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(54) MULTI-SPECIFIC ANTIGEN-BINDING MOLECULE HAVING ALTERNATIVE FUNCTION TO FUNCTION OF BLOOD COAGULATION FACTOR VIII

(57) Various bispecific antibodies that specifically bind to both blood coagulation factor IX/activated blood coagulation factor IX and blood coagulation factor X and functionally substitute for the cofactor function of blood coagulation factor VIII, that is, the function to promote

activation of blood coagulation factor X by activated blood coagulation factor IX, were produced. From these antibodies, multispecific antigen-binding molecules having a high activity of functionally substituting for blood coagulation factor VIII were successfully discovered.

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Description

Technical Field

⁵ **[0001]** The present invention relates to multispecific antigen-binding molecules that functionally substitute for blood coagulation factor VIII, a cofactor that enhances enzymatic reactions, and pharmaceutical compositions comprising such a molecule as an active ingredient.

Background Art

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[0002] Hemophilia A is a bleeding abnormality caused by a hereditary decrease or deficiency of blood coagulation factor VIII (F.VIII) function. Hemophilia A patients are generally administered with an F.VIII formulation for the bleeding (on-demand administration). In recent years, F.VIII formulations are also administered prophylactically to prevent bleeding events (preventive administration; Non-patent Documents 1 and 2). The half-life of F.VIII formulations in blood is ap-

- ¹⁵ proximately 12 to 16 hours. Therefore, for continuous prevention, F.VIII formulations are administered to patients three times a week (Non-patent Documents 3 and 4). In on-demand administrations, F.VIII formulations are also additionally administered when necessary at regular intervals to prevent rebleeding. In addition, the administration of F.VIII formulations is done intravenously. Therefore, there has been a strong need for pharmaceutical agents with a lesser burden than F.VIII formulations.
- 20 [0003] Occasionally, anti-F.VIII antibodies (inhibitors) develop in hemophilia patients. Such inhibitors cancel the effects of the F.VIII formulations. For bleeding in patients who have developed inhibitors (inhibitor patients), bypass formulations are administered. Their action mechanisms are not dependent on F.VIII function, that is, the function of catalyzing the activation of blood coagulation factor X (F.X) by activated blood coagulation factor IX (F.IXa). Therefore, in some cases, bypass formulations cannot sufficiently stop the bleeding. Accordingly, there has been a strong need for pharmaceutical
- ²⁵ agents that are not affected by the presence of inhibitors and which can functionally substitute for F.VIII. [0004] Recently, as a means for solving the problem, antibodies that functionally substitute for F.VIII and their use were disclosed (Patent Documents 1, 2, and 3). The antibodies may be effective for acquired hemophilia in which anti-F.VIII autoantibodies are present and for von Willebrand disease caused by an abnormality or deficiency of function of von Willebrand factor (vWF), but the activity of functionally substituting for F.VIII was not always sufficient. Therefore,
- ³⁰ as pharmaceutical agents exhibiting a high hemostatic effect, antibodies with a higher activity of functionally substituting for F.VIII than the above-mentioned antibodies were desired.

Prior Art Documents

35 [Patent Document]

[0005]

[Patent Document 1] WO 2005/035754
 [Patent Document 2] WO 2005/035756
 [Patent Document 3] WO 2006/109592

[Non-patent Document]

⁴⁵ [0006]

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[Non-patent Document 1] Blood 58, 1-13 (1981) [Non-patent Document 2] Nature 312, 330-337 (1984) [Non-patent Document 3] Nature 312, 337-342 (1984) [Non-patent Document4] Biochim.Biophys.Acta 871, 268-278 (1986)

Summary of the Invention

[Problems to be Solved by the Invention]

[0007] An objective of the present invention is to provide multispecific antigen-binding molecules that functionally substitute for F.VIII, a cofactor that enhances enzymatic reactions.

[Means for Solving the Problems]

[0008] As a result of dedicated research, the present inventors succeeded in discovering bispecific antibodies having a better F.Xa generation-promoting activity than known antibodies from among various bispecific antibodies that specifically bind to both F.IX/F.IXa and F.X, and substitute for the cofactor function of F.VIII, that is, the function to promote F.X activation by F.IXa (F.Xa generation-promoting function).

[0009] Furthermore, the present inventors succeeded in finding the positions in the amino acid sequences of bispecific antibodies having the activity of functionally substituting for F.VIII that are important for improving the F.Xa generation-promoting activity of these antibodies, and thus they successfully obtained bispecific antibodies in which the activity of

[0010] Specifically, the present invention relates to multispecific antigen-binding molecules that functionally substitute for F.VIII, a cofactor that enhances enzymatic reactions, and pharmaceutical compositions comprising such a molecule as an active ingredient, and specifically relates to the following:

- [1] a multispecific antigen-binding molecule that functionally substitutes for blood coagulation factor VIII, which comprises a first antigen-binding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and a second antigen-binding site that recognizes blood coagulation factor X, wherein the functional
- ²⁰ substitution for blood coagulation factor VIII results from an activated blood coagulation factor X (F.Xa) generation-promoting activity higher than the activity of a bispecific antibody (hA69-KQ/hB26-PF/hAL-AQ) which comprises an H chain comprising SEQ ID NOs: 165 and 166, and a commonly shared L chain comprising SEQ ID NO: 167;
 [2] the multispecific antigen-binding molecule of [1], which comprises a first polypeptide comprising a first antigen-binding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and a third
- ²⁵ polypeptide comprising a third antigen-binding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX, as well as a second polypeptide comprising a second antigen-binding site that recognizes blood coagulation factor X and a fourth polypeptide comprising a fourth antigen-binding site that recognizes blood coagulation factor X;
- [3] the multispecific antigen-binding molecule of [2], wherein the first polypeptide and the third polypeptide each
 comprises an antigen-binding site of an H chain or L chain of an antibody against blood coagulation factor IX or
 activated blood coagulation factor IX, respectively; and the second polypeptide and the fourth polypeptide each
 comprises an antigen-binding site of an H chain or L chain of an antibody against blood coagulation factor X,
 respectively;
- [4] the multispecific antigen-binding molecule of [3], wherein the antigen-binding site of the first polypeptide comprises
 an antigen-binding site which comprises H chain CDRs consisting of any one of the amino acid sequences selected
 from the following (a1) to (a11), or an antigen-binding site functionally equivalent thereto, and the antigen-binding
 site of the second polypeptide comprises an antigen-binding site which comprises H chain CDRs consisting of any
 one of the amino acid sequences selected from the following (b1) to (b11), or an antigen-binding site functionally
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(a1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 75, 76, and 77 (H chain CDRs of Q1), respectively;

(a2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 78, 79, and 80 (H chain CDRs of Q31), respectively;

(a3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 81, 82, and 83 (H chain CDRs of Q64), respectively;

(a4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 84, 85, and 86 (H chain CDRs of Q85), respectively;

(a5) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 87, 88, and 89 (H chain CDRs of Q153), respectively;

(a6) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 90, 91, and 92 (H chain CDRs of Q354), respectively;

(a7) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 93, 94, and 95 (H chain CDRs of Q360), respectively;

- (a8) an antigen-binding site comprising the of H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 96, 97, and 98 (H chain CDRs of Q405), respectively;
 - (a9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 99, 100, and 101 (H chain CDRs of Q458), respectively;

(a10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 102, 103, and 104 (H chain CDRs of Q460), respectively; (a11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 105, 106, and 107 (H chain CDRs of Q499), respectively; 5 (b1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 108, 109, and 110 (H chain CDRs of J232), respectively; (b2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 111, 112, and 113 (H chain CDRs of J259), respectively; (b3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 10 114, 115, and 116 (H chain CDRs of J268), respectively; (b4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 117, 118, and 119 (H chain CDRs of J300), respectively; (b5) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 120, 121, and 122 (H chain CDRs of J321), respectively; 15 (b6) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 123, 124, and 125 (H chain CDRs of J326), respectively; (b7) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 126, 127, and 128 (H chain CDRs of J327), respectively; (b8) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 20 129, 130, and 131 (H chain CDRs of J339), respectively; (b9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 132, 133, and 134 (H chain CDRs of J344), respectively; (b10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 135, 136, and 137 (H chain CDRs of J346), respectively; and 25 (b11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 174, 175, and 176 (H chain CDRs of J142), respectively; [5] the multispecific antigen-binding molecule of [3], wherein the antigen-binding site of the first polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences 30 selected from the following (a1) to (a11), or an antigen-binding site functionally equivalent thereto, and the antigenbinding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11), or an antigen-binding site functionally equivalent thereto: 35 (a1) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 35 (H chain variable region of Q1); (a2) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 36 (H chain variable region of Q31); (a3) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 37 (H 40 chain variable region of Q1); (a4) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 38 (H chain variable region of Q85); (a5) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 39 (H chain variable region of Q153); 45 (a6) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 40 (H chain variable region of Q354); (a7) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 41 (H chain variable region of Q360); (a8) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 42 (H 50 chain variable region of Q405); (a9) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 43 (H chain variable region of Q458); (a10) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 44 (H chain variable region of Q460); 55 (a11) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 45 (H chain variable region of Q499);

(b1) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 46 (H chain variable region of J232);

	(b2) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 47 (H
	chain variable region of J259);
	(b3) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 48 (H
5	chain variable region of J268); (b4) an antiagn hinding site comprising on Highein variable region aming acid acquence of SEO ID NO: 40 (Higher
5	(b4) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 49 (H chain variable region of J300);
	(b5) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 50 (H
	chain variable region of J321);
	(b6) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 51 (H
10	chain variable region of J326);
	(b7) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 52 (H
	chain variable region of J327);
	(b8) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 53 (H
45	chain variable region of J339);
15	(b9) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 54 (H
	chain variable region of J344); (b10) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 55
	(H chain variable region of J346); and
	(b11) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 172
20	(H chain variable region of J142);
	[6] the multispecific antigen-binding molecule of [3], wherein the antigen-binding sites included in the third polypeptide
	and the fourth polypeptide comprise an antigen-binding site which comprises L chain CDRs consisting of any one
	of the amino acid sequences selected from the following (c1) to (c10) or an antigen-binding site functionally equivalent
25	thereto:
	(c1) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 138,
	139, and 140 (L chain CDR of L2), respectively;
	(c2) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 141,
30	142, and 143 (L chain CDR of L45), respectively;
	(c3) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 144,
	145, and 146 (L chain CDR of L248), respectively;
	(c4) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 147,
25	148, and 149 (L chain CDR of L324), respectively;
35	(c5) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 150, 151, and 152 (L chain CDR of L334), respectively;
	(c6) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 153,
	154, and 155 (L chain CDR of L377), respectively;
	(c7) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 156,
40	157, and 158 (L chain CDR of L404), respectively;
	(c8) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 159,
	160, and 161 (L chain CDR of L406), respectively;
	(c9) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 137,
45	138, and 139 (L chain CDR of L408), respectively; and
45	(c10) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs:
	177, 178, and 179 (L chain CDR of L180), respectively;
	[7] the multispecific antigen-binding molecule of [3], wherein the antigen-binding sites included in the third polypeptide
	and the fourth polypeptide comprise an antigen-binding site which comprises an L chain variable region consisting
50	of any one of the amino acid sequences selected from the following (c1) to (c10), or an antigen-binding site functionally
	equivalent thereto:
	(c1) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 56 (L
55	chain variable region of L2);
55	(c2) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 57 (L chain variable region of L45);
	(c3) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 58 (L
	(or) an anagen binding site comprising an E chain variable region animo acid sequence of SEQ ID NO. 30 (E

chain variable region of L248);

	(c4) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 59 (L chain variable region of L324);
	(c5) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 60 (L chain variable region of L334);
5	(c6) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 61 (L chain variable region of L377);
	(c7) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 62 (L chain variable region of L404);
10	(c8) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 63 (L chain variable region of L406);
	(c9) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 64 (L chain variable region of L408); and
	(c10) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 173 (L chain variable region of L180);
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	 [8] the multispecific antigen-binding molecule of [3], wherein the first and second polypeptides further comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region; [9] the multispecific antigen-binding molecule of [3], wherein the first and second polypeptides comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region, and
20	wherein the third polypeptide and the fourth polypeptide are a commonly shared L chain; [10] the multispecific antigen-binding molecule of [8] or [9], wherein the first polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from the group consisting of the
	following (d1) to (d6) or the group consisting of the following (d7) to (d9), and the second polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from a group different
25	from that of the above-mentioned first polypeptide:
	(d1) an H chain constant region of SEQ ID NO: 65 (G4k);
	(d2) an H chain constant region of SEQ ID NO: 66 (z7); (d3) an H chain constant region of SEQ ID NO: 67 (z55);
30	(d4) an H chain constant region of SEQ ID NO: 68 (z106);
	(d5) an H chain constant region of SEQ ID NO: 69 (z118);
	(d6) an H chain constant region of SEQ ID NO: 70 (z121);
	(d7) an H chain constant region of SEQ ID NO: 71 (G4h); (d8) an H chain constant region of SEQ ID NO: 72 (z107); and
35	(d9) an H chain constant region of SEQ ID NO: 73 (z119);
	[11] the multispecific antigen-binding molecule of [8] or [9], wherein the third and fourth polypeptides comprise the antibody L chain constant region consisting of the following amino acid sequence of:
40	(e) an L chain constant region of SEQ ID NO: 74 (k);
45	[12] the multispecific antigen-binding molecule of [8] or [9], wherein the first polypeptide comprises any one antibody H chain selected from the following (a1) to (a14), the second polypeptide comprises any one antibody H chain selected from the following (b1) to (b12), and the third polypeptide and the fourth polypeptide comprise any one antibody L chain selected from the following (c1) to (c10):
	(a1) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 1 (Q1-G4k); (a2) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 2 (Q31-z7);
	(a3) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 3 (Q64-z55);
50	(a4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 10 (Q64-z7);
	(a5) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 11 (Q85-G4k); (a6) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 12 (Q153-G4k);
	(a7) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 12 (Q155-G4K);
	(a8) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 14 (Q360-G4k);
55	(a9) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 15 (Q360-z118);
	(a10) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 16 (Q405-G4k);
	(a11) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 17 (Q458-z106); (a12) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 18 (Q460-z121);

	(a13) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 19 (Q499-z118);
	(a14) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 20 (Q499-z121);
	(b1) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 4 (J268-G4h);
	(b2) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 5 (J321-G4h);
5	(b3) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 6 (J326-z107);
	(b4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 7 (J344-z107);
	(b5) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 21 (J232-G4h);
	(b6) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 22 (J259-z107);
	(b7) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 23 (J300-z107);
10	(b8) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 24 (J327-z107);
	(b9) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 25 (J327-z119);
	(b10) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 26 (J339-z119);
	(b11) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 27 (J346-z107);
	(b12) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 170 (J142-G4h);
15	(c1) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 8 (L2-k);
	(c2) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 9 (L45-k);
	(c3) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 28 (L248-k);
	(c4) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 29 (L324-k);
	(c5) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 30 (L334-k);
20	(c6) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 31 (L377-k);
	(c7) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 32 (L404-k);
	(c8) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 33 (L406-k);
	(c9) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 34 (L408-k); and
	(c10) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 171 (L180-k);
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	[13] the multispecific antigen-binding molecule of [1], wherein the first polypeptide comprises an antigen-binding
	site which binds to an epitope overlapping with an epitope that binds to an antibody consisting of the antibody H
	chain of any one of (a1) to (a14) and the antibody L chain of any one of (c1) to (c10) of [12], and the second
	polypeptide comprises an antigen-binding site which binds to an epitope overlapping with an epitope that binds to
30	an antibody consisting of the antibody H chain of any one of (b1) to (b12) and the antibody L chain of any one of
	(c1) to (c10) of [12];
	[14] the multispecific antigen-binding molecule of [8] or [9], wherein the first polypeptide comprises any one antibody
	H chain selected from the following (e1) to (e3), the second polypeptide comprises any one antibody H chain selected
	from the following (f1) to (f3), and the third polypeptide and the fourth polypeptide comprise any one antibody L
35	chain selected from the following (g1) to (g4):
	(e1) an H chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody
	consisting of an antibody H chain of any one of (a1) to (a14) and an antibody L chain of any one of (c1) to (c10), of [12];
40	(e2) an antibody H chain, wherein at least one amino acid residue selected from the amino acid residues at

idues at positions 34, 35, 49, 61, 62, 96, 98, 100, 100b, and 102 by Kabat numbering in any one antibody H chain selected from (e1) is substituted with another amino acid;

- (e3) an antibody H chain, wherein by Kabat numbering, the amino acid residue at position 34 is isoleucine, the amino acid residue at position 35 is asparagine, glutamine, or serine, the amino acid residue at position 49 is 45 serine, the amino acid residue at position 61 is arginine, the amino acid residue at position 62 is glutamic acid, the amino acid residue at position 96 is serine or threonine, the amino acid residue at position 98 is lysine or arginine, the amino acid residue at position 100 is phenylalanine or tyrosine, the amino acid residue at position 100b is glycine, or the amino acid residue at position 102 is tyrosine in any antibody H chain selected from (e1); (f1) an H chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody 50 consisting of an antibody H chain of any of (b1) to (b12) of [12] and an antibody L chain of any of (c1 to (c10) of [12]; (f2) an antibody H chain, wherein at least one amino acid residue selected from the amino acid residues at positions 35, 53, 73, 76, 96, 98, 100, and 100a by Kabat numbering in any antibody H chain of (f1) is substituted with another amino acid;
- (f3) an antibody H chain, wherein by Kabat numbering, the amino acid residue at position 35 is aspartic acid, 55 the amino acid residue at position 53 is arginine, the amino acid residue at position 73 is lysine, the amino acid residue at position 76 is glycine, the amino acid residue at position 96 is lysine or arginine, the amino acid residue at position 98 is tyrosine, the amino acid residue at position 100 is tyrosine, or the amino acid residue at position 100a is histidine in any one antibody H chain selected from (f1);

(g1) an L chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody which consists of an antibody H chain of any one of (a1) to (a14) and an antibody L chain of any one of (c1) to (c10), of [12];

