR3 of the LC of the α FXI-18623p family, α FXI-18611p family, or α FXI-18611 family, wherein an antibody of the α FXI-18623 family comprises an HC variable region having the amino acid sequence shown in SEQ ID NO:28 or 29 and an LC variable region having the amino acid sequence shown in SEQ ID NO:30; an antibody of the α FXI-18611p family comprises a heavy chain (HC) variable region having the amino acid sequence shown in SEQ ID NO:21 or 22 and a light chain (LC) variable region having the amino acid sequence shown in SEQ ID NO:25; and, an antibody of the α FXI-18611 family comprises an HC variable region having the amino acid sequence shown in SEQ ID NO:23 or 24 and an LC variable region having the amino acid sequence shown in SEQ ID NO:25. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody or antigen binding fragment comprises an HC variable region having an amino acid sequence selected from the group of amino acid sequences consisting of SEQ ID NO:21, 22, 23, and 24; and an LC variable region having the amino acid sequence shown in SEQ ID NO:25; wherein the HC variable region framework may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof and the LC variable region framework may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In further aspects or examples of the disclosure, the antibody or antigen binding fragment comprises an HC variable region having an amino acid sequence selected from the group of amino acid sequences consisting of SEQ ID NO:21, 22, 23, and 24; and an LC variable region having the amino acid sequence shown in SEQ ID NO:25.

In another aspect, there is provided an antibody or antigen binding fragment that binds the apple 3 domain of coagulation factor XI (FXI) comprising a heavy chain variable domain (V_H) comprising the amino acid sequence shown in SEQ ID NO:21, 22, 23, or 24 and a light chain variable domain (V_L) comprising the amino acid sequence shown in SEQ ID NO:25.

In further aspects or examples of the disclosure, the antibody or antigen binding fragment comprises an HC variable region having an amino acid sequence selected from

the group of amino acid sequences consisting of SEQ ID NO:28 and 29; and an LC variable region having the amino acid sequence shown in SEQ ID NO:30; wherein the HC variable region framework may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof and the LC variable region framework may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In further aspects or examples of the disclosure, the antibody or antigen binding fragment comprises an HC variable region having an amino acid sequence selected from the group of amino acid sequences consisting of SEQ ID NO:28 and 29; and an LC variable region having the amino acid sequence shown in SEQ ID NO:30.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1, IgG2, IgG3, or IgG4 isotype. In further examples, the constant domain may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof. In particular examples, the constant domain may comprise a C-terminal lysine or may lack a C-terminal lysine.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1 or IgG4 isotype. In a further example, the heavy chain constant domain is of the IgG4 isotype and further includes a substitution of the serine residue at position 228 (EU numbering) with proline, which corresponds to position 108 of SEQ ID NO:16 or 17 (Serine at position 108).

In further aspects or examples of the disclosure, the antibody comprises a HC constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain of the human kappa or lambda type.

In further aspects or examples of the disclosure, the antibody comprises a LC constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the antibody or antigen binding fragment comprises an HC having an amino acid sequence selected from the group of amino acid sequences consisting of SEQ ID NO:33, 35, 37, 39, 45, 47, 49, 51, 57, 59, 61, 63, 69, 71, 73, and 75; and an LC having amino acid sequence shown in SEQ ID NO:26.

In another aspect, there is provided an antibody that binds the apple 3 domain of coagulation factor XI (FXI) comprising a heavy chain having the amino acid sequence shown in SEQ ID NO:33, 35, 37, 39, 45, 47, 49, or 51 and a light chain having the amino acid sequence shown in SEQ ID NO:26.

In another aspect, there is provided a composition comprising an antibody that binds the apple 3 domain of coagulation factor XI (FXI) wherein the antibody comprises a heavy chain having the amino acid sequence shown in SEQ ID NO: 33, 35, 37, 39, 45, 47, 49, or 51 and a light chain having the amino acid sequence shown in SEQ ID NO:26, and a pharmaceutically acceptable carrier or diluent.

In further aspects or examples of the disclosure, the antibody or antigen binding fragment comprises an HC having an amino acid sequence selected from the group of amino acid sequences consisting of SEQ ID NO:41, 43, 53, 55, 65, 67, 77, and 79; and an LC having amino acid sequence shown in SEQ ID NO:31.

