

There are still many unmet medical needs in the haemophilia community, in particular, and in subjects with coagulopathies, in general and the present invention relates to improved compounds capable of substituting for FVIII and thus being useful for the treatment of a coagulopathy such as haemophilia A.

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SUMMARY

The present disclosure relates to compounds, which serve as a substitute for coagulation Factor VIII (FVIII) in patients suffering from a coagulopathy and in particular patients lacking functional FVIII, such as haemophilia A patients including haemophilia A patients with inhibitors.

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Hence, one example of the present disclosure relates to compounds capable of enhancing the generation of FXa and thus partially or completely restoring coagulation in patients lacking functional FVIII.

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In one example, the compound is an antibody or antigen-binding fragment thereof. In one such example, the compound is a multispecific antibody or antigen-binding fragment thereof such as a bispecific antibody or antigen-binding fragment thereof.

In one particular example, the disclosure relates to procoagulant antibodies or antigen-binding fragment thereof which serve as a substitute for FVIII in patients lacking functional FVIII, such as haemophilia A patients.

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In one such example, the antibody or antigen-binding fragment thereof is capable of binding FIX(a) and increases the enzymatic activity of FIXa towards FX, optionally also being capable of binding FX.

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In one example, the disclosure relates to a procoagulant antibody or antigen-binding fragment thereof that is capable of binding FIX(a) and FX(a), including bispecific procoagulant antibodies or antigen-binding fragment thereof which increase the enzymatic activity of FIXa towards FX.

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In one example, the disclosure relates to a procoagulant bispecific antibody or antigen-binding fragment thereof that is capable of binding to FIX(a) and FX(a).

A further example of the disclosure relates to the individual component (intermediate)

antibodies or antigen-binding fragment thereof that are part of a procoagulant antibody, such as a particular anti-FIX(a) antibody or antigen-binding fragment thereof or a particular anti-FX(a) antibody or antigen-binding fragment thereof.

A further example of the disclosure relates to the manufacture of the antibodies or antigen-binding fragment thereof - and components (intermediates) thereof - as disclosed herein.

A further example of the disclosure relates to an antibody that competes with a procoagulant antibody or antigen-binding fragment thereof, as disclosed herein, for binding to FIX(a) and/or FX(a).

5 A further example of the disclosure relates to an antibody or antigen-binding fragment thereof which shares epitope residues or epitope hot-spot residues on FIX(a) and/or FX(a) with a procoagulant antibody or antigen-binding fragment hereof, as disclosed herein.

A further example of the disclosure is directed to the procoagulant antibodies or antigen-binding fragment thereof disclosed herein for prevention and/or treatment of a coagulopathy, a disease accompanying coagulopathy, or a disease caused by coagulopathy. In one
10 example the coagulopathy is haemophilia A with or without inhibitors.

A still further example of the disclosure relates to a pharmaceutical composition comprising a procoagulant antibody or antigen-binding fragment thereof as disclosed herein formulated for the delivery of said antibody for the prevention and/or treatment of a coagulopathy, such as haemophilia A with or without inhibitors, as well as an injection device with content thereof.

15 A further example of the disclosure is directed to a kit comprising (i) an antibody or antigen-binding fragment thereof as disclosed herein such as a bispecific antibody and (ii) instructions for use.

In an aspect, there is provided a multispecific antibody or antigen-binding fragment thereof capable of stimulating the enzymatic activity of FIXa towards FX comprising a first antigen-
20 binding site capable of binding to FIX (SEQ ID NO:1) and/or the activated form thereof (FIXa), and a second antigen-binding site capable of binding to FX (SEQ ID NO:2) and/or the activated form thereof (FXa) wherein

the first antigen-binding site is capable of binding to an epitope comprising amino acid residues L337, R338, S339, T340 and K341 of FIX(a), and wherein the second antigen-
25 binding site is capable of binding an epitope comprising amino acid residues
i) E103, Q104, V108, R113, T116, L117, D119, I125, T127, E228, F229, Y230, E266, R287, P291, I292, P304, L419, K420, D423, R424, M426, K427 and T428 of FX(a)

or

ii) E103, Q104, V108, R113, T116, L117, A118, D119, I125, T127, S227, E228, Y230, R287,
30 I292, L303, P304, L419, K420, D423, R424, M426, K427 and T428 of FX(a).

In another aspect, there is provided a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof as defined above and one or more pharmaceutically acceptable carrier(s).