(g2) an L chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody which consists of an antibody H chain of any one of (b1) to (b12) and an antibody L chain of any one of (c1) to (c10), of [12];

(g3) an antibody L chain, wherein at least one amino acid residue selected from the amino acid residues at positions 27, 30, 31, 32, 50, 52, 53, 54, 55, 92, 93, 94, and 95 by Kabat numbering in the antibody L chain of either (g1) or (g2) is substituted with another amino acid; and

(g4) an antibody L chain, wherein by Kabat numbering, the amino acid residue at position 27 is lysine or arginine, the amino acid residue at position 30 is glutamic acid, the amino acid residue at position 31 is arginine, the amino acid residue at position 32 is glutamine, the amino acid residue at position 52 is serine, the amino acid residue at position 53 is arginine, the amino acid residue at position 54 is lysine, the amino acid residue at position 55 is glutamic acid, the amino acid residue at position 54 is lysine, the amino acid residue at position 55 is glutamic acid, the amino acid residue at position 92 is serine, the amino acid residue at position 93 is serine, the amino acid residue at position 94 is proline, or the amino acid residue at position 95 is proline in the antibody L chain of either (g1) or (g2);

[15] the multispecific antigen-binding molecule of any one of [1] to [14], wherein the multispecific antigen-binding molecule is a multispecific antibody;

²⁰ [16] a bispecific antibody of any one of the following (a) to (u):

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(a) a bispecific antibody (Q1-G4k/J268-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;

- (b) a bispecific antibody (Q1-G4k/J321-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;
- 30 (c) a bispecific antibody (Q31-z7/J326-z107/L2-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 2, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 8;
- (d) a bispecific antibody (Q64-z55/J344-z107/L45-k), wherein the first polypeptide is an H chain consisting of
 the amino acid sequence of SEQ ID NO: 3, the second polypeptide is an H chain consisting of the amino acid
 sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain
 of SEQ ID NO: 9;

(e) a bispecific antibody (Q64-z7/J326-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(f) a bispecific antibody (Q64-z7/J344-z107/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

- (g) a bispecific antibody (Q85-G4k/J268-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;
- (h) a bispecific antibody (Q85-G4k/J321-G4h/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;
- (i) a bispecific antibody (Q153-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

(j) a bispecific antibody (Q354-z106/J259-z107/L324-k), wherein the first polypeptide is an H chain consisting

of the amino acid sequence of SEQ ID NO: 13, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 22, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 29;

(k) a bispecific antibody (Q360-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 14, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

(I) a bispecific antibody (Q360-z118/J300-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 15, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 23, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(m) a bispecific antibody (Q405-G4k/J232-G4h/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 16, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;

(n) a bispecific antibody (Q458-z106/J346-z107/L408-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 17, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 34;

- (o) a bispecific antibody (Q460-z121/J327-z119/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 18, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;
- (p) a bispecific antibody (Q499-z118/J327-z107/L334-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(q) a bispecific antibody (Q499-z118/J327-z107/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31;

(r) a bispecific antibody (Q499-z118/J346-z107/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;

- (s) a bispecific antibody (Q499-z121/J327-z119/L404-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 32;
- (t) a bispecific antibody (Q499-z121/J339-z119/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 26, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31; and
- (u) a bispecific antibody (Q153-G4k/J142-G4h/L180-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 170, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 171;

[17] a nucleic acid encoding the multispecific antigen-binding molecule of any one of [1] to [15] or the bispecific antibody of [16];

[18] a vector inserted with the nucleic acid of [17];

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[19] a cell comprising the nucleic acid of [17] or the vector of [18];

[20] a method for producing the multispecific antigen-binding molecule of any one of [1] to [15] or the bispecific antibody of [16] by culturing the cell of [19];

⁵⁵ [21] a pharmaceutical composition comprising the multispecific antigen-binding molecule of any one of [1] to [15] or the bispecific antibody of [16], and a pharmaceutically acceptable carrier;

[22] the composition of [21], which is a pharmaceutical composition used for prevention and/or treatment of bleeding, a disease accompanying bleeding, or a disease caused by bleeding;

[23] the composition of [22], wherein the bleeding, the disease accompanying bleeding, or the disease caused by bleeding is a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII;

[24] the composition of [23], wherein the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is hemophilia A;

[25] the composition of [23], wherein the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is a disease showing emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII;

[26] the composition of [23], wherein the disease that develops and/or progresses due to a decrease or deficiency
 in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is acquired hemophilia;
 [27] the composition of [23], wherein the disease that develops and/or progresses due to a decrease in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is von Willebrand disease;

[28] a method for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding, which comprises the step of administering the multispecific antigen-binding molecule of any one of [1] to [15] or the bispecific antibody of [16], or the composition of any one of [21] to [27]; and

[29] a kit for use in the prevention and/or treatment method of [28], which comprises at least the multispecific antigenbinding molecule of any one of [1] to [15] or the bispecific antibody of [16], or the composition of any one of [21] to [27].

[0011] Furthermore, the present invention relates to:

[30] use of the multispecific antigen-binding molecule of any one of [1] to [15], the bispecific antibody of [16], or the composition of any one of [21] to [27] in the manufacture of an agent for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding; and

[31] the multispecific antigen-binding molecule of any one of [1] to [15], the bispecific antibody of [16], or the composition of any one of [21] to [27] for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding.

[0012] The present invention also relates to bispecific antibodies that functionally substitute for F.VIII, a cofactor that enhances enzymatic reactions, and pharmaceutical compositions comprising the antibody as an active ingredient, and more specifically relates to:

[32] a bispecific antibody that functionally substitutes for blood coagulation factor VIII, which comprises a first antigenbinding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and a second antigen-binding site that recognizes blood coagulation factor X, wherein the bispecific antibody is any of the following (a) to (u):

35 (a) to (u

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(a) a bispecific antibody (Q1-G4k/J268-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;

(b) a bispecific antibody (Q1-G4k/J321-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;

- (c) a bispecific antibody (Q31-z7/J326-z107/L2-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 2, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 8;
- (d) a bispecific antibody (Q64-z55/J344-z107/L45-k), wherein the first polypeptide is an H chain consisting of
 the amino acid sequence of SEQ ID NO: 3, the second polypeptide is an H chain consisting of the amino acid
 sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain
 of SEQ ID NO: 9;

(e) a bispecific antibody (Q64-z7/J326-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(f) a bispecific antibody (Q64-z7/J344-z107/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid

sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

(g) a bispecific antibody (Q85-G4k/J268-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

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(h) a bispecific antibody (Q85-G4k/J321-G4h/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(i) a bispecific antibody (Q153-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

- (j) a bispecific antibody (Q354-z106/J259-z107/L324-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 13, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 22, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 29;
- (k) a bispecific antibody (Q360-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of SEQ ID NO: 14, the second polypeptide is an H chain consisting of the amino
 acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared
 L chain of SEQ ID NO: 33;
 - (I) a bispecific antibody (Q360-z118/J300-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 15, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 23, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(m) a bispecific antibody (Q405-G4k/J232-G4h/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 16, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;

- (n) a bispecific antibody (Q458-z106/J346-z107/L408-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 17, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 34;
- (o) a bispecific antibody (Q460-z121/J327-z119/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 18, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;
- (p) a bispecific antibody (Q499-z118/J327-z107/L334-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino
 acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared
 L chain of SEQ ID NO: 30;

(q) a bispecific antibody (Q499-z118/J327-z107/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31;

(r) a bispecific antibody (Q499-z118/J346-z107/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;

(s) a bispecific antibody (Q499-z121/J327-z119/L404-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 32;

⁵⁵ (t) a bispecific antibody (Q499-z121/J339-z119/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 26, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31; and

(u) a bispecific antibody (Q153-G4k/J142-G4h/L180-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 170, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 171;

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[33] a nucleic acid encoding the bispecific antibody of [32];

- [34] a vector inserted with the nucleic acid of [33];
- [35] a cell comprising the nucleic acid of [33] or the vector of [34];
- [36] a method for producing the bispecific antibody of [32] by culturing the cell of [35];
- ¹⁰ [37] a pharmaceutical composition comprising the bispecific antibody of [32], and a pharmaceutically acceptable carrier;

[38] the composition of [37], which is a pharmaceutical composition used for prevention and/or treatment of bleeding, a disease accompanying bleeding, or a disease caused by bleeding;

[39] the composition of [38], wherein the bleeding, the disease accompanying bleeding, or the disease caused by
 ¹⁵ bleeding is a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII;
 [40] the composition of [20] wherein the disease that develops and/or progresses are deficiency.

[40] the composition of [39], wherein the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is hemophilia A;

[41] the composition of [39], wherein the disease that develops and/or progresses due to a decrease or deficiency
 in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is a disease showing emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII;
 [42] the composition of [39], wherein the disease that develops and/or progresses due to a decrease or deficiency

[42] the composition of [69], wherein the disease that develops and/or progresses due to a decrease of derivativity in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is acquired hemophilia;
 [43] the composition of [39], wherein the disease that develops and/or progresses due to a decrease in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is acquired hemophilia;

[44] a method for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding, which comprises the step of administering the bispecific antibody of [32] or the composition of any one of [37] to [43];

[32] of the composition of any one of [37] to [43]; [45] a kit for use in the prevention and/or treatment method of [44], wi

[45] a kit for use in the prevention and/or treatment method of [44], which comprises the bispecific antibody of [32], or the composition of any one of [37] to [43];

[46] use of the bispecific antibody of [32] or the composition of any one of [37] to [43] in the manufacture of an agent for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding; and [47] the bispecific antibody of [32] or the composition of any one of [37] to [43] for preventing and/or treating bleeding, a disease accompanying bleeding.

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[Effects of the Invention]

[0013] The present invention provides antibodies that recognize both an enzyme and its substrate, which are multi-specific antigen-binding molecules having a high activity of functionally substituting for F.VIII. Furthermore, the present invention provides antibodies that recognize both an enzyme and its substrate, which are multispecific antigen-binding molecules having a high activity of functionally substituting for F.VIII and a low F.Xase inhibitory action. Since humanized antibodies are generally thought to have high stability in blood and low immunogenicity, multispecific antibodies of the present invention may be very promising as pharmaceuticals.

⁴⁵ Brief Description of the Drawings

[0014]

Fig. 1 describes the F.Xase inhibitory action.

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- (a) F.VIIIa forms a complex with F.IXa (F.Xase) and activates F.X.
- (b) A bispecific antibody binds to F.IXa and F.X and activates F.X.
- (c) Both F.VIIIa and the bispecific antibody activate F.X without competition.

(d) Binding of the bispecific antibody to F.IXa and/or F.X inhibits the formation of the complex formed between F.Xase and F.X.

(e) Binding of the bispecific antibody to F.IXa and/or F.X inhibits the activity of F.Xase.

Fig. 2 describes the screening. Approximately 200 types each of genes for antibodies against human F.IXa and

human F.X were produced, and they were incorporated into animal cell expression vectors. 40,000 or more bispecific antibodies as a combination of an anti-F.IXa antibody and anti-F.X antibody were transiently expressed. F.Xa generation-promoting activity and F.Xase inhibitory action were evaluated to screen for bispecific antibodies having a high F.Xa generation-promoting activity and a low F.Xase inhibitory action. Furthermore, by substituting amino acids when necessary, prototype antibodies were produced.

- ⁵ when necessary, prototype antibodies were produced.
 Fig. 3 shows the F.Xa generation-promoting activities of hA69-KQ/hB26-PF/hAL-AQ, Q1-G4k/J268-G4h/L45-k, Q1-G4k/J321-G4h/L45-k, Q31-z7/J326-z107/L2-k, and Q64-z55/J344-z107/L45-k. The concentrations of the antibody solutions were 300, 30, and 3 µg/mL (the concentrations after mixing Human Factor IXa, Novact (registered trademark) M, Human Factor X, and the antibody solution were 100, 10, and 1 µg/mL), the enzyme reaction and color
- development were performed for ten minutes and 50 minutes, respectively. As a result, these antibodies showed a higher F.Xa generation-promoting activity compared to hA69-KQ/hB26-PF/hAL-AQ described in WO 2006/109592.
 Fig. 4 shows the F.Xa generation-promoting activity of hA69-KQ/hB26-PF/hAL-AQ, prototype antibodies, and modified antibodies with amino acid substitutions. The concentrations of the antibody solutions were 300, 30, and 3 μg/mL (the concentrations after mixing Human Factor IXa, Novact (registered trademark) M, Human Factor X, and
- ¹⁵ the antibody solution were 100, 10, and 1 μg/mL), the enzyme reaction and color development were performed for two minutes and 20 minutes, respectively. As a result, these modified antibodies showed a higher F.Xa generation-promoting activity compared to the prototype antibodies.
 Fig. 5 shows the E Xaaa inhibitary action of hA60 KO/kD26 DE/hAL A0, pretative, antibodies, and madified anti-

Fig. 5 shows the F.Xase inhibitory action of hA69-KQ/hB26-PF/hAL-AQ, prototype antibodies, and modified antibodies with amino acid substitutions.

- 20 The figure shows the effects of hA69-KQ/hB26-PF/hAL-AQ, Q1-G4k/J268-G4h/L45-k, Q31-z7/J326-z107/L2-k, Q1-G4k/J321-G4h/L45-k, Q64-z55/J344-z107/L45-k, Q85-G4k/J268-G4h/L406-k, Q85-G4k/J321-G4h/L334-k, Q64-z7/J344-z107/L406-k, Q64-z7/J326-z107/L334-k, Q153-G4k/J142-G4h/L180-k, Q405-G4k/J232-G4h/L248-k, Q360-G4k/J232-G4h/L406-k, Q153-G4k/J232-G4h/L406-k, Q458-z106/J346-z107/L408-k, Q360-z118/J300-z107/L334-k, Q499-z118/J327-z107/L377-k, Q499-z121/J327-z119/L404-k, Q499-z121/J339-z119/L377-k, Q499-z121/J327-z107/L334-k
- 25 z118/J346-z107/L248-k, Q354-z106/J259-z107/L324-k, Q460-z121/J327-z119/L334-k, and Q499-z118/J327-z107/L334-k on F.X activation by F.IXa in the presence of F.VIIIa. The F.Xase inhibitory actions of the antibodies are indicated as the value obtained by subtracting the absorbance of the antibody-free reaction solution from the absorbance of the antibody-supplemented reaction solution. The concentrations of the antibody solutions were 300 and 30 μg/mL (the concentrations after mixing Human Factor IXa, F.VIIIa, Human Factor X, and the antibody solution
- 30 were 100 and 10 μg/mL), the enzyme reaction and color development were performed for six minutes and 14 minutes, respectively. The more positive the value of F.Xase inhibitory action shown on the horizontal axis, the weaker the F.Xase inhibitory action is. As a result, hA69-KQ/hB26-PF/hAL-AQ described in WO 2006/109592 showed strong F.Xase inhibitory action. All of the antibodies of the present invention showed weaker F.Xase inhibitory action compared to hA69-KQ/hB26-PF/hAL-AQ, or did not show inhibitory action.
- Fig. 6A shows the amino acid sequences of the prototype antibodies and the modified antibodies with amino acid substitutions. When the sequence name is not indicated in the Ref column, the variable region sequence of the Name column is mentioned. A"- (hyphen)" is shown where an amino acid is absent at the number by Kabat numbering. A ". (dot)" is shown where amino acid is the same when comparing the variable region of the Name column and the Ref column, and the amino acid of the variable region of the Name column is shown where the amino acids are
- different. Amino acids found to be important for improvement of F.Xa generation-promoting activity were indicated by framing them.

Fig. 6B is a continuation of Fig. 6A.

Fig. 6C is a continuation of Fig. 6B.

Fig. 6D is a continuation of Fig. 6C.

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Mode for Carrying Out the Invention

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[0015] Multispecific antigen-binding molecules described herein comprise a first antigen-binding site and a second antigen-binding site that can specifically bind to at least two different types of antigens. While the first antigen-binding site and the second antigen-binding site are not particularly limited as long as they have an activity to bind to F.IX and/or F.IXa, and F.X, respectively, examples include sites necessary for binding with antigens, such as antibodies, scaffold molecules (antibody-like molecules) or peptides, or fragments containing such sites. Scaffold molecules are molecules that exhibit function by binding to target molecules, and any polypeptide may be used as long as they are conformationally stable polypeptides that can bind to at least one target antigen. Examples of such polypeptides include antibody variable

⁵⁵ regions, fibronectin (WO 2002/032925), protein A domain (WO 1995/001937), LDL receptor A domain (WO 2004/044011, WO 2005/040229), ankyrin (WO 2002/020565), and such, and also molecules described in documents by Nygren et al. (Current Opinion in Structural Biology, 7: 463-469 (1997); and Journal of Immunol Methods, 290: 3-28 (2004)), Binz et al. (Nature Biotech 23: 1257-1266 (2005)), and Hosse et al. (Protein Science 15: 14-27(2006)). Furthermore, as mentioned

in Curr Opin Mol Ther. 2010 Aug; 12(4): 487-95 and Drugs. 2008; 68(7): 901-12, peptide molecules that can bind to target antigens may be used.

[0016] Herein, multispecific antigen-binding molecules are not particularly limited as long as they are molecules that can bind to at least two different types of antigens, but examples include polypeptides containing the above-mentioned

- ⁵ antigen-binding sites, such as antibodies and scaffold molecules as well as their fragments, and aptamers comprising nucleic acid molecules and peptides, and they may be single molecules or multimers thereof. Preferred multispecific antigen-binding molecules include multispecific antibodies that can bind specifically to at least two different antigens. Particularly preferred examples of antibodies which have an activity of functionally substituting for F.VIII of the present invention include bispecific antibodies (BsAb) that can bind specifically to two different antigens (they may also be called
- ¹⁰ dual specific antibodies).

[0017] In the present invention, the term "commonly shared L chain" refers to an L chain that can link with two or more different H chains, and show binding ability to each antigen. Herein, the term "different H chain(s)" preferably refers to H chains of antibodies against different antigens, but is not limited thereto, and also refers to H chains whose amino acid sequences are different from each other. Commonly shared L chain can be obtained, for example, according to the method described in WO 2006/109592.

