

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 a thromboembolic disorder or disease selected from the group consisting of thrombosis, thrombosis in an individual with end-stage renal disease, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), and 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 of a thromboembolic disorder or disease selected from the group consisting of thrombosis, thrombosis in an individual with end-stage renal disease, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), and medical device-related thromboembolic disorders.

WHAT IS CLAIMED:

1. An antibody or antigen binding fragment comprising:
the six complimentary determining regions (CDRs) of an anti-FXI antibody of
the α FXI-18611p family, or α FXI-18611 family wherein the six CDRs comprise
5 (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.
- 10 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
15 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
20 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
25 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.
- 30 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;

5 (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

10 (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
15 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
20 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

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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
30 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 a thromboembolic disorder or disease selected from the group consisting of thrombosis, thrombosis in an individual with end-stage renal

disease, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), and medical device-related thromboembolic disorders.

17. An antibody or antigen binding fragment of any one of claims 1-13 for use in the treatment of a thromboembolic disorder or disease selected from the group consisting of thrombosis, thrombosis in an individual with end-stage renal disease, venous thromboembolism (VTE), Stroke Prevention in Atrial Fibrillation (SPAF), and 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.