In another aspect, there is provided a kit comprising (i) the antibody or antigen-binding fragment thereof or composition as defined above, optionally comprised by an injection device, and (ii) instructions for use.

5 In another aspect, there is provided an antibody or antigen-binding fragment thereof as defined above or the composition as defined above, for use in the treatment of haemophilia A with or without inhibitors.

In another aspect, there is provided the use of the antibody or antigen-binding fragment thereof as defined above or the composition as defined above, in the manufacture of a medicament for the treatment of haemophilia A with or without inhibitors.

10 In another aspect, there is provided the use of an antibody or antigen-binding fragment thereof capable of binding to FIX (SEQ ID NO:1) and/or the activated form thereof (FIXa) comprising a heavy chain and a light chain wherein

- a. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:36, 37 and 38, respectively, and
15 the light chain CDR1-3 sequences are identified by SEQ ID NOs:40, 41 and 42, respectively, or
- b. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:44, 45 and 46, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:48, 49 and 50, respectively, or
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- c. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:52, 53 and 54, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs: 56, 57 and 58, respectively, or
- 25 d. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:68, 69 and 70, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:72, 73 and 74, respectively, or
- e. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1203, 1204 and
30 1205, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1207, 1208 and 1209, respectively, or
- f. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1211, 1212 and 1213, respectively, and

the light chain CDR1-3 sequences are identified by SEQ ID NOs:1215, 1216 and 1217, respectively, or

- g. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1219, 1220 and 1221, respectively, and

5 the light chain CDR1-3 sequences are identified by SEQ ID NOs:1223, 1224 and 1225, respectively, or

- h. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1227, 1228 and 1229, respectively, and

10 the light chain CDR1-3 sequences are identified by SEQ ID NOs:1231, 1232 and 1233, respectively, or

- i. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1235, 1236 and 1237, respectively, and

the light chain CDR1-3 sequences are identified by SEQ ID NOs:1239, 1240 and 1241, respectively, or

- 15 j. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1243, 1244 and 1245, respectively, and

the light chain CDR1-3 sequences are identified by SEQ ID NOs:1247, 1248 and 1249, respectively;

20 wherein said antibody or antigen-binding fragment thereof is an intermediate for use in the manufacture of a bispecific antibody which is capable of binding to FIX and/or the activated form thereof (FIXa), and capable of binding to FX (SEQ ID NO:2) and/or the activated form thereof (FXa).

The disclosure may also solve further problems that will be apparent from the disclosure of the exemplary embodiments.

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BRIEF DESCRIPTION OF THE FIGURES

Figure 1A-D shows alignments of sequences representing heavy- and light chain variable domains of the anti-FIX(a) (Fig. 1A and 1B) and anti-FX(a) (Fig. 1C and 1D) IgG antibodies as disclosed herein. CDR1, 2 and 3 sequences are highlighted in bold and underlined in uppermost sequence and is representative for the remaining sequences.

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Figure 2 shows thrombin generation test (TGT) results from the bispecific antibodies bimAb05-0745, bimAb05-3761, bimAb05-3769, bimAb05-0746, bimAb05-2112, bimAb05-2113, bimAb05-2114 and ACE910 in human tissue factor activated haemophilia A platelet-poor plasma (PPP). The experiment was performed as described in Example 16. Dotted and

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stippled lines indicate the peak thrombin level (nM) observed in the absence of antibody in HA-PPP and normal PPP, respectively, and with their standard deviation indicated by dotted lines. The profiles of bimAb05-0745, bimAb05-3761, bimAb05-3769, bimAb05-0746, bimAb05-2112, bimAb05-2113 and bimAb05-2114 are indicated by down-pointing triangles,

CLAIMS

1. A multispecific antibody or antigen-binding fragment thereof capable of stimulating the enzymatic activity of FIXa towards FX comprising a first antigen-binding site capable of binding to FIX (SEQ ID NO:1) and/or the activated form thereof (FIXa), and a second antigen-binding site capable of binding to FX (SEQ ID NO:2) and/or the activated form thereof (FXa) wherein

the first antigen-binding site is capable of binding to an epitope comprising amino acid residues L337, R338, S339, T340 and K341 of FIX(a), and wherein the second antigen-binding site is capable of binding an epitope comprising amino acid residues

i) E103, Q104, V108, R113, T116, L117, D119, I125, T127, E228, F229, Y230, E266, R287, P291, I292, P304, L419, K420, D423, R424, M426, K427 and T428 of FX(a)

or

ii) E103, Q104, V108, R113, T116, L117, A118, D119, I125, T127, S227, E228, Y230, R287, I292, L303, P304, L419, K420, D423, R424, M426, K427 and T428 of FX(a).

