antibody of the αFXI-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 anibody or antigen binding fragment comprising: the six complimentary determining regions (CDRs) of an anti-FXI antibody of the αFXI-18611p family, or αFXI-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 αFXI-18623p family, αFXI-18611p family, or αFXI-18611 family and CDR1, CDR2, and CDR3 of the LC of the αFXI-18623p family, αFXI-18611p family, or αFXI-18611 family, wherein an antibody of the αFXI-118623 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 αFXI-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 αFXI-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.

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 or antigen binding fragment as aforementioned in the manufacture of a medicament for treating or preventing a thromboembolic disorder or disease selected from the group consisting of thrombosis, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), medical device-related thromboembolic disorders.

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 or antigen binding fragment as aforementioned for use in the treatment or prevention of a thromboembolic disorder or disease selected from the group consisting of thrombosis, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), medical device-related thromboembolic disorders.

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; 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.

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 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 comprise a heavy chain lacking a C-terminal lysine.

In another aspect, there is provided a composition comprising any one of the antibodies or antigen binding fragments 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.

Definitions

WHAT IS CLAIMED:

1. An antibody or antigen binding fragment comprising:

the six complimentary determining regions (CDRs) of an anti-FXI antibody of the αFXI-18611p family, or αFXI-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.

2. 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.

3. The antibody or antigen binding fragment of claim 2, wherein the antibody or antigen binding fragment comprises an HC variable domain having the amino acid sequence shown in SEQ ID NO:21, 22, 23, or 24 and CDR1, CDR2, and CDR3 of an LC variable domain having amino acid sequence shown in SEQ ID NO:25.

4. The antibody or antigen binding fragment of any one of claims 1 to 3, wherein the antibody comprises a HC constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

5. The antibody or antigen binding fragment of any one of claims 1 to 3, wherein the antibody comprises a LC constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

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

(a) 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;

(b) 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;

(c) 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

(d) 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.

7. The antibody or antigen binding fragment of claim 6, wherein the antibody further comprises a HC constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

8. The antibody or antigen binding fragment of claim 6, wherein the antibody further comprises a LC constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

9. The antibody or antigen binding fragment of any one of claims 1 to 3, 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

10. The antibody or antigen binding fragment of claim 1 or 3, wherein the antibody comprises:

(a) an 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 or 4; 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: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.

11. The antibody or antigen binding fragment of claim 10, wherein the antibody comprises an HC constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

12. The antibody or antigen binding fragment of claim 10, wherein the antibody comprises an LC constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

13. 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:33, 35, 37, 39, 45, 47, 49, 51, 57, 59, 61, 63, 69, 71, 73, or 75; and

an LC having the amino acid sequence shown in SEQ ID NO: 26

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.

14. An isolated nucleic acid molecule encoding the light chain variable domain or the heavy chain variable domain of any of the antibodies or antigen binding fragments of claims 1-13.

15. A composition comprising the antibody or antigen binding fragment of any one of claims 1-13 and a pharmaceutically acceptable carrier or diluent.

16. Use of an antibody or antigen binding fragment of any one of claim 1-13 in the manufacture of a medicament for treating or preventing a thromboembolic disorder or disease selected from the group consisting of thrombosis, venous thromboembolism (VTE),

Stroke Prevention in Atrial Fibrillation (SPAF), medical device-related thromboembolic disorders.

17. An antibody or antigen binding fragment of any one of claims 1-13 for use in the treatment or prevention of a thromboembolic disorder or disease selected from the group consisting of thrombosis, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), medical device-related thromboembolic disorders.

18. 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; 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.

19. The method of claim 18, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:21, 22, 23, or 24 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:25.

20. The method of claim 18, wherein the antibody comprises a heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype.

21. The method of claim 18, wherein the antibody comprises a heavy chain constant domain of the IgG4 isotype.

22. The method of claim 18, wherein the antibody comprises a heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

23. The method of claim 18, wherein the light chain comprises a human kappa light chain or human lambda light chain.

24. The method of claim 18, wherein the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

25. The method of claim 18, wherein the host cell is a Chinese hamster ovary cell or a human embryo kidney 293 cell.

26. The method of claim 18, wherein the host cell is a yeast or filamentous fungus cell.

27. A composition comprising any one of the antibodies or antigen binding fragments of claims 1-13, 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.

28. The composition of claim 27, wherein the antibody comprises a heavy chain constant domain of the IgG1, IgG2, IgG3, or IgG4 isotype.

29. The composition of claim 27, wherein the antibody comprises a heavy chain constant domain of the IgG4 isotype.

30. The composition of claim 27, wherein the antibody comprises a heavy chain constant domain comprising the amino acid sequence shown in SEQ ID NO:16, 17, 18, or 19.

31. The composition of claim 27, wherein the light chain comprises a human kappa light chain or human lambda light chain.

32. The composition of claim 27, wherein the antibody comprises a light chain constant domain comprising the amino acid sequence shown in SEQ ID NO:20.

33. The composition of claim 27, wherein the host cell is a Chinese hamster ovary cell or a human embryo kidney 293 cell.

34. The composition of claim 27, wherein the host cell is a yeast or filamentous fungus cell.

35. 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.

36. The antibody or antigen binding fragment of claim 35, wherein the antibody further comprises a heavy chain constant domain having the amino acid sequence shown in SEQ ID NO:16 or 17 and a light chain constant domain having the amino acid sequence shown in SEQ ID NO:20.

37. The antibody or antigen binding fragment of Claim 36, wherein the antibody further comprises a heavy chain constant domain of the IgG1 isotype that lacks N-glycosylation of the asparagine at position 297.

38. A composition comprising the antibody or antigen binding fragment of claim 35 and a pharmaceutically acceptable carrier or diluent.

39. 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.

40. 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.