The present disclosure further provides an antibody or antigen binding fragment comprising (a) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 28 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:30; (b) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 29 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:30; (b) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 21 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25; (c) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO:22 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25; (d) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 23 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25, or (e) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 24 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25.

In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In particular examples, the HC and LC variable regions may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In particular examples, the HC and LC constant domains may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof. In particular examples, the constant domain may comprise a C-terminal lysine or may lack a C-terminal lysine.

In particular examples, the HC and LC variable regions may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof and the HC and LC constant domains may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof. In particular examples, the constant domain may comprise a C-terminal lysine or may lack a C-terminal lysine.

In further aspects or examples of the disclosure, the antibody further comprises a HC constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19 or a variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In further aspects or examples of the disclosure, the antibody further comprises a LC constant domain comprising the amino acid sequence shown in SEQ ID NO:20 or a variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

5 In a further aspect or example of the disclosure, the antibody or antigen binding fragment comprises (a) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 28 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:30; (b) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 29 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:30; (c) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 21 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25; (d) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO:22 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25; (e) a heavy chain
15 (HC) variable domain having the amino acid sequence shown in SEQ ID NO:23 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25; (f) a heavy chain (HC) variable domain having the amino acid sequence shown in SEQ ID NO: 24 and a light chain (LC) variable domain having the amino acid sequence shown in SEQ ID NO:25; (g) variant of (a), (b), (c), (d), (e), or (f) wherein the HC variable region framework comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof; or, (h) variant of (a), (b), (c), (d), (e), (f), or (g) wherein the LC variable region framework comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

The present disclosure further provides an antibody comprising (a) a heavy chain
25 (HC) having a constant domain and a variable domain wherein the variable domain comprises a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3; (b) a heavy chain (HC) having a constant domain and a variable domain wherein the variable domain comprises a
30 heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:4; or (c) a heavy chain (HC) having a constant domain and a variable domain wherein the variable domain comprises a

heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:8, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:9, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:10. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1, IgG2, IgG3, or IgG4 isotype. In further examples, the constant domain may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof as compared to the amino acid sequence of the native heavy chain constant domain for the human IgG1, IgG2, IgG3, or IgG4 isotype. In particular examples, the constant domain may comprise a C-terminal lysine or may lack a C-terminal lysine.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1 or IgG4 isotype. In a further example, the heavy chain constant domain is of the IgG4 isotype and further includes a substitution of the serine residue at position 228 (EU numbering) with proline, which corresponds to position 108 of SEQ ID NO:16 or 17 (Serine at position 108).

In further aspects or examples of the disclosure, the antibody comprises a IgG4 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16 or 17. In further examples, the constant domain may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In further aspects or examples of the disclosure, the antibody comprises a IgG1 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:18 or 19. In further examples, the constant domain may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

The present disclosure further provides an antibody or antigen binding fragment comprising:

(a) a light chain (LC) having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7; or

(b) a light chain (LC) having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:11, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:12, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:13. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the light chain (LC) comprises a human kappa light chain or human lambda light chain or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the antibody comprises a IgG4 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16 or 17 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody comprises a IgG1 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:18 or 19 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

The present disclosure further provides an antibody or antigen binding fragment comprising:

(a) a heavy chain (HC) having a constant domain and a variable domain wherein the variable domain comprises a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3; and

(b) a light chain (LC) having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7. In another aspect, there is provided an antibody or antigen binding fragment comprising (a) a heavy chain complementarity determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, an HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and an HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3 or 4 and (b) a light chain complementarity determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, an LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and an LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the light chain comprises a human kappa light chain or human lambda light chain, or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the antibody comprises an heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof compared to the amino acid sequence of the native IgG1, IgG2, IgG3, or IgG4 isotype, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In further examples, the constant domain may comprise a C-terminal lysine or may lack a C-terminal lysine.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1 or IgG4 isotype or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In a further example, the heavy chain constant domain is of the IgG4 isotype and further includes a substitution of the serine residue at position 228 (EU numbering) with proline, which corresponds to position 108 of SEQ ID NO:16 or 17 (Serine at position 108).