2. The antibody or antigen-binding fragment thereof according to claim 1, wherein the first antigen-binding site comprises

a. a paratope comprising amino acid residues H30, D31, W53, S102, S104, Y106 and N107 in the heavy chain variable domain (SEQ ID NO:51) and amino acid residues Y91 and S92 in the light chain variable domain (SEQ ID NO:55), optionally comprising one or two substitution(s) in the nine recited paratope amino acid residues,

and the second antigen-binding site comprises

b. a paratope comprising amino acid residues K23, G24, S25, G26, Y27, W33, D52, S54, D55, Y57, S77, L99, H100, Y101, Y102, N103 and S104 in the heavy chain variable domain (SEQ ID NO:483) and amino acid residues S30, S31, Y33, Y50, Q52, S54, R55, R57, Y92 and D94 in the light chain variable domain (SEQ ID NO:487), optionally comprising one, two or three substitutions in the 27 recited paratope amino acid residues, or

c. a paratope comprising amino acid residues K23, S25, G26, Y27, F29, W33, D52, S54, D55, F57, S77, H100, Y101, Y102, N103 and S104 in the heavy chain variable domain (SEQ ID NO:467) and amino acid residues V29, S30, S31, Y33, Y50, Q52, S54, R55, R57 and D94 in the light chain variable domain (SEQ ID NO:471),

optionally comprising one, two or three substitutions in the 26 recited paratope amino acid residues.

3. The antibody or antigen-binding fragment thereof according to claim 2 wherein said
5 substitutions are conservative substitutions.

4. A multispecific antibody or antigen-binding fragment thereof capable of binding to FIX
(SEQ ID NO:1) and/or the activated form thereof (FIXa), and capable of binding to FX (SEQ
ID NO:2) and/or the activated form thereof (FXa), wherein said multispecific antibody
10 comprises an anti-FIX(a) antibody or antigen-binding fragment thereof comprising a heavy
chain and a light chain, and an anti-FX(a) antibody or antigen-binding fragment thereof
comprising a heavy chain and a light chain,
wherein

- a. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
15 NOs:36, 37 and 38, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
NOs:40, 41 and 42, respectively, and
the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
NOs:468, 469 and 470, respectively, and
20 the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
NOs:472, 473 and 474, respectively, or
- b. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
NOs:36, 37 and 38, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
25 NOs:40, 41 and 42, respectively, and
the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
NOs:484, 485 and 486, respectively, and
the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
NOs:488, 489 and 490, respectively, or
- c. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
30 NOs:44, 45 and 46, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
NOs:48, 49 and 50, respectively, and
the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
35 NOs: 468, 469 and 470, respectively, and

the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 472, 473 and 474, respectively, or

- d. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 52, 53 and 54, respectively, and

5 the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 56, 57 and 58, respectively, and

the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 468, 469 and 470, respectively, and

10 the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 472, 473 and 474, respectively, or

- e. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 52, 53 and 54, respectively, and

the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 56, 57 and 58, respectively, and

15 the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 484, 485 and 486, respectively, and

the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 488, 489 and 490, respectively, or

- f. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 68, 69 and 70, respectively, and

20 the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 72, 73 and 74, respectively, and

the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 468, 469 and 470, respectively, and

25 the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 472, 473 and 474, respectively, or

- g. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 68, 69 and 70, respectively, and

30 the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 72, 73 and 74, respectively, and

the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs: 484, 485 and 486, respectively, and

the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs: 488, 489 and 490, respectively, or

- h. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1203, 1204 and 1205, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:1207, 1208 and 1209, respectively, and
5 the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:468, 469 and 470, respectively, and
the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:472, 473, and 474, respectively, or
- i. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
10 NOs:1211, 1212 and 1213, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:1215, 1216 and 1217, respectively, and
the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:468, 469 and 470, respectively, and
15 the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:472, 473, and 474, respectively, or
- j. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1219, 1220 and 1221, respectively and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
20 NOs:1223, 1224 and 1225, respectively, and
the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:468, 469 and 470, respectively, and
the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:472, 473, and 474, respectively, or
- k. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
25 NOs:1227, 1228 and 1229, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:1231, 1232 and 1233, respectively, and
the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
30 NOs:468, 469 and 470, respectively, and
the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID NOs:472, 473, and 474, respectively, or
- l. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
35 NOs:1235, 1236 and 1237, respectively, and
the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID

NOs:1239, 1240 and 1241, respectively, and
 the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
 NOs:468, 469 and 470, respectively, and
 the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
 5 NOs:472, 473, and 474, respectively, or

m. the anti-FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
 NOs:1243, 1244 and 1245, respectively, and
 the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
 NOs:1247, 1248 and 1249, respectively, and
 10 the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID
 NOs:468, 469 and 470, respectively, and
 the anti-FX(a) antibody light chain CDR1-3 sequences are identified by SEQ ID
 NOs:472, 473, and 474, respectively.

15 **5.** The antibody or antigen-binding fragment thereof according to claim 4, wherein the anti-
 FIX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:52, 53 and
 54, respectively, and the anti-FIX(a) antibody light chain CDR1-3 sequences are identified by
 SEQ ID NOs:56, 57 and 58, respectively, and
 the anti-FX(a) antibody heavy chain CDR1-3 sequences are identified by SEQ ID NOs:468,
 20 469 and 470, respectively, and the anti-FX(a) antibody light chain CDR1-3 sequences are
 identified by SEQ ID NOs:472, 473 and 474, respectively.

6. The antibody or antigen-binding fragment thereof according to claim 4,
 wherein the anti-FIX(a) antibody or antigen-binding fragment thereof comprises

- 25 a. a heavy chain variable domain identified by SEQ ID NO:35 and a light chain
 variable domain identified by SEQ ID NO:39, or
 b. a heavy chain variable domain identified by SEQ ID NO:43 and a light chain
 variable domain identified by SEQ ID NO:47, or
 c. a heavy chain variable domain identified by SEQ ID NO:51 and a light chain
 30 variable domain identified by SEQ ID NO:55, or
 d. a heavy chain variable domain identified by SEQ ID NO:67 and a light chain
 variable domain identified by SEQ ID NO:71, or
 e. a heavy chain variable domain identified by SEQ ID NO:1202 and a light chain
 variable domain identified by SEQ ID NO:1206, or

- f. a heavy chain variable domain identified by SEQ ID NO:1210 and a light chain variable domain identified by SEQ ID NO:1214, or
- g. a heavy chain variable domain identified by SEQ ID NO:1218 and a light chain variable domain identified by SEQ ID NO:1222, or
- h. a heavy chain variable domain identified by SEQ ID NO:1226 and a light chain variable domain identified by SEQ ID NO:1230, or
- i. a heavy chain variable domain identified by SEQ ID NO:1234 and a light chain variable domain identified by SEQ ID NO:1238, or
- j. a heavy chain variable domain identified by SEQ ID NO:1242 and a light chain variable domain identified by SEQ ID NO:1246,

and wherein the anti-FX(a) antibody or antigen-binding fragment thereof comprises

- k. a heavy chain variable domain identified by SEQ ID NO:467 and a light chain variable domain identified by SEQ ID NO:471, or
- l. a heavy chain variable domain identified by SEQ ID NO:483 and a light chain variable domain identified by SEQ ID NO:487; or

wherein both said heavy chain variable domain and light chain variable domain in said anti-FIX(a) antibody or antigen-binding fragment thereof and said anti-FX(a) antibody or antigen-binding fragment thereof are at least 96, 97, 98, 99, 99.1 or 99.2 % identical to the recited SEQ ID NOS.

7. The antibody or antigen-binding fragment thereof according to any of claims 4-6, wherein the anti-FIX(a) antibody or antigen-binding fragment thereof comprises a heavy chain variable domain identified by SEQ ID NO:51 and a light chain variable domain identified by SEQ ID NO:55, and wherein the anti-FX(a) antibody or antigen-binding fragment thereof comprises a heavy chain variable domain identified by SEQ ID NO:467 and a light chain variable domain identified by SEQ ID NO:471.

8. The antibody or antigen-binding fragment thereof according to any of the previous claims wherein said antibody or antigen-binding fragment thereof is a bispecific antibody.

9. The antibody or antigen-binding fragment thereof according to any of the previous claims wherein the isotype of said antibody or antigen-binding fragment thereof is IgG1 or IgG4.