- ¹⁵ method described in WO 2006/109592. [0018] The multispecific antigen-binding molecules of the present invention (preferably bispecific antibodies) are antibodies having specificity to two or more different antigens, or molecules comprising fragments of such antibodies. The antibodies of the present invention are not particularly limited, but are preferably monoclonal antibodies. Monoclonal antibodies used in the present invention include not only monoclonal antibodies derived from animals such as humans,
- ²⁰ mice, rats, hamsters, rabbits, sheep, camels, and monkeys, but also include artificially modified gene recombinant antibodies such as chimeric antibodies, humanized antibodies, and bispecific antibodies.
 [0019] Furthermore, the L chains of an antibody which will become a multispecific antigen-binding molecule of the present invention may be different, but preferably have commonly shared L chains.
- [0020] Multispecific antigen-binding molecules of the present invention are preferably recombinant antibodies produced using genetic recombination techniques (See, for example, Borrebaeck CAK and Larrick JW, THERAPEUTIC MONO-CLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990). Recombinant antibodies can be obtained by cloning DNAs encoding antibodies from hybridomas or antibody-producing cells, such as sensitized lymphocytes, that produce antibodies, inserting them into suitable vectors, and then introducing them into hosts (host cells) to produce the antibodies.
- [0021] Furthermore, antibodies of the present invention may include not only whole antibodies but also antibody fragments and low-molecular-weight antibodies (minibodies), and modified antibodies.
 [0022] For example, antibody fragments or minibodies include diabodies (Dbs), linear antibodies, and single chain antibody (hereinafter, also denoted as scFvs) molecules. Herein, an "Fv" fragment is defined as the smallest antibody fragment that comprises a complete antigen recognition site and binding site.
- 35 [0023] An "Fv" fragment is a dimer (VH-VL dimer) in which an H chain variable region (VH) and an L chain variable region (VL) are strongly linked by non-covalent binding. The three complementarity determining regions (CDRs) of each of the variable regions interact with each other to form an antigen-binding site on the surface of the VH-VL dimer. Six CDRs confer the antigen-binding site to an antibody. However, one variable region (or half of the Fv comprising only three CDRs specific to an antigen) alone can recognize and bind to an antigen, though its affinity is lower than that of the entire binding site.
- **[0024]** An Fab fragment (also called F(ab)) further comprises an L chain constant region and an H chain constant region (CH1). An Fab' fragment differs from an Fab fragment in that it additionally comprises several residues derived from the carboxyl terminus of the H chain CH1 region, comprising one or more cysteines from the hinge region of the antibody. Fab'-SH refers to an Fab' in which one or more cysteine residues of its constant region comprise a free thiol
- ⁴⁵ group. An F(ab') fragment is produced by cleavage of disulfide bonds between the cysteine residues in the hinge region of F(ab')₂ pepsin digest. Other chemically bound antibody fragments are also known to those skilled in the art.
 [0025] Diabodies are bivalent minibodies constructed by gene fusion (Holliger, P. et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993); EP 404,097; WO 93/11161). Diabodies are dimers consisting of two polypeptide chains, in which each polypeptide chain comprises an L chain variable region (VL) and an H chain variable region (VH) linked with a
- 50 linker short enough to prevent association of these two domains within the same chain, for example, a linker of preferably 2 to 12 amino acids, more preferably 3 to 10 amino acids, particularly about 5 amino acids. The polypeptide chain form a dimer since the linker between the VL and VH encoded on the same polypeptide is too short to form a single chain variable region fragment. Therefore, diabodies comprise two antigen-binding sites.
- [0026] A single-chain antibody or an scFv antibody fragment comprises the VH and VL regions of an antibody, and these regions exist in a single polypeptide chain. In general, an Fv polypeptide further comprises a polypeptide linker between the VH and VL regions, and this enables an scFv to form a structure necessary for antigen binding (for a review on scFvs, see Pluckthun "The Pharmacology of Monoclonal Antibodies" Vol. 113 (Rosenburg and Moore ed. (Springer Verlag, New York) pp.269-315, 1994). In the context of the present invention, linkers are not particularly limited so long

as they do not inhibit the expression of the antibody variable regions linked at their ends.

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[0027] IgG-type bispecific antibodies can be secreted from hybrid hybridomas (quadromas) produced by fusing two kinds of hybridomas that produce IgG antibodies (Milstein C et al. Nature 1983, 305: 537-540). They can also be secreted by taking the L chain and H chain genes constituting the two kinds of IgGs of interest, a total of four kinds of genes, and introducing them into cells to coexpress the genes.

- **[0028]** In this case, by introducing suitable amino acid substitutions to the CH3 regions of the H chains, IgGs having a heterogeneous combination of H chains can be preferentially secreted (Ridgway JB et al. Protein Engineering 1996, 9: 617-621; Merchant AM et al. Nature Biotechnology 1998, 16: 677-681; WO 2006/106905; Davis JH et al. Protein Eng Des Sel. 2010, 4: 195-202).
- 10 [0029] Regarding the L chains, since diversity of L chain variable regions is lower than that of H chain variable regions, commonly shared L chains that can confer binding ability to both H chains may be obtained. The antibodies of the present invention comprise commonly shared L chains. Bispecific IgGs can be efficiently expressed by introducing the genes of the commonly shared L chain and both H chains into cells.
- [0030] Bispecific antibodies may be produced by chemically crosslinking Fab's. Bispecific F(ab')₂ can be produced, for example, by preparing Fab' from an antibody, using it to produce a maleimidized Fab' with ortho-phenylenedimaleimide (o-PDM), and then reacting this with Fab' prepared from another antibody to crosslink Fab's derived from different antibodies (Keler T et al. Cancer Research 1997, 57: 4008-4014). The method of chemically linking an Fab'thionitrobenzoic acid (TNB) derivative and an antibody fragment such as Fab'-thiol (SH) is also known (Brennan M et al. Science 1985, 229: 81-83).
- 20 [0031] Instead of a chemical crosslink, a leucine zipper derived from Fos and Jun may also be used. Preferential formation of heterodimers by Fos and Jun is utilized, even though they also form homodimers. Fab' to which Fos leucine zipper is added, and another Fab' to which Jun leucine zipper is added are expressed and prepared. Monomeric Fab'-Fos and Fab'-Jun reduced under mild conditions are mixed and reacted to form bispecific F(ab')₂ (Kostelny SA et al. J. of Immunology, 1992, 148: 1547-53). This method can be applied not only to Fab's but also to scFvs, Fvs, and such.
- [0032] Furthermore, bispecific antibodies including sc(Fv)₂ such as IgG-scFv (Protein Eng Des Sel. 2010 Apr; 23(4): 221-8) and BiTE (Drug Discov Today. 2005 Sep 15; 10(18): 1237-44.), DVD-Ig (Nat Biotechnol. 2007 Nov; 25(11): 1290-7. Epub 2007 Oct 14.; and MAbs. 2009 Jul; 1(4): 339-47. Epub 2009 Jul 10.), and also others (IDrugs 2010, 13: 698-700) including two-in-one antibodies (Science. 2009 Mar 20; 323(5921): 1610-4; and Immunotherapy. 2009 Sep; 1(5): 749-51.), Tri-Fab, tandem scFv, and diabodies are known (MAbs. 2009 November; 1(6): 539-547). In addition,
- ³⁰ even when using molecular forms such as scFv-Fc and scaffold-Fc, bispecific antibodies can be produced efficiently by preferentially secreting a heterologous combination of Fcs (Ridgway JB et al., Protein Engineering 1996, 9: 617-621; Merchant AM et al. Nature Biotechnology 1998, 16: 677-681; WO 2006/106905; and Davis JH et al., Protein Eng Des Sel. 2010, 4: 195-202.).
- [0033] A bispecific antibody may also be produced using a diabody. A bispecific diabody is a heterodimer of two crossover scFv fragments. More specifically, it is produced by forming a heterodimer using VH(A)-VL(B) and VH(B)-VL(A) prepared by linking VHs and VLs derived from two kinds of antibodies, A and B, using a relatively short linker of about 5 residues (Holliger P et al. Proc Natl. Acad. Sci. USA 1993, 90: 6444-6448).

[0034] The desired structure can be achieved by linking the two scFvs with a flexible and relatively long linker comprising about 15 residues (single chain diabody: Kipriyanov SM et al. J. of Molecular Biology. 1999, 293: 41-56), and conducting appropriate amino acid substitutions (knobs-into-holes: Zhu Z et al. Protein Science. 1997, 6: 781-788; VH/VL interface engineering: Igawa T et al. Protein Eng Des Sel. 2010, 8: 667-77).

[0035] An sc(Fv)₂ that can be produced by linking two types of scFvs with a flexible and relatively long linker, comprising about 15 residues, may also be a bispecific antibody (Mallender WD et al. J. of Biological Chemistry, 1994, 269: 199-206).
 [0036] Examples of modified antibodies include antibodies linked to various molecules such as polyethylene glycol

(PEG). The antibodies of the present invention include such modified antibodies. In the context of the present invention, the substance to which the modified antibodies are linked is not limited. Such modified antibodies can be obtained by chemically modifying obtained antibodies. Such methods are well established in the art.

[0037] The antibodies of the present invention include human antibodies, mouse antibodies, rat antibodies, or such, and their origins are not limited. They may also be genetically modified antibodies, such as chimeric or humanized antibodies.

[0038] Methods for obtaining human antibodies are known in the art. For example, transgenic animals carrying the entire repertoire of human antibody genes can be immunized with desired antigens to obtain desired human antibodies (see International Patent Application WO 93/12227, WO 92/03918, WO 94/02602, WO 94/25585, WO 96/34096, and WO 96/33735).

⁵⁵ **[0039]** Genetically modified antibodies can also be produced using known methods. Specifically, for example, chimeric antibodies may comprise H chain and L chain variable regions of an immunized animal antibody, and H chain and L chain constant regions of a human antibody. Chimeric antibodies can be obtained by linking DNAs encoding the variable regions of the antibody derived from the immunized animal, with DNAs encoding the constant regions of a human

antibody, inserting this into an expression vector, and then introducing it into host cells to produce the antibodies. [0040] Humanized antibodies are modified antibodies often referred to as "reshaped" human antibodies. A humanized antibody is constructed by transferring the CDRs of an antibody derived from an immunized animal to the complementarity determining regions of a human antibody. Conventional genetic recombination techniques for such purposes are known

- ⁵ (see European Patent Application Publication No. EP 239400; International Publication No. WO 96/02576; Sato K et al., Cancer Research 1993, 53: 851-856; International Publication No. WO 99/51743).
 [0041] The multispecific antigen-binding molecules of the present invention are those that recognize and/or F.IXa, and F.X, and functionally substitute for cofactor function of F.VIII, and characterized in that the molecules have a higher F.Xa generation-promoting activity compared to hA69-KQ/hB26-PF/hAL-AQ (described in WO 2006/109592) which is
- 10 known as a bispecific antibody that functionally substitutes for F.VIII. Furthermore, antibodies of the present invention usually have a structure which comprises a variable region of an anti-F.IXa antibody and a variable region of an anti-F.X antibody.

[0042] More specifically, the present invention provides a multispecific antigen-binding molecule that functionally substitutes for F.VIII, which comprises a first antigen-binding site that recognizes and/or F.IXa and a second antigen-binding

- ¹⁵ site that recognizes F.X, wherein the function that substitutes for the function of F.VIII is caused by a higher F.Xa generation-promoting activity compared to the activity of the bispecific antibody (hA69-KQ/hB26-PF/hAL-AQ) which comprises H chains consisting of SEQ ID NOs: 165 and 166, and a commonly shared L chain consisting of SEQ ID NO: 167.
- [0043] A multispecific antigen-binding molecule of the present invention comprises a first polypeptide and a third ²⁰ polypeptide comprising an antigen-binding site that recognizes and/or F.IXa, and a second polypeptide and a fourth polypeptide comprising an antigen-binding site that recognizes F.X. The first polypeptide and the third polypeptide, and the second polypeptide and the fourth polypeptide each include the antigen-binding site of the antibody H chain and the antigen-binding site of the antibody L chain.
- [0044] For example, in a multispecific antigen-binding molecule of the present invention, the first polypeptide and the third polypeptide include an antigen-binding site of an H chain and L chain of an antibody against or F.IXa, respectively; and the second polypeptide and the fourth polypeptide comprise an antigen-binding site of an H chain and L chain of an antibody against F.X, respectively.

[0045] At this time, the antigen-binding sites of the antibody L chain included in the first polypeptide and the third polypeptide, and the second polypeptide and the fourth polypeptide may be commonly shared L chains.

- 30 [0046] A polypeptide comprising an antigen-binding site of an antibody L chain in the present invention is preferably a polypeptide which comprises all or a part of the sequence of the antibody L chain which binds to F.IX, F.IXa and/or F.X.
 [0047] Preferred embodiments of the antigen-binding site of the first polypeptide of an antibody of the present invention specifically include antigen-binding sites comprising the amino acid sequences of:
- Q1 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 75, 76, and 77, respectively);
 Q31 H chain each CDR1, 2, and 3 sequences (SEQ ID NOs: 78, 79, and 80, respectively);
 Q64 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 81, 82, and 83, respectively);
 Q85 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 84, 85, and 86, respectively);
 Q153 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 87, 88, and 89, respectively);
 Q354 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 90, 91, and 92, respectively);
 Q360 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 93, 94, and 95, respectively);
 Q405 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 96, 97, and 98, respectively);
 Q458 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 99, 100, and 101, respectively);
 Q460 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 102, 103, and 104, respectively); and
 Q499 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 105, 106, and 107, respectively) mentioned in the
 - later-described Examples, or antigen-binding sites that are functionally equivalent to them.

[0048] Preferred embodiments of the antigen-binding site of a second polypeptide specifically include, for example, antigen-binding sites comprising the amino acid sequences of:

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J232 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 108, 109, and 110, respectively); J259 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 111, 112, and 113, respectively); J268 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 114, 115, and 116, respectively); J300 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 117, 118, and 119, respectively); J321 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 120, 121, and 122, respectively); J326 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 123, 124, and 125, respectively); J327 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 126, 127, and 128, respectively); J339 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 129, 130, and 131, respectively);

J344 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 132, 133, and 134, respectively);

- J346 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 135, 136, and 137, respectively); and
- J142 H chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 174, 175, and 176, respectively) mentioned in the laterdescribed Examples, or antigen-binding sites that are functionally equivalent to them.
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[0049] More specifically, the present invention provides multispecific antigen-binding molecules, wherein the antigenbinding site of the first polypeptide comprises an antigen-binding site which comprises H chain CDRs consisting of any one of the amino acid sequences selected from the following (a1) to (a11), or an antigen-binding site functionally equivalent thereto, and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises H 10 chain CDRs consisting of any one of the amino acid sequences selected from the following (b1) to (b11), or an antigenbinding site functionally equivalent thereto: (a1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 75, 76, and 77 (H chain CDRs of Q1), respectively; 15 (a2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 78, 79, and 80 (H chain CDRs of Q31), respectively; (a3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 81, 82, and 83 (H chain CDRs of Q64), respectively; (a4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 84, 85, and 86 (H chain CDRs of Q85), respectively; 20 (a5) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 87, 88, and 89 (H chain CDRs of Q153), respectively; (a6) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 90, 91, and 92 (H chain CDRs of Q354), respectively; 25 (a7) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 93, 94, and 95 (H chain CDRs of Q360), respectively; (a8) an antigen-binding site comprising the of H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 96, 97, and 98 (H chain CDRs of Q405), respectively; (a9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 99, 100, 30 and 101 (H chain CDRs of Q458), respectively; (a10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 102, 103, and 104 (H chain CDRs of Q460), respectively; (a11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 105, 106, and 107 (H chain CDRs of Q499), respectively; 35 (b1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 108, 109, and 110 (H chain CDRs of J232), respectively; (b2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 111, 112, and 113 (H chain CDRs of J259), respectively; (b3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 114, 40 115, and 116 (H chain CDRs of J268), respectively; (b4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 117, 118, and 119 (H chain CDRs of J300), respectively; (b5) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 120, 121, and 122 (H chain CDRs of J321), respectively; 45 (b6) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 123, 124, and 125 (H chain CDRs of J326), respectively; (b7) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 126, 127, and 128 (H chain CDRs of J327), respectively; (b8) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 129, 50 130, and 131 (H chain CDRs of J339), respectively; (b9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 132, 133, and 134 (H chain CDRs of J344), respectively; (b10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 135, 136, and 137 (H chain CDRs of J346), respectively; and 55 (b11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 174, 175, and 176 (H chain CDRs of J142), respectively.

[0050] Preferred embodiments of the antigen-binding site of the third and fourth polypeptides specifically include, for

example, antigen-binding sites comprising the amino acid sequences of:

L2 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 138, 139, and 140, respectively); L45 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 141, 142, and 143, respectively); 5 L248 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 144, 145, and 146, respectively); L324 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 147, 148, and 149, respectively); L334 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 150, 151, and 152, respectively); L377 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 153, 154, and 155, respectively); L404 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 156, 157, and 158, respectively); 10 L406 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 159, 160, and 161, respectively); L408 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 162, 163, and 164, respectively); and L180 L chain each CDR1, 2, and 3 sequence (SEQ ID NOs: 177, 178, and 179, respectively) mentioned in the laterdescribed Examples, or antigen-binding sites that are functionally equivalent to them. 15 [0051] More specifically, the present invention provides multispecific antigen-binding molecules, wherein the antigenbinding sites included in the third polypeptide and the fourth polypeptide comprise an antigen-binding site which comprises L chain CDRs consisting of any one of the amino acid sequences selected from the following (c1 to (c10), or an antigenbinding site functionally equivalent thereto: 20 (c1) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 138, 139, and 140 (L chain CDR of L2), respectively; (c2) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 141, 142, and 143 (L chain CDR of L45), respectively; (c3) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 144, 145, 25 and 146 (L chain CDR of L248), respectively; (c4) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 147, 148, and 149 (L chain CDR of L324), respectively; (c5) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 150, 151, and 152 (L chain CDR of L334), respectively; 30 (c6) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 153, 154, and 155 (L chain CDR of L377), respectively;

(c7) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 156, 157, and 158 (L chain CDR of L404), respectively;

(c8) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 159, 160, and 161 (L chain CDR of L406), respectively;

(c9) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 137, 138, and 139 (L chain CDR of L408), respectively; and

(c10) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 177, 178, and 179 (L chain CDR of L180), respectively.