In further aspects or examples of the disclosure, the antibody comprises a IgG4 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16 or 17 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions,

additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody comprises a IgG1 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:18 or 19 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

The present disclosure further provides an antibody or antigen binding fragment comprising:

(a) a heavy chain (HC) having a constant domain and a variable domain wherein the variable domain comprises a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:4; and

(b) a light chain (LC) having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the light chain comprises a human kappa light chain or human lambda light chain, or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the antibody comprises an heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or

combinations thereof compared to the amino acid sequence of the native IgG1, IgG2, IgG3, or IgG4 isotype, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In further examples, the constant domain may comprise a C-terminal lysine or may
5 lack a C-terminal lysine.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1 or IgG4 isotype or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor
10 XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In a further example, the heavy chain constant domain is of the IgG4 isotype and further includes a substitution of the serine residue at position 228 (EU numbering) with proline, which corresponds to position 108 of SEQ ID NO:16 or 17 (Serine at position 108).

In further aspects or examples of the disclosure, the antibody comprises a IgG4
15 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16 or 17 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody comprises a IgG1
20 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:18 or 19 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.
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The present disclosure further provides an antibody or antigen binding fragment comprising:

(a) a heavy chain (HC) having a constant domain and a variable domain wherein the variable domain comprises a heavy chain-complementary determining region (HC-CDR) 1
30 having the amino acid sequence shown in SEQ ID NO:8, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:9, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:10; and

(b) a light chain (LC) having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:11, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:12, and a LC-CDR 3 having the amino acid sequence shown in
5 SEQ ID NO:13. In further examples, the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the light chain comprises a human kappa light chain or human lambda light chain or variant thereof comprising 1, 2, 3, 4, 5,
10 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the antibody comprises an heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype or variant thereof comprising 1,
15 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof compared to the amino acid sequence of the native IgG1, IgG2, IgG3, or IgG4 isotype, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In
20 further examples, the constant domain may comprise a C-terminal lysine or may lack a C-terminal lysine.

In further aspects or examples of the disclosure, the antibody comprises a heavy chain constant domain of the human IgG1 or IgG4 isotype or variant thereof comprising 1, 2, 3,
25 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX. In a further example, the heavy chain constant domain is of the IgG4 isotype and further includes a substitution of the serine residue at position 228 (EU numbering) with proline, which
30 corresponds to position 108 of SEQ ID NO:16 or 17 (Serine at position 108).

In further aspects or examples of the disclosure, the antibody comprises a IgG4 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16 or 17 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions,

additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody comprises a IgG1 heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:18 or 19 or variant thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof, wherein the antibody or antigen binding fragment binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the present disclosure provides an antibody comprising: (a) a heavy chain (HC) having a constant domain and a variable domain wherein the variable domain comprises (i) an HC framework and heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:8, an HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:9, and an HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:10; (ii) an HC framework and heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, an HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and an HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3; (iii) an HC framework and heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, an HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and an HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:4; (iv) variant of (i), (ii), or (iii) wherein at least one of HC CDR 1, HC-CDR 2, or CDR 3 comprises 1, 2, or 3 amino acid substitutions, additions, deletions, or combinations thereof; or (v) variant of (i), (ii), (iii), or (iv) wherein the HC framework comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof; (b) a light chain (LC) having a constant domain and a variable domain wherein the variable domain comprises (i) an LC framework and light chain comprising a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:11, an LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:12, and an LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:13; (ii) an LC framework and light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, an LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and an LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7; (iii) variant of (i) or (ii) wherein at least one of

LC CDR 1, LC-CDR 2, or LC-CDR 3 comprises 1, 2, or 3 amino acid substitutions, additions, deletions, or combinations thereof; or (iv) variant of (i), (ii), or (iii) wherein the LC framework comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof; or (c) an HC from (a) and an LC from (b); wherein the antibody binds the apple 3 domain of coagulation factor XI (FXI) and inhibits activation of FXI and/or Factor XIa-mediated activation of Factor IX.

