(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.

SUMMARY

In one aspect, there is provided an antibody or antigen binding fragment comprising: (i) at least the six complimentary determining regions (CDRs) of an anti-FXI antibody of the αFXI-18623p family or (ii) at least the six complimentary determining regions (CDRs) an anti-FXI antibody of the αFXI-18623p 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 αFXI-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.

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

In another aspect, there is provided use of an antibody as defined herein for the manufacture of a medicament for treating a thromboembolic disorder or disease.

In another aspect, there is provided an antibody as defined herein for use in the treatment of a thromboembolic disorder or disease.

BRIEF DESCRIPTION OF THE INVENTION

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

WHAT IS CLAIMED:

1. An antibody or antigen binding fragment comprising:

(i) at least the six complimentary determining regions (CDRs) of an anti-FXI antibody of the αFXI-18623p family or (ii) at least the six complimentary determining regions (CDRs) an anti-FXI antibody of the αFXI-18623p 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 αFXI-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.

2. The antibody or antigen binding fragment of claim 1, wherein the antibody comprises:

(a) an HC 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: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) an 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.

3. The antibody or antigen binding fragment of claim 2, wherein the antibody comprises an HC constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

4. The antibody or antigen binding fragment of claim 2, wherein the antibody comprises an LC constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

5. The antibody or antigen binding fragment of claim 1, wherein the antibody comprises:

an HC having the amino acid sequence shown in SEQ ID NO:41, 43, 53, 55, 65, 67, 77, or 79, and variants thereof comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, additions, deletions, or combinations thereof; and

an LC having the amino acid sequence shown in SEQ ID NO:31, and variants 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.

6. A composition comprising the antibody or antigen binding fragment of any one of claims 1-5 and a pharmaceutically acceptable carrier or diluent.

7. Use of an antibody of any one of claim 1-5 for the manufacture of a medicament for treating a thromboembolic disorder or disease.

8. An antibody of any one of claims 1-5 for use in the treatment of a thromboembolic disorder or disease.