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[0052] The amino acid sequences of the H chain variable regions of Q1, Q31, Q64, Q85, Q153, Q354, Q360, Q405, Q458, Q460, and Q499 of the present invention are indicated by the following SEQ ID NOs, respectively.

Q1: SEQ ID NO: 35 Q31: SEQ ID NO: 36 Q64: SEQ ID NO: 37 Q85: SEQ ID NO: 38 Q153: SEQ ID NO: 39 Q354: SEQ ID NO: 40 50 Q360: SEQ ID NO: 41 Q405: SEQ ID NO: 42 Q458: SEQ ID NO: 43 Q460: SEQ ID NO: 44 Q499: SEQ ID NO: 45

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[0053] The amino acid sequences of the H chain variable regions of J232, J259, J268, J300, J321, J326, J327, J339, J344, J346, and J142 of the present invention are indicated by the following SEQ ID NOs, respectively.

	J232: SEQ ID NO: 46
	J259: SEQ ID NO: 47
	J268: SEQ ID NO: 48
	J300: SEQ ID NO: 49
5	J321: SEQ ID NO: 50
	J326: SEQ ID NO: 51
	J327: SEQ ID NO: 52
	J339: SEQ ID NO: 53
	J344: SEQ ID NO: 54
10	J346: SEQ ID NO: 55
	J142: SEQ ID NO: 172

[0054] More specifically, the present invention provides multispecific antigen-binding molecules, wherein the antigen-binding site of the first polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (a1) to (a11), or an antigen-binding site functionally equivalent thereto, and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (a1) to (a11), or an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11), or an antigen-binding site functionally equivalent thereto:

20 (a1) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 35 (H chain variable region of Q1); (a2) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 36 (H chain variable region of Q31); (a3) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 37 (H chain 25 variable region of Q1): (a4) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 38 (H chain variable region of Q85); (a5) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 39 (H chain variable region of Q153); 30 (a6) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 40 (H chain variable region of Q354); (a7) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 41 (H chain variable region of Q360); (a8) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 42 (H chain 35 variable region of Q405); (a9) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 43 (H chain variable region of Q458); (a10) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 44 (H chain variable region of Q460): 40 (a11) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 45 (H chain variable region of Q499); (b1) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 46 (H chain variable region of J232); (b2) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 47 (H chain 45 variable region of J259); (b3) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 48 (H chain variable region of J268); (b4) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 49 (H chain variable region of J300); 50 (b5) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 50 (H chain variable region of J321); (b6) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 51 (H chain variable region of J326); (b7) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 52 (H chain 55 variable region of J327); (b8) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 53 (H chain variable region of J339); (b9) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 54 (H chain

variable region of J344);

(b10) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 55 (H chain variable region of J346); and

(b11) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 172 (H chain variable region of J142).

[0055] In addition, the amino acid sequences of the L chain variable regions of L2, L45, L248, L324, L334, L377, L404, L406, L408, and L180 of the present invention are indicated by the following SEQ ID NOs, respectively.

10	L2: SEQ ID NO: 56 L45: SEQ ID NO: 57
	L248: SEQ ID NO: 58
	L324: SEQ ID NO: 59
	L334: SEQ ID NO: 60
15	L377: SEQ ID NO: 61
	L404: SEQ ID NO: 62
	L406: SEQ ID NO: 63
	L408: SEQ ID NO: 64
	L180: SEQ ID NO: 173

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[0056] More specifically, the present invention provides multispecific antigen-binding molecules, wherein the antigenbinding sites included in the third polypeptide and the fourth polypeptide comprise an antigen-binding site which comprises an L chain variable region consisting of any one of the amino acid sequences selected from the following (c1 to (c10) or an antigen-binding site functionally equivalent thereto:

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(c1) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 56 (L chain variable region of L2);

(c2) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 57 (L chain variable region of L45);

(c3) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 58 (L chain variable region of L248);

(c4) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 59 (L chain variable region of L324);

(c5) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 60 (L chain variable region of L334);

(c6) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 61 (L chain variable region of L377);

(c7) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 62 (L chain variable region of L404);

40 (c8) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 63 (L chain variable region of L406);

(c9) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 64 (L chain variable region of L408); and

(c10) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 173 (L chain variable region of L180).

[0057] The amino acid sequences of CDR1 to 3 and FR1 to 4 in each of the sequences are as described in Figs. 3A to D [0058] When producing a full-length antibody using the variable regions disclosed in the present invention, without particular limitations, constant regions well known to those skilled in the art may be used. For example, constant regions described in "Sequences of proteins of immunological interest", (1991), U.S. Department of Health and Human Services.

- ⁵⁰ described in "Sequences of proteins of immunological interest", (1991), U.S. Department of Health and Human Services. Public Health Service National Institutes of Health, or "An efficient route to human bispecific IgG", (1998). Nature Biotechnology vol. 16, 677-681 can be used. Preferred examples of the antibody constant regions of the present invention include the constant regions of IgG antibodies. When using the constant region of an IgG antibody, its type is not limited, and a constant region of IgG subclass such as IgG1, IgG2, IgG3, or IgG4 may be used. Furthermore, amino acid
- ⁵⁵ mutations may be introduced into the constant region of these IgG subclasses. Amino acid mutations to be introduced may be, for example, those that enhance or decrease binding to Fcγ receptors (Proc Natl Acad Sci USA. 2006 Mar 14; 103(11): 4005-10; and MAbs. 2009 Nov; 1(6): 572-9), or enhance or decrease binding to FcRn (J Biol Chem. 2001 Mar 2; 276(9): 6591-604; Int Immunol. 2006 Dec; 18(12): 1759-69; and J Biol Chem. 2006 Aug 18; 281(33): 23514-24), but

are not limited thereto. Two types of H chains must be heterologously associated to produce a bispecific antibody. The knobs-into-holes technology (J Immunol Methods. 2001 Feb 1; 248(1-2): 7-15; and J Biol Chem. 2010 Jul 2; 285(27): 20850-9), the electrostatic repulsion technology (WO 2006/106905), the SEEDbody technology (Protein Eng Des Sel. 2010 Apr; 23(4): 195-202), and such may be used for heterologous association of two types of H chains *via* a CH3

- ⁵ domain. Furthermore, the antibodies of the present invention may be those with a modified or deficient sugar chain. Examples of antibodies having modified sugar chains include glycosylation-engineered antibodies (such as WO 99/54342), antibodies with defucosylated sugar chains (WO 00/61739, WO 02/31140, WO 2006/067847, WO 2006/067913, etc.), and antibodies having a sugar chain with bisecting GlcNAc (such as WO 02/79255). Known examples of methods for producing sugar chain-deficient IgG antibodies include the method of introducing a mutation to asparagine
- ¹⁰ at position 297 in the EU numbering (J Clin Pharmacol. 2010 May; 50(5): 494-506), and the method of producing IgG using *Escherichia coli* (J Immunol Methods. 2002 May 1; 263(1-2): 133-47; and J Biol Chem. 2010 Jul 2; 285(27): 20850-9). Furthermore, heterogeneity accompanying deletion of C-terminal lysine in IgG, and heterogeneity accompanying mispairing of disulfide bonds in the hinge region of IgG2 can be decreased by introducing amino acid deletions/substitutions (WO 2009/041613).
- ¹⁵ **[0059]** The present invention provides, for example, multispecific antigen-binding molecules, wherein the first and second polypeptides comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region.

[0060] Furthermore, the present invention provides multispecific antigen-binding molecules, wherein the first polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from

- ²⁰ the group consisting of the following (d1) to (d6) or the group consisting of the following (d7) to (d9), and the second polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from a group different from that of the above-mentioned first polypeptide:
 - (d1) an H chain constant region of SEQ ID NO: 65 (G4k);
 - (d2) an H chain constant region of SEQ ID NO: 66 (z7);

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- (d3) an H chain constant region of SEQ ID NO: 67 (z55);
- (d4) an H chain constant region of SEQ ID NO: 68 (z106);
- (d5) an H chain constant region of SEQ ID NO: 69 (z118);
- (d6) an H chain constant region of SEQ ID NO: 70 (z121);
- (d7) an H chain constant region of SEQ ID NO: 71 (G4h);
 - (d8) an H chain constant region of SEQ ID NO: 72 (z107); and
 - (d9) an H chain constant region of SEQ ID NO: 73 (z119).

[0061] Furthermore, the present invention provides a multispecific antigen-binding molecule, wherein the third and fourth polypeptides comprise an antibody L chain constant region consisting of the following amino acid sequence of:

(e) an L chain constant region of SEQ ID NO: 74 (k).

[0062] In the present invention, the phrase "functionally substitute for F.VIII" means that and/or F.IXa, and F.X is recognized, and activation of F.X is promoted (F.Xa generation is promoted).

[0063] In the present invention, "F.Xa generation-promoting activity" can be confirmed by evaluating the multispecific antigen-binding molecules of the present invention using, for example, a measurement system comprising F.XIa (F.IX activating enzyme), F.IX, F.X, F synthetic substrate S-2222 (synthetic substrate of F.Xa), and phospholipids. This measurement system shows the correlation between the severity of the disease and clinical symptoms in hemophilia A cases

- ⁴⁵ (Rosen S, Andersson M, Blomba¨ck M et al. Clinical applications of a chromogenic substrate method for determination of FVIII activity. Thromb Haemost 1985, 54: 811-23). That is, in the present measurement system, test substances that show higher F.Xa generation-promoting activity are expected to show better hemostatic effects against bleeding episodes in hemophilia A. With these results, if a multispecific antigen-binding molecule having activity of functionally substituting for F.VIII is a molecule having a higher activity than hA69-KQ/hB26-PF/hAL-AQ, it may yield excellent blood coagulation-
- ⁵⁰ promoting activity, and excellent effects may be obtained as a pharmaceutical component for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding. To obtain excellent effects as the above-mentioned pharmaceutical component, for example, F.Xa generation-promoting activity measured under the conditions described in [Example 2] is preferably not less than that of hA69-KQ/hB26-PF/hAL-AQ, and in particular, the activity is more preferably the same as or not less than that of Q153-G4k/J142-G4h/L180-k. Herein, the "F.Xa generation-promoting".
- ⁵⁵ activity" is the value obtained by subtracting the change in absorbance upon 20 minutes in a solvent from the change in absorbance upon 20 minutes in an antibody solution.

[0064] A preferred embodiment of the present invention is a multispecific antibody that functionally substitutes for F.VIII, which recognizes and/or F.IXa, and F.X.

[0065] The above-mentioned multispecific antibodies of the present invention are preferably antibodies which comprise H chain CDRs of anti-F.IX/F.IXa antibodies or CDRs functionally equivalent to them, and H chain CDRs of anti-F.X antibodies or CDRs functionally equivalent to them.

[0066] Furthermore, the antibodies of the present invention are preferably antibodies comprising an antigen-binding site having:

- H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 75, 76, and 77 (H chain CDRs of Q1), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 78, 79, and 80 (H chain CDRs of Q31), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 81, 82, and 83 (H chain CDRs of Q64), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 84, 85, and 86 (H chain CDRs of Q85), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 87, 88, and 89 (H chain CDRs of Q153), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 90, 91, and 92 (H chain CDRs of Q354), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 90, 91, and 92 (H chain CDRs of Q354), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 93, 94, and 95 (H chain CDRs of Q360), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 96, 97, and 98 (H chain CDRs of Q405), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 99, 100, and 101 (H chain CDRs of Q405), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 99, 100, and 101 (H chain CDRs of Q458), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 99, 100, and 101 (H chain CDRs of Q458), respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 102, 103, and 104 (H chain CDRs of Q460), respectively; or
 - H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 105, 106, and 107 (H chain CDRs of Q499), respectively,
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in an anti-F.IX/IXa antibody, or an antigen-binding site functionally equivalent to it, and an antigen-binding site comprising:

H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 108, 109, and 110 (H chain CDRs of J232), respectively;

- H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 111, 112, and 113 (H chain CDRs of J259), respectively;
 H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 114, 115, and 116 (H chain CDRs of J268),
- respectively; H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 117, 118, and 119 (H chain CDRs of J300), respectively;
- H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 120, 121, and 122 (H chain CDRs of J321), respectively;
 - H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 123, 124, and 125 (H chain CDRs of J326), respectively;
- ³⁵ H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 126, 127, and 128 (H chain CDRs of J327), respectively;

H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 129, 130, and 131 (H chain CDRs of J339), respectively;

H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 132, 133, and 134 (H chain CDRs of J334), respectively;

the amino acid sequences of H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 135, 136, and 137 (H chain CDRs of J346), respectively; or

H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs 174, 175, and 176 (H chain CDRs of J142), respectively,

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in an anti-F.X antibody, or an antigen-binding site functionally equivalent to it.

[0067] In the present invention, "antigen-binding sites are functionally equivalent" means that the activities of functionally substituting for F.VIII possessed by the multispecific antigen-binding molecules having the antigen-binding sites are equivalent.

- ⁵⁰ **[0068]** In the present invention, the term "equivalent" does not necessarily have to mean the same degree of activity, and the activity may be enhanced, or the activity may be decreased as long as there is an activity higher than that of hA69-KQ/hB26-PF/hAL-AQ according to the measurement system described above, or preferably F.Xa generation-promoting activity measured under the conditions described in [Example 2] is equivalent to or not less than that of Q153-G4k/J142-G4h/L180-k.
- ⁵⁵ **[0069]** The above-mentioned antibodies may have one or more amino acid substitutions, deletions, additions, and/or insertions in the variable region (CDR sequences and/or FR sequences) of the amino acid sequence as long as they have an activity higher than that of hA69-KQ/hB26-PF/hAL-AQ according to the measurement system described above at page 35, lines 11-30, or preferably F.Xa generation-promoting activity measured under the conditions described in

[Example 2] is equivalent to or not less than that of Q153-G4k/J142-G4h/L180-k. A method of introducing mutations into proteins is well known to those skilled in the art as a method for introducing one or more amino acid substitutions, deletions, additions, and/or insertions into an amino acid sequence. For example, those skilled in the art can prepare a desired mutant functionally equivalent to a multispecific polypeptide multimer having the activity of functionally substituting

- ⁵ for F.VIII by introducing appropriate mutations into the amino acid sequence using site-directed mutagenesis (Hashimoto-Gotoh, T, Mizuno, T, Ogasahara, Y, and Nakagawa, M. (1995) An oligodeoxyribonucleotide-directed dual amber method for site-directed mutagenesis. Gene 152: 271-275; Zoller, MJ, and Smith, M. (1983) Oligonucleotide-directed mutagenesis of DNA fragments cloned into M13 vectors. Methods Enzymol. 100: 468-500; Kramer, W, Drutsa, V, Jansen, HW, Kramer, B, Pflugfelder, M, and Fritz, HJ (1984) The gapped duplex DNA approach to oligonucleotide-directed mutation
- ¹⁰ construction. Nucleic Acids Res. 12, 9441-9456; Kramer W, and Fritz HJ (1987) Oligonucleotide-directed construction of mutations via gapped duplex DNA Methods. Enzymol. 154: 350-367; and Kunkel, TA (1985) Rapid and efficient site-specific mutagenesis without phenotypic selection. Proc Natl Acad Sci USA. 82: 488-492) and such. [0070] As such, antibodies of the present invention also include antibodies with one or more amino acid mutations in
- the variable region, and having an activity higher than that of hA69-KQ/hB26-PF/hAL-AQ according to the measurement
 system described above at page 35, lines 11-30, or preferably F.Xa generation-promoting activity measured under the conditions described in [Example 2] is equivalent to or not less than that of Q153-G4k/J142-G4h/L180-k.
 [0071] When an amino acid residue is altered, the amino acid is preferably mutated for a different amino acid(s) that
- conserves the properties of the amino acid side-chain. Examples of amino acid side chain properties are: hydrophobic amino acids (A, I, L, M, F, P, W, Y, and V), hydrophilic amino acids (R, D, N, C, E, Q, G, H, K, S, and T), amino acids containing aliphatic side chains (G, A, V, L, L, and P), amino acids containing hydroxyl group-containing side chains (S)
- ²⁰ containing aliphatic side chains (G, A, V, L, I, and P), amino acids containing hydroxyl group-containing side chains (S, T, and Y), amino acids containing sulfur-containing side chains (C and M), amino acids containing carboxylic acid- and amide-containing side chains (D, N, E, and Q), amino acids containing basic side chains (R, K, and H), and amino acids containing aromatic side chains (H, F, Y, and W) (amino acids are represented by one-letter codes in parentheses). Amino acid substitutions within each group are called conservative substitutions. It is already known that a polypeptide
- ²⁵ containing a modified amino acid sequence in which one or more amino acid residues in a given amino acid sequence are deleted, added, and/or substituted with other amino acids can retain the original biological activity (Mark, D. F. et al., Proc. Natl. Acad. Sci. USA; (1984) 81: 5662-6; Zoller, M. J. and Smith, M., Nucleic Acids Res. (1982) 10: 6487-500; Wang, A. et al., Science (1984) 224: 1431-3; Dalbadie-McFarland, G. et al., Proc. Natl. Acad. Sci. USA (1982) 79: 6409-13). Such mutants have an amino acid identity of at least 70%, more preferably at least 75%, even more preferably
- at least 80%, still more preferably at least 85%, yet more preferably at least 90%, and most preferably at least 95%, with the variable regions (for example, CDR sequences, FR sequences, or whole variable regions) of the present invention. Herein, sequence identity is defined as the percentage of residues identical to those in the original amino acid sequence of the heavy chain variable region or light chain variable region, determined after the sequences are aligned and gaps are appropriately introduced to maximize the sequence identity as necessary. The identity of amino acid sequences can be determined by the method described below.
- **[0072]** Alternatively, the amino acid sequences of variable regions that have a substitution, deletion, addition, and/or insertion of one or more amino acids in the amino acid sequence of the variable regions (CDR sequences and/or FR sequences) and have an activity higher than that of hA69-KQ/hB26-PF/hAL-AQ according to the measurement system described above at page 35, lines 11-30, or preferably F.Xa generation-promoting activity measured under the conditions
- 40 described in [Example 2] is equivalent to or not less than that of Q153-G4k/J142-G4h/L180-k can be obtained from nucleic acids that hybridize under stringent conditions to nucleic acid composed of the nucleotide sequence encoding the amino acid sequence of the variable regions. Stringent hybridization conditions to isolate a nucleic acid that hybridizes under stringent conditions to a nucleic acid that includes the nucleotide sequence encoding the amino acid sequence of the variable regions include, for example, the conditions of 6 M urea, 0.4% SDS, 0.5x SSC, and 37°C, or hybridization
- ⁴⁵ conditions with stringencies equivalent thereto. With more stringent conditions, for example, the conditions of 6 M urea, 0.4% SDS, 0.1x SSC, and 42°C, isolation of nucleic acids with a much higher homology can be expected. The sequences of the isolated nucleic acids can be determined by the known methods described below. The overall nucleotide sequence homology of the isolated nucleic acid is at least 50% or higher sequence identity, preferably 70% or higher, more preferably 90% or higher (for example, 95%, 96%, 97%, 98%, 99%, or higher).
- 50 [0073] Nucleic acids that hybridize under stringent conditions to a nucleic acid composed of the nucleotide sequence encoding the amino acid sequence of the variable regions can also be isolated using, instead of the above-described methods using hybridization techniques, gene amplification methods such as polymerase chain reaction (PCR) using primers synthesized based on the information of nucleotide sequence encoding the amino acid sequence of the variable regions.
- ⁵⁵ **[0074]** The identity of one nucleotide sequence or amino acid sequence to another can be determined using the algorithm BLAST, by Karlin and Altschul (Proc. Natl. Acad. Sci. USA (1993) 90: 5873-7). Programs such as BLASTN and BLASTX were developed based on this algorithm (Altschul et al., J. Mol. Biol. (1990) 215: 403-10). To analyze nucleotide sequences according to BLASTN based on BLAST, the parameters are set, for example, as score = 100 and

wordlength = 12. On the other hand, parameters used for the analysis of amino acid sequences by BLASTX based on BLAST include, for example, score = 50 and wordlength = 3. Default parameters for each program are used when using the BLAST and Gapped BLAST programs. Specific techniques for such analyses are known in the art (see the website of the National Center for Biotechnology Information (NCBI), Basic Local Alignment Search Tool (BLAST); http://www.nc-bi.nlm.nih.gov).