In further aspects or examples of the disclosure, the antibody of claim 18, wherein the HC constant domain comprises the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

In further aspects or examples of the disclosure, the antibody of claim 18 or 19, wherein the LC constant domain comprises the amino acid sequence shown in SEQ ID NO:20.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 33 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 35 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 45 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 47 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 49 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 51 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 59 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 61 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

5 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 63 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 69 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

10 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 33 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 71 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

15 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 73 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 75 and a light chain having the amino acid sequence shown in SEQ ID NO: 26.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 39 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

25 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 41 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 43 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

30 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 53 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 55 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

5 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 57 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 65 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

10 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 67 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 69 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

15 The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 77 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

The present disclosure further provides an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 79 and a light chain having the amino acid sequence shown in SEQ ID NO: 31.

20 The present disclosure further provides an antibody or antigen binding fragment that cross-blocks or competes with the binding of an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 33, 35, 37, 45, 47, 49, 51, 59, 61, 63, 69, 71, 73, or 75 and a light chain having the amino acid sequence shown in SEQ ID NO: 26; or an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 39, 41, 43, 53, 55, 57, 65, 67, 69, 77, or 79 and a light chain having the amino acid sequence shown in SEQ ID NO: 31 with the proviso that the antibody or antigen binding fragment does not comprise murine or rat amino acid sequences.

30 In a further example, the antibody or antigen binding fragment does not comprise non-human amino acid sequences.

In a further example, the antibody comprises (i) a human IgG1 constant domain or variant or modified derivative thereof or (ii) a human IgG4 constant domain or variant or modified derivative thereof.

5 In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

10 In a further example, the IgG4 constant domain is a variant that comprises at least a substitution of the serine at position 228 (EU numbering) or position 108 as shown herein with a proline residue.

In a further example, the IgG1 or IgG4 constant domain is a variant that at least lacks a lysine at the C-terminus.

15 In a further example, the antibody or antigen binding fragment comprises variable domain sequences comprising a framework characteristic of human antibodies.

The present disclosure further provides a human antibody or antigen binding fragment that cross-blocks or competes with the binding of an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO: 33, 35, 37, 45, 47, 49, 51, 59, 61, 20 63, 69, 71, 73, or 75 and a light chain having the amino acid sequence shown in SEQ ID NO: 26; or an antibody comprising a heavy chain having the amino acid sequence shown in SEQ ID NO:39, 41, 43, 53, 55, 57, 65, 67, 69, 77, or 79 and a light chain having the amino acid sequence shown in SEQ ID NO:31.

25 In a further example, the antibody or antigen binding fragment does not comprise non-human amino acid sequences.

In a further example, the antibody comprises (i) a human IgG1 constant domain or variant or modified derivative thereof or (ii) a human IgG4 constant domain or variant or modified derivative thereof.

30 In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

5 In a further example, the IgG4 constant domain is a variant that comprises at least a substitution of the serine at position 228 (EU numbering) or position 108 as shown herein with a proline residue.

In a further example, the IgG1 or IgG4 constant domain is a variant that at least lacks a lysine at the C-terminus.

10 In a further example, the antibody or antigen binding fragment comprises variable domain sequences comprising a framework characteristic of human antibodies.

The present disclosure further provides an antibody or antigen binding fragment that binds to an epitope on coagulation factor XI (FXI) comprising the amino acid sequence YATRQFPSLEHRNICL (SEQ ID NO:82) and amino acid sequence HTQTGTPTRITKL (SEQ ID NO:83) with the proviso that the antibody or antigen binding fragment does not comprise
15 murine or rat amino acid sequences. In particular examples, the binding to the epitope is determined by hydrogen deuterium exchange mass spectrometry.

In a further example, the antibody or antigen binding fragment does not comprise non-human amino acid sequences.

20 In a further example, the antibody comprises (i) a human IgG1 constant domain or variant or modified derivative thereof or (ii) a human IgG4 constant domain or variant or modified derivative thereof.

In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

25 In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, or 4 amino acid substitutions, additions, deletions, or combinations thereof.

30 In a further example, the IgG4 constant domain is a variant that comprises at least a substitution of the serine at position 228 (EU numbering) or position 108 as shown herein with a proline residue.

In a further example, the IgG1 or IgG4 constant domain is a variant that at least lacks a lysine at the C-terminus.