10. The antibody or antigen-binding fragment thereof according to any of the previous claims wherein said antibody or antigen-binding fragment thereof is a procoagulant antibody or antigen-binding fragment thereof.

5 **11.** The antibody or antigen-binding fragment thereof according to any of claims 4-10 wherein said antibody or antigen-binding fragment thereof is capable of stimulating the enzymatic activity of FIXa.

10 **12.** A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any of claims 1-11 and one or more pharmaceutically acceptable carrier(s).

15 **13.** A kit comprising (i) the antibody or antigen-binding fragment thereof or composition according to any of the previous claims, optionally comprised by an injection device, and (ii) instructions for use.

20 **14.** The antibody or antigen-binding fragment thereof according to any one of claims 1-11 or the composition according to claim 12, for use in the treatment of haemophilia A with or without inhibitors.

25 **15.** Use of the antibody or antigen-binding fragment thereof according to any one of claims 1-11 or the composition according to claim 12, in the manufacture of a medicament for the treatment of haemophilia A with or without inhibitors.

30 **16.** An antibody or antigen-binding fragment thereof capable of binding to FIX (SEQ ID NO:1) and/or the activated form thereof (FIXa) comprising a heavy chain and a light chain wherein

 a. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:36, 37 and 38, respectively, and

35 the light chain CDR1-3 sequences are identified by SEQ ID NOs:40, 41 and 42, respectively, or

 b. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:44, 45 and 46, respectively, and

40 the light chain CDR1-3 sequences are identified by SEQ ID NOs:48, 49 and 50, respectively, or

- c. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:52, 53 and 54, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs: 56, 57 and 58, respectively, or
- 5 d. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:68, 69 and 70, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:72, 73 and 74, respectively, or
- 10 e. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1203, 1204 and 1205, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1207, 1208 and 1209, respectively, or
- 15 f. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1211, 1212 and 1213, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1215, 1216 and 1217, respectively, or
- 20 g. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1219, 1220 and 1221, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1223, 1224 and 1225, respectively, or
- 25 h. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1227, 1228 and 1229, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1231, 1232 and 1233, respectively, or
- 30 i. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1235, 1236 and 1237, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1239, 1240 and 1241, respectively, or
- j. the heavy chain CDR1-3 sequences are identified by SEQ ID NOs:1243, 1244 and 1245, respectively, and
the light chain CDR1-3 sequences are identified by SEQ ID NOs:1247, 1248 and 1249, respectively;

wherein said antibody or antigen-binding fragment thereof is an intermediate for use
35 in the manufacture of a bispecific antibody which is capable of binding to FIX and/or

the activated form thereof (FIXa), and capable of binding to FX (SEQ ID NO:2) and/or the activated form thereof (FXa).

17. The antibody or antigen-binding fragment thereof according to claim 16, wherein the antibody or antigen-binding fragment thereof comprises

- a. a heavy chain variable domain identified by SEQ ID NO:35 and a light chain variable domain identified by SEQ ID NO:39, or
- b. a heavy chain variable domain identified by SEQ ID NO:43 and a light chain variable domain identified by SEQ ID NO:47, or
- c. a heavy chain variable domain identified by SEQ ID NO:51 and a light chain variable domain identified by SEQ ID NO:55, or
- d. a heavy chain variable domain identified by SEQ ID NO:67 and a light chain variable domain identified by SEQ ID NO:71, or
- e. a heavy chain variable domain identified by SEQ ID NO:1202 and a light chain variable domain identified by SEQ ID NO:1206, or
- f. a heavy chain variable domain identified by SEQ ID NO:1210 and a light chain variable domain identified by SEQ ID NO:1214, or
- g. a heavy chain variable domain identified by SEQ ID NO:1218 and a light chain variable domain identified by SEQ ID NO:1222, or
- h. a heavy chain variable domain identified by SEQ ID NO:1226 and a light chain variable domain identified by SEQ ID NO:1230, or
- i. a heavy chain variable domain identified by SEQ ID NO:1234 and a light chain variable domain identified by SEQ ID NO:1238, or
- j. a heavy chain variable domain identified by SEQ ID NO:1242 and a light chain variable domain identified by SEQ ID NO:1246.

18. The antibody or antigen-binding fragment thereof according to claim 17, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable domain identified by SEQ ID NO:51 and a light chain variable domain identified by SEQ ID NO:55.