[0075] The present invention also provides antibodies that bind to an epitope overlapping with an epitope bound by the antibodies described above.

[0076] Whether an antibody recognizes an epitope overlapping with an epitope that is recognized by another antibody can be confirmed by the competition between the two antibodies against the epitope. Competition between the antibodies

- 10 can be evaluated by competitive binding assays using means such as enzyme-linked immunosorbent assay (ELISA), fluorescence energy transfer method (FRET), and fluorometric microvolume assay technology (FMAT (Registered trade-mark)). The amount of antibodies bound to an antigen indirectly correlate with the binding ability of candidate competitor antibodies (test antibodies) that competitively bind to the overlapping epitope. In other words, as the amount of or the affinity of test antibodies against the overlapping epitope increases, the amount of antibodies bound to the antigen
- ¹⁵ decreases, and the amount of test antibodies bound to the antigen increases. Specifically, appropriately labeled antibodies and antibodies to be evaluated are simultaneously added to the antigens, and the thus bound antibodies are detected using the label. The amount of antibodies bound to the antigen can be easily determined by labeling the antibodies beforehand. This label is not particularly limited, and the labeling method is selected according to the assay technique used. The labeling method includes fluorescent labeling, radiolabeling, enzymatic labeling, and such.
- 20 [0077] For example, fluorescently labeled antibodies and unlabeled antibodies or test antibodies are simultaneously added to beads immobilized with F.IX, F.IXa or F.X, and the labeled antibodies are detected by fluorometric microvolume assay technology.

[0078] Herein, the "antibody that binds to the overlapping epitope" refers to an antibody that can reduce the binding of the labeled antibody by at least 50% at a concentration that is usually 100 times higher, preferably 80 times higher, mere preferably 50 times higher and still mere preferably 50 times higher then

- ²⁵ more preferably 50 times higher, even more preferably 30 times higher, and still more preferably 10 times higher than a concentration at which the non-labeled antibody reduces the binding of the labeled antibody by 50% (IC₅₀). [0079] Multispecific antigen-binding molecules, which have antigen-binding sites of antibodies that bind to epitopes overlapping with epitopes bound by the above-mentioned antibodies, may yield an excellent activity of functionally substituting for F.VIII. Furthermore, in antigen-binding sites of antibodies that bind to epitopes
- ³⁰ bound by the above-mentioned antibodies, one or more amino acids may be altered to obtain a better activity of functionally substituting for F.VIII. Multispecific antigen-binding molecules having a better activity of functionally substituting for F.VIII can be obtained by altering the amino acids of the antigen-binding sites and selecting multispecific antigen-binding molecules having an activity higher than that of hA69-KQ/hB26-PF/hAL-AQ according to the measurement system described above, or preferably having an F.Xa generation-promoting activity measured under the conditions described
- ³⁵ in [Example 2] that is equivalent to or not less than that of Q153-G4k/J142-G4h/L180-k. To obtain an excellent activity of functionally substituting for F.VIII of the present invention, the following amino acid alterations are particularly preferred.

(1) At least one amino acid residue selected from the amino acid residues at positions 34, 35, 49, 61, 62, 96, 98, 100, 100b, and 102 by Kabat numbering in the H chain of the antibody that recognizes and/or F.IXa is substituted with a different amino acid.

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(2) At least one amino acid residue selected from the amino acid residues at positions 35, 53, 73, 76, 96, 98, 100, and 100a by Kabat numbering in the H chain of the antibody that recognizes F.X is substituted with a different amino acid.

(3) At least one amino acid residue selected from the amino acid residues at positions 27, 30, 31, 32, 50, 52, 53, 54, 55, 92, 93, 94, and 95 by Kabat numbering in the antibody L chain is substituted with a different amino acid.

- ⁴⁵ 54, 55, 92, 93, 94, and 95 by Kabat numbering in the antibody L chain is substituted with a different amino acid. Furthermore, in the present invention, preferred antibody amino acids for obtaining a better activity of functionally substituting for F.VIII include those mentioned in (4) to (6) below. Regarding these amino acids, the antibody H chain may originally have such amino acids, or antibody H chain amino acids may be modified to have such a sequence.
- 50 (4) An antibody H chain which recognizes and/or F.IXa, wherein, by Kabat numbering, the amino acid residue at position 34 is isoleucine, the amino acid residue at position 35 is asparagine, glutamine, or serine, the amino acid residue at position 61 is arginine, the amino acid residue at position 62 is glutamic acid, the amino acid residue at position 96 is serine or threonine, the amino acid residue at position 98 is lysine or arginine, the amino acid residue at position 100 is phenylalanine or tyrosine, the amino acid residue at position 102 is tyrosine.
- at position 100b is glycine, or the amino acid residue at position 102 is tyrosine.
 (5) An antibody H chain which recognizes F.X, wherein, by Kabat numbering, the amino acid residue at position 35 is aspartic acid, the amino acid residue at position 53 is arginine, the amino acid residue at position 73 is lysine, the amino acid residue at position 76 is glycine, the amino acid residue at position 96 is lysine or arginine, the amino

acid residue at position 98 is tyrosine, the amino acid residue at position 100 is tyrosine, or the amino acid residue at position 100a is histidine.

(6) An antibody L chain, wherein, by Kabat numbering, the amino acid residue at position 27 is lysine or arginine, the amino acid residue at position 30 is glutamic acid, the amino acid residue at position 31 is arginine, the amino acid residue at position 32 is glutamine, the amino acid residue at position 50 is arginine or glutamine, the amino acid residue at position 52 is serine, the amino acid residue at position 53 is arginine, the amino acid residue at position 54 is lysine, the amino acid residue at position 93 is serine, the amino acid residue at position 94 is proline, or the amino acid residue at position 95 is proline.

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[0080] Among the above-mentioned antibody amino acid residues of (1) to (6), favorable positions of amino acid residues for obtaining a particularly excellent F.VIII-fike activity are shown in the following (1) to (3).

(1) Amino acid residues at positions 34, 35, 61, 98, 100, and 100b, particularly amino acid residues at positions 61 and 100, by Kabat numbering in the H chain of the antibody that recognizes and/or F.IXa.

(2) Amino acid residues at positions 35, 53, 73, 96, 98, 100, and 100a by Kabat numbering in the H chain of the antibody that recognizes F.X.

(3) Amino acid residues at positions 27, 30, 31, 32, 50, 52, 53, 93, 94, and 95, and particularly amino acid residues at positions 27, 30, 31, 50, 53, 94, and 95, by Kabat numbering in the antibody L chain.

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[0081] Specifically, the present invention provides multispecific antigen-binding molecules, wherein a first polypeptide comprises any of the antibody H chains selected from the following (a1) to (a 14) and any of the antibody L chains selected from the following (c1) to (c10), and the second polypeptide comprises any of the antibody H chains selected from the following (b1) to (b12) and any of the antibody L chains selected from the following (c1 to (c10):

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(a1) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 1 (Q1-G4k);

(a2) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 2 (Q31-z7);

(a3) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 3 (Q64-z55);

(a4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 10 (Q64-z7);

30 (a5) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 11 (Q85-G4k); (a6) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 12 (Q153-G4k); (a7) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 13 (Q354-z106); (a8) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 14 (Q360-G4k); (a9) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 15 (Q360-z118); 35 (a10) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 16 (Q405-G4k); (a11) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 17 (Q458-z106); (a12) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 18 (Q460-z121); (a13) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 19 (Q499-z118); (a14) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 20 (Q499-z121); 40 (b1) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 4 (J268-G4h); (b2) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 5 (J321-G4h); (b3) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 6 (J326-z107); (b4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 7 (J344-z107); (b5) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 21 (J232-G4h); 45 (b6) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 22 (J259-z107); (b7) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 23 (J300-z107); (b8) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 24 (J327-z107); (b9) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 25 (J327-z119); (b10) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 26 (J339-z119); 50 (b11) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 27 (J346-z107); (b12) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 170 (J142-G4h); (c1) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 8 (L2-k); (c2) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 9 (L45-k); (c3) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 28 (L248-k); 55 (c4) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 29 (L324-k); (c5) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 30 (L334-k); (c6) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 31 (L377-k); (c7) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 32 (L404-k);

(c8) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 33 (L406-k);

(c9) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 34 (L408-k); and

(c10) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 171 (L180-k).

⁵ [0082] The present invention also provides multispecific antigen-binding molecules, wherein the first polypeptide comprises an antigen-binding site which binds to an epitope overlapping with an epitope that binds to an antibody consisting of the antibody H chain of any one of (a1) to (a14) and the antibody L chain of any one of (c1) to (c10) described above, and the second polypeptide comprises an antigen-binding site which binds to an epitope overlapping with an epitope overlapping with an epitope that binds to an antibody consisting of the antibody H chain of any one of (b1) to (b12) and the antibody L chain of any one of (c1) to (c10) described above.

[0083] Furthermore, the present invention provides multispecific antigen-binding molecules, wherein the first polypeptide comprises any one antibody H chain selected from the following (e1) to (e3), the second polypeptide comprises any one antibody H chain selected from the following (f1) to (f3), and the third polypeptide and the fourth polypeptide comprise any one antibody L chain selected from the following (g1) to (g4):

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(e1) an H chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody consisting of an antibody H chain of any one of (a1) to (a14) and an antibody L chain of any one of (c1) to (c10) described above; (e2) an antibody H chain, wherein at least one amino acid residue selected from the amino acid residues at positions 34, 35, 49, 61, 62, 96, 98, 100, 100b, and 102 by Kabat numbering in any one antibody H chain selected from (e1) described above is substituted with another amino acid;

- (e3) an antibody H chain, wherein by Kabat numbering, the amino acid residue at position 34 is isoleucine, the amino acid residue at position 35 is asparagine, glutamine, or serine, the amino acid residue at position 49 is serine, the amino acid residue at position 61 is arginine, the amino acid residue at position 62 is glutamic acid, the amino acid residue at position 96 is serine or threonine, the amino acid residue at position 98 is lysine or arginine, the amino acid residue at position 100 is phenylalanine or tyrosine, the amino acid residue at position 100b is glycine,
- or the amino acid residue at position 102 is tyrosine in any antibody H chain selected from (e1) described above; (f1) an H chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody consisting of an antibody H chain of any of (b1) to (b12) described above and an antibody L chain of any of (c1) to (c10) described above;
- (f2) an antibody H chain, wherein at least one amino acid residue selected from the amino acid residues at positions
 35, 53, 73, 76, 96, 98, 100, and 100a by Kabat numbering in any antibody H chain of (f1) described above is substituted with another amino acid;

(f3) an antibody H chain, wherein by Kabat numbering, the amino acid residue at position 35 is aspartic acid, the amino acid residue at position 53 is arginine, the amino acid residue at position 73 is lysine, the amino acid residue at position 76 is glycine, the amino acid residue at position 96 is lysine or arginine, the amino acid residue at position

98 is tyrosine, the amino acid residue at position 100 is tyrosine, or the amino acid residue at position 100a is histidine in any one antibody H chain selected from (f1) described above;

(g1) an L chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody which consists of an antibody H chain of any one of (a1) to (a14) and an antibody L chain of any one of (c1) to (c10) described above;

(g2) an L chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody which consists of an antibody H chain of any one of (b1) to (b12) and an antibody L chain of any one of (c1) to (c10) described above;

(g3) an antibody L chain, wherein at least one amino acid residue selected from the amino acid residues at positions
 27, 30, 31, 32, 50, 52, 53, 54, 55, 92, 93, 94, and 95 by Kabat numbering in the antibody L chain of either (g1) or
 (g2) described above is substituted with another amino acid; and
 (g4) an antibody L chain, wherein by Kabat numbering, the amino acid residue at position 27 is lysine or arginine,

the amino acid residue at position 30 is glutamic acid, the amino acid residue at position 21 is systere of arginine, acid residue at position 32 is glutamine, the amino acid residue at position 50 is arginine or glutamine, the amino acid residue at position 52 is serine, the amino acid residue at position 53 is arginine, the amino acid residue at position 54 is lysine, the amino acid residue at position 55 is glutamic acid, the amino acid residue at position 92 is serine, the amino acid residue at position 93 is serine, the amino acid residue at position 94 is proline, or the amino acid residue at position 95 is proline in the antibody L chain of either (g1) or (g2) described above.

⁵⁵ **[0084]** Amino acid substitutions can be performed on the antibodies (clones) of the present invention to avoid deamidation, methionine oxidation, and such, or to structurally stabilize the antibodies.

[0085] The method for obtaining multispecific antigen-binding molecules of the present invention is not particularly limited, and may be any method. Bispecific antibodies can be generated according to the methods described in WO

2006/109592, WO 2005/035756, WO 2006/106905, or WO 2007/114325, which are known as examples of the method for producing the bispecific antibodies; and then desired antibodies having a cofactor function-substituting activity can be selected and obtained.

- **[0086]** For example, the bispecific antibody described in any of the following (a) to (u) is provided by the present invention:
 - (a) a bispecific antibody (Q1-G4k/J268-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9; (b) a bispecific antibody (Q1-G4k/J321-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the
- amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9; (c) a bispecific antibody (Q31-z7/J326-z107/L2-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 2, the second polypeptide is an H chain consisting of the amino acid sequence of

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- SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 8;
 (d) a bispecific antibody (Q64-z55/J344-z107/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 3, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;
 (e) a bispecific antibody (Q64-z7/J326-z107/L334-k), wherein the first polypeptide is an H chain consisting of the
- 20 amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(f) a bispecific antibody (Q64-z7/J344-z107/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID

NO: 33; (g) a bispecific antibody (Q85-G4k/J268-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33:

(h) a bispecific antibody (Q85-G4k/J321-G4h/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

- (i) a bispecific antibody (Q153-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;
- (j) a bispecific antibody (Q354-z106/J259-z107/L324-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 13, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 22, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 29;

(k) a bispecific antibody (Q360-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 14, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

(I) a bispecific antibody (Q360-z118/J300-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 15, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 23, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

- (m) a bispecific antibody (Q405-G4k/J232-G4h/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 16, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;
- (n) a bispecific antibody (Q458-z106/J346-z107/L408-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 17, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 34;

(o) a bispecific antibody (Q460-z121/J327-z119/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 18, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

- (p) a bispecific antibody (Q499-z118/J327-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;
- (q) a bispecific antibody (Q499-z118/J327-z107/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31;

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(r) a bispecific antibody (Q499-z118/J346-z107/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;

(s) a bispecific antibody (Q499-z121/J327-z119/L404-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 32;

(t) a bispecific antibody (Q499-z121/J339-z119/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 26, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31; and

- (u) a bispecific antibody (Q153-G4k/J142-G4h/L180-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 170, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 171.
- 30 [0087] Amino acid sequences, molecular weights, isoelectric points, or presence or absence and form of sugar chains of the antibodies of the present invention vary depending on cells or hosts that produce the antibodies or purification methods described later. However, as long as the obtained antibodies have functions equivalent to the antibodies of the present invention, they are included in the present invention. For example, when an antibody of the present invention is expressed in prokaryotic cells such as *E. coli*, a methionine residue will be added to the N terminus of the original article antibodies and be antibodies.
- antibody amino acid sequence. Antibodies of the present invention also comprise such antibodies.
 [0088] Bispecific antibodies of the present invention can be produced by methods known to those skilled in the art.
 [0089] Based on the obtained sequence of the anti-F.IX/F.IXa antibody or anti-F.X antibody, the anti-F.IX/F.IXa antibody or anti-F.X antibody can be prepared, for example, by genetic recombination techniques known to those skilled in the art. Specifically, a polynucleotide encoding an antibody can be constructed based on the sequence of the anti-F.IX/F.IXa
- antibody or anti-F.X antibody, inserted into an expression vector, and then expressed in appropriate host cells (see for example, Co, M. S. et al., J. Immunol. (1994) 152, 2968-2976; Better, M. and Horwitz, A. H., Methods Enzymol. (1989) 178, 476-496; Pluckthun, A. and Skerra, A., Methods Enzymol. (1989) 178, 497-515; Lamoyi, E., Methods Enzymol. (1986) 121, 652-663; Rousseaux, J. et al., Methods Enzymol. (1986) 121, 663-669; Bird, R. E. and Walker, B. W., Trends Biotechnol. (1991) 9, 132-137).
- ⁴⁵ [0090] The vectors include M13 vectors, pUC vectors, pBR322, pBluescript, and pCR-Script. Alternatively, when aiming to subclone and excise cDNA, the vectors include, for example, pGEM-T, pDIRECT, and pT7, in addition to the vectors described above. Expression vectors are particularly useful when using vectors for producing the antibodies of the present invention. For example, when aiming for expression in *E. coli* such as JM109, DH5α, HB101, and XL1-Blue, the expression vectors not only have the characteristics that allow vector amplification in *E. coli*, but must also carry a
- ⁵⁰ promoter that allows efficient expression in *E. coli,* for example, lacZ promoter (Ward et al., Nature (1989) 341: 544-546; FASEB J. (1992) 6: 2422-2427), araB promoter (Better et al., Science (1988) 240: 1041-1043), T7 promoter or such. Such vectors include pGEX-5X-1 (Pharmacia), "QIAexpress system" (Qiagen), pEGFP, or pET (in this case, the host is preferably BL21 that expresses T7 RNA polymerase) in addition to the vectors described above.
- [0091] The expression plasmid vectors may contain signal sequences for antibody secretion. As a signal sequence for antibody secretion, a pelB signal sequence (Lei, S. P. et al J. Bacteriol. (1987) 169: 4379) may be used when a protein is secreted into the *E. coli* periplasm. The vector can be introduced into host cells by calcium chloride or electroporation methods, for example.