In a further example, the antibody or antigen binding fragment comprises variable domain sequences comprising a framework characteristic of human antibodies.

The present disclosure further provides a human antibody or antigen binding fragment that binds to an epitope on coagulation factor XI (FXI) comprising the amino acid sequence YATRQFPSLEHRNICL (SEQ ID NO:82) and amino acid sequence HTQTGTPTRITKL (SEQ ID NO:83) with the proviso that the antibody comprises (i) a human IgG1 constant domain or variant or modified derivative thereof or (ii) a human IgG4 constant domain or variant or modified derivative thereof. In particular examples, the binding to the epitope is determined by hydrogen deuterium exchange mass spectrometry.

In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In a further example, the IgG4 constant domain is a variant that comprises at least a substitution of the serine at position 228 (EU numbering) or position 108 as shown herein with a proline residue.

In a further example, the IgG1 or IgG4 constant domain is a variant that at least lacks a lysine at the C-terminus.

In a further example, the antibody or antigen binding fragment comprises variable domain sequences comprising a framework characteristic of human antibodies.

In another aspect, there is provided an isolated nucleic acid molecule encoding the light chain variable domain or the heavy chain variable domain of any one of the aforementioned antibodies or antigen binding fragments.

The present disclosure further provides a humanized antibody or antigen binding fragment that binds to an epitope on coagulation factor XI (FXI) comprising the amino acid sequence YATRQFPSLEHRNICL (SEQ ID NO:82) and amino acid sequence HTQTGTPTRITKL (SEQ ID NO:83) with the proviso that the antibody comprises (i) a human IgG1 constant domain or variant or modified derivative thereof or (ii) a human IgG4 constant domain or variant or modified derivative thereof. In particular examples, the binding to the epitope is determined by hydrogen deuterium exchange mass spectrometry.

In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

5 In a further example, the IgG1 or IgG4 constant domain is a variant that comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof.

In a further example, the IgG4 constant domain is a variant that comprises at least a substitution of the serine at position 228 (EU numbering) or position 108 as shown herein with a proline residue.

10 In a further example, the IgG1 or IgG4 constant domain is a variant that at least lacks a lysine at the C-terminus.

In a further example, the antibody or antigen binding fragment comprises variable domain sequences comprising a framework characteristic of human antibodies.

15 The present disclosure further provides an isolated nucleic acid molecule encoding the light chain variable domain or the heavy chain variable domain of any one of the aforementioned antibodies or antigen binding fragments.

In another aspect, there is provided a composition comprising the antibody or antigen binding fragment as aforementioned and a pharmaceutically acceptable carrier or diluent.

20 The present disclosure further provides a method of treating a thromboembolic disorder or disease in a subject comprising administering to the subject an effective amount of the antibody or antigen binding fragment of any one of the aforementioned antibodies or antigen binding fragments.

25 The present disclosure further provides a method of treating a thromboembolic disorder or disease in a subject comprising administering to a subject in need thereof an effective amount of the antibody or antigen binding fragments of any one of the aforementioned antibodies or antigen binding fragments.

The present disclosure further provides for the use of an antibody of any one of the aforementioned antibodies or antigen binding fragments for the manufacture of a medicament for treating a thromboembolic disorder or disease. In another aspect, there is provided use of an antibody as aforementioned in the manufacture of a medicament for treating a thromboembolic disorder or disease.

The present disclosure further provides an antibody of any one of the aforementioned antibodies or antigen binding fragments for the treatment of a thromboembolic disorder or disease. In another aspect, there is provided an antibody as aforementioned for use in the treatment of a thromboembolic disorder or disease.

10

The present disclosure further provides a method for producing an antibody or antigen binding fragment comprising (i) a heavy chain having a constant domain and a variable domain wherein the variable domain comprises a heavy chain comprising a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3 or 4; and (ii) a light chain having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7, the method comprising providing a host cell comprising a nucleic acid molecule encoding the heavy chain and a nucleic acid molecule encoding the light chain; and cultivating the host cell under conditions and a time sufficient to produce the antibody or antigen binding fragment.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain of the IgG4 isotype.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

In further aspects or examples of the disclosure, the light chain comprises a human kappa light chain or human lambda light chain.

In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the host cell is a Chinese hamster ovary cell or a human embryo kidney 293 cell.

In further aspects or examples of the disclosure, the host cell is a yeast or filamentous fungus cell.

The present disclosure further provides a method for producing an antibody or antigen binding fragment comprising (i) a heavy chain having a constant domain and a variable domain wherein the variable domain comprises a heavy chain comprising a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR

3 having the amino acid sequence shown in SEQ ID NO:3 or 4; and (ii) a light chain having a constant domain and a variable domain wherein the variable domain comprises a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7, the method comprising providing a host cell comprising a nucleic acid molecule encoding the heavy chain and a nucleic acid molecule encoding the light chain; and cultivating the host cell under conditions and a time sufficient to produce the antibody or antigen binding fragment.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain of the IgG4 isotype.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

In further aspects or examples of the disclosure, the light chain comprises a human kappa light chain or human lambda light chain.

In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the host cell is a Chinese hamster ovary cell or a human embryo kidney 293 cell.

In further aspects or examples of the disclosure, the host cell is a yeast or filamentous fungus cell.

A method for producing an antibody or antigen binding fragment comprising (i) a heavy chain variable domain comprising a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3 or 4 or an HC-CDR 1 having the amino acid sequence shown in SEQ ID NO:8, an HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:9, and an HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:10; and (ii) a light chain variable domain comprising a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7 or an LC-

CDR 1 having the amino acid sequence shown in SEQ ID NO:11, an LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:12, and an LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:13, the method comprising: providing a host cell comprising a nucleic acid molecule encoding the heavy chain and a nucleic acid molecule encoding the light chain; and cultivating the host cell under conditions and a time sufficient to produce the antibody or antigen binding fragment.

In another aspect, there is provided a method for producing an antibody or antigen-binding fragment comprising:

(i) a heavy chain variable domain comprising a heavy chain-complementary determining region (HC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:1, a HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:2, and a HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:3 or 4 or an HC-CDR 1 having the amino acid sequence shown in SEQ ID NO:8, an HC-CDR 2 having the amino acid sequence shown in SEQ ID NO:9, and an HC-CDR 3 having the amino acid sequence shown in SEQ ID NO:10; and

(ii) a light chain variable domain comprising a light chain-complementary determining region (LC-CDR) 1 having the amino acid sequence shown in SEQ ID NO:5, a LC-CDR 2 having the amino acid sequence shown in SEQ ID NO:6, and a LC-CDR 3 having the amino acid sequence shown in SEQ ID NO:7, the method comprising:

providing a host cell comprising a nucleic acid molecule encoding the heavy chain and a nucleic acid molecule encoding the light chain; and cultivating the host cell under conditions and a time sufficient to produce the antibody or antigen binding fragment.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain of the IgG4 isotype.

In further aspects or examples of the disclosure the antibody comprises a heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

In further aspects or examples of the disclosure, the light chain comprises a human kappa light chain or human lambda light chain.

In further aspects or examples of the disclosure, the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

In further aspects or examples of the disclosure, the host cell is a Chinese hamster ovary cell or a human embryo kidney 293 cell.

5 In further aspects or examples of the disclosure, the host cell is a yeast or filamentous fungus cell.

The present disclosure further provides a composition comprising any one of the aforementioned antibodies and a pharmaceutically acceptable carrier. In particular examples, the composition comprises a mixture of antibodies comprising a heavy chain having a C-terminal lysine and antibodies comprising a heavy chain lacking a C-terminal lysine. In particular
10 examples, the composition comprises an antibody disclosed herein wherein the predominant antibody form comprises a heavy chain having a C-terminal lysine. In particular examples, the composition comprises an antibody disclosed herein wherein the predominant antibody form comprises a heavy chain lacking a C-terminal lysine. In particular examples, the composition comprises an antibody disclosed herein wherein about 100% of the antibodies in the composition
15 comprise a heavy chain lacking a C-terminal lysine.

In another aspect, there is provided a composition comprising any one of the antibodies as aforementioned, wherein the antibody or antigen binding fragment is obtained from a host cell comprising a nucleic acid molecule encoding the heavy chain and a nucleic acid molecule encoding the light chain.

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Definitions