[0092] In addition to vectors for E. coli, the vectors for producing the antibodies of the present invention include

mammalian expression vectors (for example, pcDNA3 (Invitrogen), pEF-BOS (Nucleic Acids. Res. 1990, 18(17): p5322), pEF, and pCDM8), insect cell-derived expression vectors (for example, the "Bac-to-BAC baculovirus expression system" (Gibco-BRL) and pBacPAK8), plant-derived expression vectors (for example, pMH1 and pMH2), animal virus-derived expression vectors (for example, pHSV, pMV, and pAdexLcw), retroviral expression vectors (for example, pZIPneo),

- ⁵ yeast expression vectors (for example, "Pichia Expression Kit" (Invitrogen), pNV11, and SP-Q01), and *Bacillus subtilis* expression vectors (for example, pPL608 and pKTH50), for example.
 [0093] When aiming for expression in animal cells such as CHO, COS, and NIH3T3 cells, the expression plasmid vectors must have a promoter essential for expression in cells, for example, SV40 promoter (Mulligan et al., Nature (1979) 277: 108), MMLV-LTR promoter, EFIα promoter (Mizushima et al., Nucleic Acids Res. (1990) 18: 5322), and
- CMV promoter, and more preferably they have a gene for selecting transformed cells (for example, a drug resistance gene that allows evaluation using an agent (neomycin, G418, or such)). Vectors with such characteristics include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, and pOP13, for example.
 [0094] In addition, the following method can be used for stable gene expression and gene amplification in cells: CHO
- cells deficient in a nucleic acid synthesis pathway are introduced with a vector that carries a DHFR gene which com pensates for the deficiency (for example, pSV2-dhfr (Molecular Cloning 2nd edition, Cold Spring Harbor Laboratory Press, 1989)), and the vector is amplified using methotrexate (MTX). Alternatively, the following method can be used for transient gene expression: COS cells with a gene expressing SV40 T antigen on their chromosome are transformed with a vector with an SV40 replication origin (pcD and such). Replication origins derived from polyoma virus, adenovirus, bovine papilloma virus (BPV), and such can also be used. To amplify gene copy number in host cells, the expression
- vectors may further carry selection markers such as aminoglycoside transferase (APH) gene, thymidine kinase (TK) gene, *E. coli* xanthine-guanine phosphoribosyltransferase (Ecogpt) gene, and dihydrofolate reductase (dhfr) gene. [0095] The antibodies of the present invention obtained by the methods described above can be isolated from inside host cells or from outside the cells (the medium, or such), and purified to homogeneity. The antibodies can be isolated and purified by methods routinely used for isolating and purifying antibodies, and the type of method is not limited. For
- ²⁵ example, the antibodies can be isolated and purified by appropriately selecting and combining column chromatography, filtration, ultrafiltration, salting-out, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-poly-acrylamide gel electrophoresis, isoelectrofocusing, dialysis, recrystallization, and such.
 [0096] The chromatographies include, for example, affinity chromatography, ion exchange chromatography, hydro-

[U096] The chromatographies include, for example, affinity chromatography, ion exchange chromatography, hydrophobic chromatography, gel filtration, reverse phase chromatography, and adsorption chromatography (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press, 1996). The chromatographic methods described above can be conducted using liquid chromatography, for example, HPLC and FPLC. Columns that can be used for affinity chromatography include protein A columns and protein G columns. Columns using protein A include, for example, Hyper D, POROS, and Sepharose FF (GE Amersham Biosciences). The present invention includes antibodies that are highly purified using these purification methods.

- ³⁵ **[0097]** The obtained antibodies can be purified to homogeneity. Separation and purification of the antibodies can be performed using conventional separation and purification methods used for ordinary proteins. For example, the antibodies can be separated and purified by appropriately selecting and combining column chromatography such as affinity chromatography, filtration, ultrafiltration, salting-out, dialysis, SDS polyacrylamide gel electrophoresis, isoelectric focusing, and such, without limitation (Antibodies : A Laboratory Manual. Ed Harlow and David Lane, Cold Spring Harbor Labo-
- 40 ratory, 1988). Columns used for affinity chromatography include, for example, protein A columns and protein G columns. [0098] In one embodiment of antibodies of the present invention, since the antibodies of the present invention functionally substitute for cofactor F.VIII, they are expected to become effective pharmaceutical agents against diseases resulting from decrease in activity (function) of this cofactor. Examples of the above-mentioned diseases include bleeding, diseases accompanying bleeding, or a disease caused by bleeding. In particular, there may have excellent therapeutic
- effects on hemophilias, in which bleeding disorders are caused by a deficiency or decrease of F.VIII/F.VIIIa function. Among the hemophilias, they are expected to become excellent therapeutic agents for hemophilia A, in which bleeding disorders are caused by a hereditary deficiency or decrease of F.VIII/F.VIIIa function.
 [0099] The present invention provides (pharmaceutical) compositions comprising the antibodies of the present inven-
- tion and pharmaceutically acceptable carriers. For example, the antibodies of the present invention that recognize both
 F.IX or F.IXa and F.X, and functionally substitute for F.VIII are expected to become pharmaceuticals (pharmaceutical compositions) or pharmaceutical agents for preventing and/or treating bleeding, diseases accompanying bleeding, diseases caused by bleeding, and the like.

[0100] In the context of the present invention, bleeding, diseases accompanying bleeding, and/or diseases caused by bleeding preferably refer to diseases that develop and/or progress due to reduction or deficiency in activity of F.VIII and/or activated coagulation factor VIII (F.VIIIa). Such diseases include the above-described hemophilia A, diseases in which an inhibitor against F.VIII /F.VIIIa appear, acquired hemophilia, von Willebrand's disease, and such, but are not particularly limited thereto.

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[0101] Pharmaceutical compositions used for therapeutic or preventive purposes, which comprise antibodies of the

present invention as active ingredients, can be formulated by mixing, if necessary, with suitable pharmaceutically acceptable carriers, vehicles, and such that are inactive against the antibodies. For example, sterilized water, physiological saline, stabilizers, excipients, antioxidants (such as ascorbic acid), buffers (such as phosphate, citrate, histidine, and other organic acids), antiseptics, surfactants (such as PEG and Tween), chelating agents (such as EDTA), and binders

- ⁵ may be used. They may also comprise other low-molecular-weight polypeptides, proteins such as serum albumin, gelatin, and immunoglobulins, amino acids such as glycine, glutamine, asparagine, glutamic acid, asparagic acid, methionine, arginine, and lysine, sugars and carbohydrates such as polysaccharides and monosaccharides, and sugar alcohols such as mannitol and sorbitol. When preparing an aqueous solution for injection, physiological saline and isotonic solutions comprising glucose and other adjuvants such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride may
- ¹⁰ be used, and if necessary, in combination with appropriate solubilizers such as alcohol (for example, ethanol), polyalcohols (such as propylene glycol and PEG), and nonionic surfactants (such as polysorbate 80, polysorbate 20, poloxamer 188, and HCO-50). By mixing hyaluronidase into the formulation, a larger fluid volume can be administered subcutaneously (Expert Opin Drug Deliv. 2007 Jul; 4(4): 427-40).
- [0102] If necessary, antibodies of the present invention may be encapsulated in microcapsules (e.g., those made of hydroxymethylcellulose, gelatin, and poly(methylmetacrylate)), or incorporated as components of colloidal drug delivery systems (e.g., liposomes, albumin microspheres, microemulsion, nanoparticles, and nanocapsules) (see, for example, "Remington's Pharmaceutical Science 16th edition", Oslo Ed. (1980)). Methods for preparing the pharmaceutical agents as controlled-release pharmaceutical agents are also well known, and such methods may be applied to the antibodies of the present invention (Langer et al., J. Biomed. Mater. Res. 15: 267-277 (1981); Langer, Chemtech. 12: 98-105 (1982);
- ²⁰ U.S. Patent No. 3,773,919; European Patent Application Publication No. EP 58,481; Sidman et al., Biopolymers 22: 547-556 (1983); EP 133,988).

[0103] The dose of a pharmaceutical composition of the present invention may be appropriately determined by considering the dosage form, method of administration, patient age and body weight, symptoms of the patient, type of the disease, and degree of progress of the disease, and is ultimately decided by physicians. Generally, the daily dose for

- ²⁵ an adult is 0.1 mg to 2,000 mg at once or in several portions. The dose is more preferably 0.2 to 1,000 mg/day, even more preferably 0.5 to 500 mg/day, still more preferably 1 to 300 mg/day, yet more preferably 3 to 100 mg/day, and most preferably 5 to 50 mg/day. These doses may vary, depending on the patient body weight and age, and the method of administration; however, selection of suitable dosage is well within the purview of those skilled in the art. Similarly, the dosing period may be appropriately determined depending on the therapeutic progress.
- ³⁰ **[0104]** Furthermore, the present invention provides genes or nucleic acids encoding the antibodies of the present invention. In addition, gene therapy may be performed by incorporating genes or nucleic acids encoding the antibodies of the present invention into vectors for gene therapy. In addition to direct administration using naked plasmids, methods of administration include administration after packaging into liposomes and such, forming a variety of virus vectors such as retrovirus vectors, adenovirus vectors, vaccinia virus vectors, poxvirus vectors, adeno-associated virus vectors, and
- ³⁵ HVJ vectors (see Adolph "Viral Genome Methods" CRC Press, Florida (1996)), or coating with carrier beads such as colloidal gold particles (WO 93/17706, and such). However, so long as the antibodies are expressed *in vivo* and their activities are exercised, any method can be used for administration. Preferably, a sufficient dose can be administered by a suitable parenteral route (such as injecting or infusing intravenously, intraperitoneally, subcutaneously, intradermally, intramuscularly, into adipose tissues or mammary glands; inhalation; gas-driven particle bombardment (using electron
- 40 gun and such); or mucosal route such as nasal drops). Alternatively, the genes encoding the antibodies of the present invention may be administered into blood cells, bone marrow cells, and such *ex vivo* using liposome transfection, particle bombardment (U.S. Patent No. 4,945,050), or viral infection, and the cells may be reintroduced into patients. Any gene encoding an antibody of the present invention may be used in gene therapy, and its examples include genes comprising nucleotide sequences encoding the CDRs of Q1, Q31, Q64, Q85, Q153, Q354, Q360, Q405, Q458, Q460, Q499, J232,
- ⁴⁵ J259, J268, J300, J321, J326, J327, J339, J344, J346, J142, L2, L45, L248, L324, L334, L377, L404, L406, L408, and L180 described above.

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[0105] The present invention also provides methods for preventing and/or treating bleeding, diseases accompanying bleeding, and/or diseases caused by bleeding, such methods comprising the step of administering the antibodies or compositions of the present invention. The antibodies or compositions can be administered, for example, by the above-mentioned methods.

[0106] Furthermore, the present invention provides kits to be used for the above-mentioned methods, such kits comprising at least an antibody or composition of the present invention. In addition, the kits may include, packaged therewith, a syringe, injection needle, pharmaceutically acceptable medium, alcohol-soaked cotton, adhesive bandage, instructions describing the method of use, and the like.

⁵⁵ **[0107]** The present invention also relates to use of a multispecific antigen-binding molecule, a bispecific antibody, or a composition of the present invention in the manufacture of an agent for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding.

[0108] Furthermore, the present invention relates to a multispecific antigen-binding molecule, a bispecific antibody,

or a composition of the present invention for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by bleeding.

[0109] All prior art references cited herein are incorporated by reference into this description.

5 Examples

[0110] Herein below, the present invention will be specifically described with reference to the Examples, but it is not to be construed as being limited thereto.

¹⁰ [Example 1] Production of Bispecific Antibodies Having F.Xa Generation-Promoting Activity

[0111] In WO 2006/109592, hA69-KQ/hB26-PF/hAL-AQ was obtained as a bispecific antibody having an activity of functionally substituting for F.VIII. However, there was the possibility that this antibody has an inhibiting action on the reaction in which F.IXa activates F.X using F.VIIIa as a cofactor.

- ¹⁵ **[0112]** As shown in Fig. 1, antibodies that bind to F.IX/F.IXa or F.X may inhibit the formation of the F.IXa-F.VIIIa complex (Factor Xase (F.Xase)), or inhibit F.Xase activity (activation of F.X). Hereafter, inhibition of F.Xase formation and/or action of inhibiting F.Xase activity will be mentioned as F.Xase inhibitory action. F.Xase inhibitory action is the inhibition of a coagulation reaction in which F.VIIIa serves as the cofactor, which may suppress the remaining F.VIII function in a patient or the function of the administered F.VIII formulation. Therefore, it is desirable that F.Xa generation-
- ²⁰ promoting activity, which is the objective of the bispecific antibody, is high, while F.Xase inhibitory action is low. In particular, for patients maintaining F.VIII function and patients receiving treatment with a F.VIII formulation, it is more desirable that F.Xa generation-promoting activity and F.Xase inhibitory action are separated as much as possible. [0113] However, F.Xase inhibitory action is due to the binding to the antigen (F.IXa and/or F.X), which is fundamental property of the antibody. On the other hand, a bispecific antibody having F.Xa generation-promoting action (functionally)
- ²⁵ substituting for F.VIII) also needs to bind to the antigens (F.IXa and F.X). Therefore, it is predicted that it is extremely difficult to obtain bispecific antibodies that do not have an F.Xase inhibitory action but have an F.Xa generation-promoting activity (functionally substituting for F.VIII). Similarly, it is predicted that it is extremely difficult to decrease an F.Xase inhibitory action while increasing the target F.Xa generation-promoting activity by introducing amino acid substitutions in a bispecific antibody.
- 30 [0114] The present inventors prepared genes for approximately 200 types of antibodies against human F.IXa and human F.X, respectively, using a method known to those skilled in the art, which is the method of obtaining antibody genes from antibody-producing cells of animals immunized with an antigen (human F.IXa or human F.X), and introducing amino acid substitutions, when necessary. Each antibody gene was incorporated into an animal cell expression vector. [0115] 40,000 or more bispecific antibodies as anti-F.IXa antibody and anti-F.X antibody combinations were transiently
- ³⁵ expressed by simultaneously transfecting the anti-human F.IXa antibody H chain expression vector, the anti-human F.X antibody H chain expression vector, and the commonly shared antibody L chain expression vector into mammalian cells such as HEK293H cells. As a comparative control, bispecific antibody hA69-KQ/hB26-PF/hAL-AQ (SEQ ID NOs: 165/166/167) described in WO 2006/109592 was prepared.
- [0116] Since the mutations mentioned in WO 2006/106905 or WO 1996/027011 were introduced into the CH3 domain of each H chain, it was thought that bispecific antibodies were mainly expressed. Antibodies in the cell culture supernatant were purified by a method known to those skilled in the art using Protein A.

[0117] The present inventors measured the F.Xa generation-promoting activity of these antibodies by the method described below. All reactions were performed at room temperature.

[0118] Five μL of antibody solution diluted with Tris-buffered saline containing 0.1% bovine serum albumin (hereafter referred to as TBSB) was mixed with 2.5 μL of 27 ng/mL Human Factor IXa beta (Enzyme Research Laboratories) and 2.5 μL of 6 IU/mL of Novact (registered trademark) M (Kaketsuken), and then incubated in a 384-well plate at room temperature for 30 minutes.

[0119] The enzyme reaction in this mixed solution was initiated by adding 5 μ L of 24.7 μ g/mL of Human Factor X (Enzyme Research Laboratories), and ten minutes later, 5 μ L of 0.5 M EDTA was added to stop the reaction. The

- ⁵⁰ coloring reaction was initiated by adding 5 μL of coloring substrate solution. After a 50-minute coloring reaction, the change in absorbance at 405 nm was measured using the SpectraMax 340PC³⁸⁴ (Molecular Devices). F.Xa generation-promoting activity was indicated as the value obtained by subtracting the absorbance of the antibody-free reaction solution from the absorbance of the antibody-supplemented reaction solution.
- [0120] TBCP (TBSB containing 93.75 μM phospholipid solution (SYSMEX CO.), 7.5 mM CaCl₂, and 1.5 mM MgCl₂) was used as the solvent for Human Factor IXa, Novact (registered trademark) M, and Human Factor X. A coloring substrate solution S-2222[™] (CHROMOGENIX) was dissolved in purified water at 1.47 mg/mL, and then used in this assay.

[0121] To evaluate the F.Xase inhibitory action of the antibodies, the present inventors measured the effects on F.X

activation by F.IXa in the presence of F.VIIIa using the following method. All reactions were performed at room temperature.

[0122] Five μ L of antibody solution diluted with Tris-buffered saline containing 0.1% bovine serum albumin (hereafter referred to as TBSB) was mixed with 2.5 μ L of 80.9 ng/mL Human Factor IXa beta (Enzyme Research Laboratories), and then incubated in a 384-well plate at room temperature for 30 minutes.

- **[0123]** 2.5 μ L of 1.8 IU/mL of F.VIIIa (production method will be descried later) was further added, and 30 seconds later, the enzyme reaction in this mixed solution was initiated by adding 5 μ L of 24.7 μ g/mL of Human Factor X (Enzyme Research Laboratories). Six minutes later, 5 μ L of 0.5 M EDTA was added to stop the reaction. The coloring reaction was initiated by adding 5 μ L of coloring substrate solution. After a 14-minute coloring reaction, the change in absorbance
- 10 at 405 nm was measured using the SpectraMax 340PC³⁸⁴ (Molecular Devices). F.Xase inhibitory action of an antibody was indicated as the value obtained by subtracting the absorbance of the antibody-free reaction solution from the absorbance of the antibody-supplemented reaction solution.

[0124] F.VIIIa was prepared by mixing 5.4 IU/mL of Kogenate (registered trademark) FS (Bayer HealthCare) and 1.11 μ g/mL of Human alpha Thrombin (Enzyme Research Laboratories) at a volume ratio of 1:1, incubating at room temper-

¹⁵ ature for one minute, and then adding 7.5 U/mL of Hirudin (Merck KgaA) at a quantity that is half the volume of the mixture solution. The prepared solution was defined as 1.8 IU/mL of FVIIIa, and one minute after addition of Hirudin, this was used for assays.

[0125] TBCP (TBSB containing 93.75 μM phospholipid solution (SYSMEX CO.), 7.5 mM CaCl₂, and 1.5 mM MgCl₂) was used for the solvent for Human Factor IXa, Human Factor X, Kogenate (registered trademark) FS, Human alpha

- ²⁰ Thrombin, and Hirudin. A coloring substrate solution S-2222[™] (CHROMOGENIX) was dissolved in purified water at 1.47 mg/mL, and then used in this assay.
 [0126] The F.Xa generation-promoting activities of each of the bispecific antibodies are indicated in Figs. 3 and 4, and the F.Xase inhibitory actions of each of the bispecific antibodies are indicated in Fig. 5. Various amino acid substitutions
- that increase the F.Xa generation-promoting activity have been found, but as expected, most of the amino acid substitutions that increase the F.Xa generation-promoting activity increased F.Xase inhibitory action as well, and suppressing F.Xase inhibitory action while increasing F.Xa generation-promoting activity was very difficult.
 [0127] Under such circumstances, the inventors of the present application obtained Q1-G4k/J268-G4h/L45-k, Q1-G4k/J321-G4h/L45-k, Q31-z7/J326-z107/L2-k, Q64-z55/J344-z107/L45-k as bispecific antibodies with a high F.Xa generation-promoting activity increased generation.
- eration-promoting activity and a low F.Xase inhibitory action. In addition, Q1-G4k (SEQ ID NO: 1), Q31-z7 (SEQ ID NO: 2), and Q64-z55 (SEQ ID NO: 3) were obtained as anti-human F.IXa antibody H chains, J268-G4h (SEQ ID NO: 4), J321-G4h (SEQ ID NO: 5), J326-z107 (SEQ ID NO: 6), and J344-z107 (SEQ ID NO: 7) were obtained as prototype anti-human F.X antibody H chains, and L2-k (SEQ ID NO: 8) and L45-k (SEQ ID NO: 9) were obtained as prototype commonly shared antibody L chains. The character before the hyphen in the sequence name indicates the variable region and the character after the hyphen indicates the constant region. Each bispecific antibody name is indicated by listing the sequence names of each chain to be transfected.
- [0128] Most of the bispecific antibodies having F.Xa generation-promoting activity close to that of hA69-KQ/hB26-PF/hAL-AQ had high F.Xase inhibitory action as expected, but these bispecific antibodies (Q1-G4k/J268-G4h/L45-k, Q1-G4k/J321-G4h/L45-k, Q31-z7/J326-z107/L2-k, Q64-z55/J344-z107/L45-k) were found to have higher F.Xa generation-promoting activity and lower F.Xase inhibitory action than hA69-KQ/hB26-PF/hAL-AQ described in WO
- 40 2006/109592. The present inventors conducted examinations to further increase the F.Xa generation-promoting activity and reduce the F.Xase inhibitory action using these four antibodies as prototype antibodies. Screening of bispecific antibodies that increase F.Xa generation-promoting activity and reduce F.Xase inhibitory action is indicated in Fig. 2.
 - [Example 2] Production of Modified Antibodies
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[0129] The present inventors introduced various combinations of amino acid mutations that affect the F.Xa generationpromoting activities and F.Xase inhibitory actions found in Example 1 to each of the chains of the prototype antibodies by a method known to those skilled in the art such as PCR for introducing mutations and evaluated the combinations of modified chains on a large scale to screen for amino acid substitutions that will further increase the F.Xa generationpromoting activities and reduce the F.Xase inhibitory actions of the four prototype antibodies.

- **[0130]** Each of the modified bispecific antibodies with amino acid substitutions were expressed transiently and purified by methods similar to those for the prototype antibodies. The F.Xa generation-promoting activities of the antibodies were measured using the following method. All reactions were performed at room temperature.
- [0131] Five μL of antibody solution diluted with Tris-buffered saline containing 0.1% bovine serum albumin (hereafter referred to as TBSB) was mixed with 2.5 μL of 27 ng/mL Human Factor IXa beta (Enzyme Research Laboratories) and 2.5 μL of 6 IU/mL of Novact (registered trademark) M (Kaketsuken), and then incubated in a 384-well plate at room temperature for 30 minutes.

[0132] The enzyme reaction in this mixed solution was initiated by adding 5 μ L of 24.7 μ g/mL of Human Factor X

(Enzyme Research Laboratories), and two minutes later, 5 μ L of 0.5 M EDTA was added to stop the reaction. The coloring reaction was initiated by adding 5 μ L of coloring substrate solution. After a 20-minute coloring reaction, the change in absorbance at 405 nm was measured using the SpectraMax 340PC³⁸⁴ (Molecular Devices). F.Xa generation-promoting activity was indicated as the value obtained by subtracting the absorbance of the antibody-free reaction solution from the absorbance of the antibody-supplemented reaction solution.

- ⁵ solution from the absorbance of the antibody-supplemented reaction solution. [0133] TBCP (TBSB containing 93.75 μM phospholipid solution (SYSMEX CO.), 7.5 mM CaCl₂, and 1.5 mM MgCl₂) was used as the solvent for Human Factor IXa, Novact (registered trademark) M, and Human Factor X. A coloring substrate solution S-2222[™] (CHROMOGENIX) was dissolved in purified water at 1.47 mg/mL, and then used in this assay.
- ¹⁰ **[0134]** F.Xase inhibitory actions of the antibodies were also evaluated by previously described methods.

[0135] The F.Xa generation-promoting activities of each of the modified bispecific antibodies are indicated in Fig. 4, and the F.Xase inhibitory actions of each of the bispecific antibodies are indicated in Fig. 5.

[0136] The inventors of the present application obtained Q85-G4k/J268-G4h/L406-k, Q85-G4k/J321-G4h/L334-k, Q64-z7/J344-z107/L406-k, and Q64-z7/J326-z107/L334-k as bispecific antibodies with a high F.Xa generation-promoting activity and a low F.Xase inhibitory action. In addition, they discovered Q64-z7 (SEQ ID NO: 10) and Q85-G4k (SEQ ID NO: 11) as the anti-human F.IXa antibody H chain, and L334-k (SEQ ID NO: 30) and L406-k (SEQ ID NO: 33) as the

- commonly shared antibody L chains with increased F.Xa generation-promoting activity. Though F.Xase inhibitory actions increased slightly, F.Xa generation-promoting activity increased greatly in Q85-G4k/J268-G4h/L406-k, Q85-G4k/J321-G4h/L334-k, Q64-z7/J344-z107/L406-k, and Q64-z7/J326-z107/L334-k. Since these modified antibodies have very large
- F.Xa generation-promoting activities compared to increase in F.Xase inhibitory actions, the F.Xa generation-promoting activity and the F.Xase inhibitory action could further be separated compared to the prototype antibodies. This way, combinations that suppress the F.Xase inhibitory action and increase the F.Xa generation-promoting activity were discovered.
- [0137] While a higher F.Xa generation-promoting activity is preferred for the discovered prototype antibodies to functionally substitute for F.VIII by bispecific antibodies, lower F.Xase inhibitory action was considered favorable to clinically use for patients maintaining F.VIII functions or patients receiving treatment with F.VIII formulations. Therefore, further modifications were performed to produce bispecific antibodies in which F.Xase inhibitory action is not increased while F.Xa generation-promoting activity is further increased.
- [0138] As a result, Q153-G4k/J232-G4h/L406-k, Q354-z106/J259-z107/L324-k, Q360-G4k/J232-G4h/L406-k, Q360-z118/J300-z107/L334-k, Q405-G4k/J232-G4h/L248-k, Q458-z106/J346-z107/L408-k, Q460-z121/J327-z119/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L334-k, Q499-z118/J327-z107/L377-k, and Q153-G4k/J142-G4h/L180-k were obtained as bispecific antibodies with a high F.Xa generation-promoting activity and a low F.Xase inhibitory action. In addition, the Inventors discovered Q153-G4k (SEQ ID NO: 12), Q354-z106 (SEQ ID NO: 13), Q360-G4k (SEQ ID NO: 14), Q360-z118 (SEQ ID NO: 15),
- ³⁵ Q405-G4k (SEQ ID NO: 16), Q458-z106 (SEQ ID NO: 17), Q460-z121 (SEQ ID NO: 18), Q499-z118 (SEQ ID NO: 19), and Q499-z121 (SEQ ID NO: 20) as the anti-human F.IXa antibody H chain, J232-G4h (SEQ ID NO: 21), J259-z107 (SEQ ID NO: 22), J300-z107 (SEQ ID NO: 23), J327-z107 (SEQ ID NO: 24), J327-z119 (SEQ ID NO: 25), J339-z119 (SEQ ID NO: 26), J346-z107 (SEQ ID NO: 27), J142-G4h (SEQ ID NO: 170) as the anti-human F.X antibody H chains with increased F.Xa generation-promoting activity, and L248-k (SEQ ID NO: 28), L324-k (SEQ ID NO: 29), L377-k (SEQ
- ID NO: 31), L404-k (SEQ ID NO: 32), L408-k (SEQ ID NO: 34), and L180-k (SEQ ID NO: 171) as the commonly shared antibody L chains.
 [0139] Since these antibodies have very high F.Xa generation-promoting activities while having suppressed F.Xase

inhibitory actions, they may have very useful properties for patients maintaining an F.VIII function and patients receiving treatment with F.VIII formulations. Since antibodies generally have long half-lives, and can be administered subcutaneously, these bispecific antibodies may be of great value to hemophilia A patients, when compared to existing replacement

therapy by intravenous administration of existing F.VIII formulations for hemophilia A. **[0140]** Sequence comparisons of the variable regions of each of the chains used in Example 1 and Example 2 are shown in Figs. 6A to D. For example, to enhance the F.Xa generation-promoting activity of a bispecific antibody, the following amino acids were found to be important: in the anti-human F.IXa antibody H chain, isoleucine at position 34,

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- ⁵⁰ asparagine, glutamine, or serine at position 35, serine at position 49, arginine at position 61, glutamic acid at position 62, serine or threonine at position 96, lysine or arginine at position 98, serine or glutamic acid at position 99, phenylalanine or tyrosine at position 100, glycine at position 100b, tyrosine at position 102, and such; in the anti-human F.X antibody H chain, aspartic acid at position 35, arginine at position 53, lysine at position 73, glycine at position 76, lysine or arginine at position 96, tyrosine at position 98, tyrosine at position 100, histidine at position 100a, and such; in the commonly
- ⁵⁵ shared antibody L chain, lysine or arginine at position 27, glutamic acid at position 30, arginine at position 31, glutamine at position 32, arginine or glutamine at position 50, serine at position 52, arginine at position 53, lysine at position 54, glutamic acid at position 55, serine at position 92, serine at position 93, proline at position 94, proline at position 95, and such (the variable region amino acids are numbered by Kabat numbering (Kabat EA et al. 1991. Sequences of Proteins)

of Immunological Interest. NIH)).

Industrial Applicability

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- ⁵ **[0141]** The present invention provides multispecific antigen-binding molecules having a high activity of functionally substituting for F.VIII, which are antibodies that recognize both an enzyme and its substrate. Furthermore, the present invention provides multispecific antigen-binding molecules with a high activity of functionally substituting for F.VIII and a low F.Xase inhibitory action, which are antibodies that recognize both an enzyme and its substrate.
- [0142] Since humanized antibodies may generally have high stability in blood and low immunogenicity, multispecific antibodies of the present invention may be very promising as pharmaceuticals.
 - [0143] Furthermore, the present invention relates to the following items:
- A multispecific antigen-binding molecule that functionally substitutes for blood coagulation factor VIII, which comprises a first antigen-binding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and a second antigen-binding site that recognizes blood coagulation factor X, wherein the functional substitution for blood coagulation factor VIII results from an activated blood coagulation factor X (F.Xa) generation-promoting activity higher than the activity of a bispecific antibody (hA69-KQ/hB26-PF/hAL-AQ) which comprises an H chain comprising SEQ ID NOs: 165 and 166, and a commonly shared L chain comprising SEQ ID NO: 167.
- 20 2. The multispecific antigen-binding molecule of item 1, which comprises a first polypeptide comprising a first antigenbinding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and a third polypeptide comprising a third antigen-binding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX, as well as a second polypeptide comprising a second antigen-binding site that recognizes blood coagulation factor X and a fourth polypeptide comprising a fourth antigen-binding site that recognizes blood coagulation factor X.

3. The multispecific antigen-binding molecule of item 2, wherein the first polypeptide and the third polypeptide each comprises an antigen-binding site of an H chain or L chain of an antibody against blood coagulation factor IX or activated blood coagulation factor IX, respectively; and the second polypeptide and the fourth polypeptide each comprises an antigen-binding site of an H chain or L chain of an antibody against blood coagulation factor X, respectively.

4. The multispecific antigen-binding molecule of item 3, wherein the antigen-binding site of the first polypeptide comprises an antigen-binding site which comprises H chain CDRs consisting of any one of the amino acid sequences selected from the following (a1) to (a11), or an antigen-binding site functionally equivalent thereto, and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises H chain CDRs consisting of any one of the amino acid sequences selected from the following (b1) to (b11), or an antigen-binding site functionally equivalent thereto.

40 (a1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 75, 76, and 77 (H chain CDRs of Q1), respectively; (a2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 78, 79, and 80 (H chain CDRs of Q31), respectively; (a3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 81, 45 82, and 83 (H chain CDRs of Q64), respectively; (a4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 84, 85, and 86 (H chain CDRs of Q85), respectively; (a5) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 87, 88, and 89 (H chain CDRs of Q153), respectively; 50 (a6) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 90, 91, and 92 (H chain CDRs of Q354), respectively; (a7) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 93, 94, and 95 (H chain CDRs of Q360), respectively; (a8) an antigen-binding site comprising the of H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 55 96, 97, and 98 (H chain CDRs of Q405), respectively; (a9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 99, 100, and 101 (H chain CDRs of Q458), respectively; (a10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs:

102, 103, and 104 (H chain CDRs of Q460), respectively; (a11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 105, 106, and 107 (H chain CDRs of Q499), respectively; (b1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 5 108, 109, and 110 (H chain CDRs of J232), respectively; (b2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 111, 112, and 113 (H chain CDRs of J259), respectively; (b3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 114, 115, and 116 (H chain CDRs of J268), respectively; 10 (b4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 117, 118, and 119 (H chain CDRs of J300), respectively; (b5) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 120, 121, and 122 (H chain CDRs of J321), respectively; (b6) an antigen-binding site comprising the H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 15 123, 124, and 125 (H chain CDRs of J326), respectively; (b7) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 126, 127, and 128 (H chain CDRs of J327), respectively; (b8) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 129, 130, and 131 (H chain CDRs of J339), respectively; 20 (b9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 132, 133, and 134 (H chain CDRs of J344), respectively; (b10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 135, 136, and 137 (H chain CDRs of J346), respectively; and (b11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 amino acid sequences of SEQ ID NOs: 25 174, 175, and 176 (H chain CDRs of J142), respectively. 5. The multispecific antigen-binding molecule of item 3, wherein the antigen-binding site of the first polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (a1) to (a11), or an antigen-binding site functionally equivalent thereto, 30 and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11), or an antigen-binding site functionally equivalent thereto: (a1) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 35 (H 35 chain variable region of Q1); (a2) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 36 (H chain variable region of Q31); (a3) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 37 (H chain variable region of Q1); 40 (a4) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 38 (H chain variable region of Q85); (a5) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 39 (H chain variable region of Q153); (a6) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 40 (H 45 chain variable region of Q354); (a7) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 41 (H chain variable region of Q360); (a8) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 42 (H chain variable region of Q405); 50 (a9) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 43 (H chain variable region of Q458); (a10) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 44 (H chain variable region of Q460); (a11) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 45 55 (H chain variable region of Q499); (b1) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 46 (H chain variable region of J232);

(b2) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 47 (H

	chain variable region of J259);
	(b3) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 48 (H
	chain variable region of J268);
r.	(b4) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 49 (H
5	chain variable region of J300); (b5) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 50 (H
	chain variable region of J321);
	(b6) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 51 (H
	chain variable region of J326);
10	(b7) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 52 (H
	chain variable region of J327);
	(b8) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 53 (H
	chain variable region of J339);
15	(b9) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 54 (H chain variable region of J344);
10	(b10) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 55
	(H chain variable region of J346); and
	(b11) an antigen-binding site comprising an H chain variable region amino acid sequence of SEQ ID NO: 172
	(H chain variable region of J142).
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	6. The multispecific antigen-binding molecule of item 3, wherein the antigen-binding sites included in the third
	polypeptide and the fourth polypeptide comprise an antigen-binding site which comprises L chain CDRs consisting
	of any one of the amino acid sequences selected from the following (c1) to (c10), or an antigen-binding site functionally equivalent thereto:
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	(c1) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 138,
	139, and 140 (L chain CDR of L2), respectively;
	(c2) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 141,
	142, and 143 (L chain CDR of L45), respectively;
30	(c3) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 144, 145, and 146 (L chain CDR of L248), respectively;
	(c4) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 147,
	148, and 149 (L chain CDR of L324), respectively;
	(c5) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 150,
35	151, and 152 (L chain CDR of L334), respectively;
	(c6) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 153,
	154, and 155 (L chain CDR of L377), respectively;
	(c7) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 156,
40	157, and 158 (L chain CDR of L404), respectively; (c8) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 159,
	160, and 161 (L chain CDR of L406), respectively;
	(c9) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs: 137,
	138, and 139 (L chain CDR of L408), respectively; and
	(c10) an antigen-binding site comprising an L chain CDR1, 2, and 3 amino acid sequences of SEQ ID NOs:
45	177, 178, and 179 (L chain CDR of L180), respectively.
	7. The multispecific antigen-binding molecule of item 3, wherein the antigen-binding sites included in the third
	polypeptide and the fourth polypeptide comprise an antigen-binding site which comprises an L chain variable region
	consisting of any one of the amino acid sequences selected from the following (c1) to (c10), or an antigen-binding
50	site functionally equivalent thereto:
	(c1) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 56 (L
	chain variable region of L2); (a2) an antigan binding aite comprising on Labein variable region amine acid acquance of SEO ID NO: 57 (L
55	(c2) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 57 (L chain variable region of L45);
	(c3) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 58 (L
	chain variable region of L248);
	(c4) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 59 (L

	chain variable region of L324); (c5) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 60 (L
	chain variable region of L334); (c6) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 61 (L
5	chain variable region of L377);
	(c7) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 62 (L chain variable region of L404);
	(c8) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 63 (L chain variable region of L406);
10	(c9) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 64 (L chain variable region of L408); and
	(c10) an antigen-binding site comprising an L chain variable region amino acid sequence of SEQ ID NO: 173 (L chain variable region of L180).
15	8. The multispecific antigen-binding molecule of item 3, wherein the first and second polypeptides further comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region.
20	9. The multispecific antigen-binding molecule of item 3, wherein the first and second polypeptides comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region, and wherein the third polypeptide and the fourth polypeptide are a commonly shared L chain.
25	10. The multispecific antigen-binding molecule of item 8 or 9, wherein the first polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from the group consisting of the following (d1) to (d6) or the group consisting of the following (d7) to (d9), and the second polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from a group different from that of the above-mentioned first polypeptide:
30	 (d1) an H chain constant region of SEQ ID NO: 65 (G4k); (d2) an H chain constant region of SEQ ID NO: 66 (z7); (d3) an H chain constant region of SEQ ID NO: 67 (z55); (d4) an H chain constant region of SEQ ID NO: 68 (z106);
35	 (d4) an H chain constant region of SEQ ID NO: 69 (z118); (d5) an H chain constant region of SEQ ID NO: 70 (z121); (d7) an H chain constant region of SEQ ID NO: 71 (G4h); (d8) an H chain constant region of SEQ ID NO: 72 (z107); and (d9) an H chain constant region of SEQ ID NO: 73 (z119).
40	11. The multispecific antigen-binding molecule of item 8 or 9, wherein the third and fourth polypeptides comprise the antibody L chain constant region consisting of the following amino acid sequence of:
	(e) an L chain constant region of SEQ ID NO: 74 (k).
45	12. The multispecific antigen-binding molecule of item 8 or 9, wherein the first polypeptide comprises any one antibody H chain selected from the following (a1) to (a14), the second polypeptide comprises any one antibody H chain selected from the following (b1) to (b12), and the third polypeptide and the fourth polypeptide comprise any one antibody L chain selected from the following (c1) to (c10):
50	 (a1) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 1 (Q1-G4k); (a2) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 2 (Q31-z7); (a3) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 3 (Q64-z55); (a4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 10 (Q64-z7);
55	 (a4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 10 (Q04-27), (a5) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 11 (Q85-G4k); (a6) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 12 (Q153-G4k); (a7) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 13 (Q354-z106); (a8) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 14 (Q360-G4k); (a9) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 15 (Q360-z118); (a10) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 16 (Q405-G4k);

	(a11) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 17 (Q458-z106);
	(a12) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 18 (Q460-z121);
	(a13) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 19 (Q499-z118);
	(a14) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 20 (Q499-z121);
5	(b1) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 4 (J268-G4h);
	(b2) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 5 (J321-G4h);
	(b3) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 6 (J326-z107);
	(b4) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 7 (J344-z107);
	(b5) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 21 (J232-G4h);
10	(b6) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 22 (J259-z107);
	(b7) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 23 (J300-z107);
	(b8) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 24 (J327-z107);
	(b9) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 25 (J327-z119);
	(b10) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 26 (J339-z119);
15	(b11) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 27 (J346-z107);
	(b12) an antibody H chain consisting of the amino acid sequence of SEQ ID NO: 170 (J142-G4h);
	(c1) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 8 (L2-k);
	(c2) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 9 (L45-k);
	(c3) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 28 (L248-k);
20	(c4) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 29 (L324-k);
	(c5) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 30 (L334-k);
	(c6) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 31 (L377-k);
	(c7) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 32 (L404-k);
	(c8) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 33 (L406-k);
25	(c9) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 34 (L408-k); and
	(c10) an antibody L chain consisting of the amino acid sequence of SEQ ID NO: 171 (L180-k).

- 13. The multispecific antigen-binding molecule of item 1, wherein the first polypeptide comprises an antigen-binding site which binds to an epitope overlapping with an epitope that binds to an antibody consisting of the antibody H chain of any one of (a1) to (a14) and the antibody L chain of any one of (c1) to (c10) of item 12, and the second polypeptide comprises an antigen-binding site which binds to an epitope overlapping with an epitope overlapping with an epitope overlapping with an epitope that binds to an antibody consisting of the antibody L chain of any one of (c1) to (c10) of item 12, and the second an antibody consisting of the antibody H chain of any one of (b1) to (b12) and the antibody L chain of any one of (c1) to (c10) of item 12.
- ³⁵ 14. The multispecific antigen-binding molecule of item 8 or 9, wherein the first polypeptide comprises any one antibody H chain selected from the following (e1) to (e3), the second polypeptide comprises any one antibody H chain selected from the following (f1) to (f3), and the third polypeptide and the fourth polypeptide comprise any one antibody L chain selected from the following (g1) to (g4):
- 40 (e1) an H chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody consisting of an antibody H chain of any one of (a1) to (a14) and an antibody L chain of any one of (c1) to (c10), of claim 12;

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(e2) an antibody H chain, wherein at least one amino acid residue selected from the amino acid residues at positions 34, 35, 49, 61, 62, 96, 98, 100, 100b, and 102 by Kabat numbering in any one antibody H chain selected from (e1) is substituted with another amino acid;

(e3) an antibody H chain, wherein by Kabat numbering, the amino acid residue at position 34 is isoleucine, the amino acid residue at position 35 is asparagine, glutamine, or serine, the amino acid residue at position 49 is serine, the amino acid residue at position 61 is arginine, the amino acid residue at position 62 is glutamic acid, the amino acid residue at position 96 is serine or threonine, the amino acid residue at position 98 is lysine or arginine, the amino acid residue at position 100 is phenylalanine or tyrosine, the amino acid residue at position 100 is glycine, or the amino acid residue at position 102 is tyrosine in any antibody H chain selected from (e1); (f1) an H chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody consisting of an antibody H chain of any of (b1) to (b12) of claim 12 and an antibody L chain of any of (c1) to (c10) of claim 12;

⁵⁵ (f2) an antibody H chain, wherein at least one amino acid residue selected from the amino acid residues at positions 35, 53, 73, 76, 96, 98, 100, and 100a by Kabat numbering in any antibody H chain of (f1) is substituted with another amino acid;

(f3) an antibody H chain, wherein by Kabat numbering, the amino acid residue at position 35 is aspartic acid,

the amino acid residue at position 53 is arginine, the amino acid residue at position 73 is lysine, the amino acid residue at position 76 is glycine, the amino acid residue at position 96 is lysine or arginine, the amino acid residue at position 98 is tyrosine, the amino acid residue at position 100 is tyrosine, or the amino acid residue at position 100 is tyrosine, or the amino acid residue at position 100 is histidine in any one antibody H chain selected from (f1);

⁵ (g1) an L chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody which consists of an antibody H chain of any one of (a1) to (a14) and an antibody L chain of any one of (c1) to (c10), of claim 12;

(g2) an L chain of an antibody which binds to an epitope overlapping with an epitope bound by an antibody which consists of an antibody H chain of any one of (b1) to (b12) and an antibody L chain of any one of (c1) to (c10), of claim 12;

(g3) an antibody L chain, wherein at least one amino acid residue selected from the amino acid residues at positions 27, 30, 31, 32, 50, 52, 53, 54, 55, 92, 93, 94, and 95 by Kabat numbering in the antibody L chain of either (g1) or (g2) is substituted with another amino acid; and

(g4) an antibody L chain, wherein by Kabat numbering, the amino acid residue at position 27 is lysine or arginine,
 the amino acid residue at position 30 is glutamic acid, the amino acid residue at position 31 is arginine, the amino acid residue at position 32 is glutamine, the amino acid residue at position 50 is arginine or glutamine, the amino acid residue at position 52 is serine, the amino acid residue at position 53 is arginine, the amino acid residue at position 54 is lysine, the amino acid residue at position 55 is glutamic acid, the amino acid residue at position 92 is serine, the amino acid residue at position 93 is serine, the amino acid residue at position 94 is proline, or the amino acid residue at position 95 is proline in the antibody L chain of either (g1) or (g2).

15. The multispecific antigen-binding molecule of any one of items 1 to 14, wherein the multispecific antigen-binding molecule is a multispecific antibody.

²⁵ 16. A bispecific antibody of any one of the following (a) to (u):

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(a) a bispecific antibody (Q1-G4k/J268-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;

(b) a bispecific antibody (Q1-G4k/J321-G4h/L45-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 9;

- (c) a bispecific antibody (Q31-z7/J326-z107/L2-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 2, the second polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 8;
- (d) a bispecific antibody (Q64-z55/J344-z107/L45-k), wherein the first polypeptide is an H chain consisting of
 the amino acid sequence of SEQ ID NO: 3, the second polypeptide is an H chain consisting of the amino acid
 sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain
 of SEQ ID NO: 9;

(e) a bispecific antibody (Q64-z7/J326-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(f) a bispecific antibody (Q64-z7/J344-z107/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 10, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

(g) a bispecific antibody (Q85-G4k/J268-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;

⁵⁵ (h) a bispecific antibody (Q85-G4k/J321-G4h/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 11, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;

(i) a bispecific antibody (Q153-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of zSEQ ID NO: 33;

- ⁵ (j) a bispecific antibody (Q354-z106/J259-z107/L324-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 13, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 22, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 29;
- (k) a bispecific antibody (Q360-G4k/J232-G4h/L406-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of zSEQ ID NO: 14, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 33;
 - (I) a bispecific antibody (Q360-z118/J300-z107/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 15, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 23, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;
 - (m) a bispecific antibody (Q405-G4k/J232-G4h/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 16, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;
 - (n) a bispecific antibody (Q458-z106/J346-z107/L408-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 17, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of zSEQ ID NO: 34;
- (o) a bispecific antibody (Q460-z121/J327-z119/L334-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 18, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 30;
- (p) a bispecific antibody (Q499-z118/J327-z107/L334-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of zSEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino
 acid sequence of zSEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared
 L chain of SEQ ID NO: 30;
 - (q) a bispecific antibody (Q499-z118/J327-z107/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31;
 - (r) a bispecific antibody (Q499-z118/J346-z107/L248-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 19, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 28;
 - (s) a bispecific antibody (Q499-z121/J327-z119/L404-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 32;
- (t) a bispecific antibody (Q499-z121/J339-z119/L377-k), wherein the first polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 20, the second polypeptide is an H chain consisting of the amino acid sequence of zSEQ ID NO: 26, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of SEQ ID NO: 31; and
- (u) a bispecific antibody (Q153-G4k/J142-G4h/L180-k), wherein the first polypeptide is an H chain consisting
 of the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of the amino
 acid sequence of SEQ ID NO: 170, and the third polypeptide and the fourth polypeptide are a commonly shared
 L chain of SEQ ID NO: 171.
- 17. A nucleic acid encoding the multispecific antigen-binding molecule of any one of items 1 to 15 or the bispecific antibody of item 16.

18. A vector inserted with the nucleic acid of item 17.

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19. A cell comprising the nucleic acid of item 17 or the vector of item 18.

20. A method for producing the multispecific antigen-binding molecule of any one of items 1 to 15 or the bispecific antibody of item 16 by culturing the cell of item 19.

- 21. A pharmaceutical composition comprising the multispecific antigen-binding molecule of any one of items 1 to 15 or the bispecific antibody of item 16, and a pharmaceutically acceptable carrier.
- 22. The composition of item 21, which is a pharmaceutical composition used for prevention and/or treatment of bleeding, a disease accompanying bleeding, or a disease caused by bleeding.

23. The composition of item 22, wherein the bleeding, the disease accompanying bleeding, or the disease caused by bleeding is a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII.

24. The composition of item 23, wherein the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is hemophilia A.

25. The composition of item 23, wherein the disease that develops and/or progresses due to a decrease or deficiency
 in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is a disease showing emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII.

26. The composition of item 23, wherein the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is acquired hemophilia.

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27. The composition of item 23, wherein the disease that develops and/or progresses due to a decrease in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII is von Willebrand disease.

28. A method for preventing and/or treating bleeding, a disease accompanying bleeding, or a disease caused by
 ³⁰ bleeding, which comprises the step of administering the multispecific antigen-binding molecule of any one of items
 1 to 15 or the bispecific antibody of item 16, or the composition of any one of items 21 to 27.

29. A kit for use in the prevention and/or treatment method of item 28, which comprises at least the multispecific antigen-binding molecule of any one of items 1 to 15 or the bispecific antibody of item 16, or the composition of any one of items 21 to 27.

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SEQUENCE LISTING

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	Val Val Ser Val 305	L Leu Thr Val Leu His 310	Gln Asp Trp Leu Asn 315	Gly Lys 320
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	Asp :		C 1 m	T ~~	₩ ∍1	•	a 1		D	C1.v	Lus	Glv	Leu	Glu	Trp	Val
			35	пр	Vai	Arg	GIN	40	PIO	Gry	цуб	0-1	45			
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35	Pro Ser Val	. Phe Leu Phe 245	Pro Pro Lys Pro 250	Lys Asp Thr I	Leu Met Ile 255
	Ser Arg Thr	Pro Glu Val 260	Thr Cys Val Val 265	-	Ser Gln Glu 270
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	Glu Tyr Lys	Cys Lys Val 325	Ser Asn Lys Gly 330	Leu Pro Ser S	Ser Ile Glu 335
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35 40	Gln V 1 Ser I Asp J Ser S 5	> 1 /al Leu Ele Ser 50 Gly	9 Gln Arg Gln 35 Ile Arg	Leu 20 Trp Ser Phe	5 Ser Val Pro Thr	Cys Arg Ser Ile 70	Ala Gln Gly 55 Ser	Ala 40 Gln Arg	Ser 25 Pro Ser Asp	10 Gly Gly Thr Asn	Phe Lys Tyr Ser 75	Thr Gly Tyr 60 Lys	Phe Leu 45 Arg Asn	Ser 30 Glu Arg Thr	15 Tyr Trp Glu Leu	Tyr Val Val Tyr 80
35 40 45	Gln V 1 Ser I Asp I Ser S 5 Lys 0 65	> 1 /al Leu Ile Ser 50 Sly	9 Gln Arg Gln 35 Ile Arg Met	Leu 20 Trp Ser Phe Asn	5 Ser Val Pro Thr Ser 85	Cys Arg Ser Ile 70 Leu	Ala Gln Gly 55 Ser Arg	Ala 40 Gln Arg Ala	Ser 25 Pro Ser Asp Glu	10 Gly Gly Thr Asn Asp 90	Phe Lys Tyr Ser 75 Thr	Thr Gly Tyr 60 Lys Ala	Phe Leu 45 Arg Asn Val	Ser 30 Glu Arg Thr Tyr	15 Tyr Trp Glu Leu Tyr 95	Tyr Val Val Tyr 80 Cys

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	Thr Le	u Pro 355	Pro	Ser	Gln	Lys	Glu 360	Met	Thr	Lys	Asn	Gln 365	Val	Ser	Leu
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5	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr V 405 410 4	/al Asp 415
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-	Asn Ser	Gly Ala	Leu T	hr Ser	Gly Val	His Thr	Phe Pro	Ala Val	Leu

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	Gln Pro 385	Glu Asn	Asn Ty: 39		r Thr Pro	Pro Val Leu 395	Asp Ser Asp 400
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	Gln Ser	Ser Gly 1	Leu Tyr	Ser Leu	Ser Ser	Val Val	Thr Val	Pro Ser

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	Leu Phe	Pro Pro	Lys Pro 245	Lys Asp	o Thr Leu Met 250	Ile Ser Arc	g Thr Pro 255
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	Lys Val Ser Asn Lys 325	Gly Leu Pro Ser Ser 330		Ile Ser 335
25	Lys Ala Lys Gly Gln 340	Pro Arg Glu Pro Glr 345	n Val Tyr Thr Leu 350	Pro Pro
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35	Lys Gly Phe Tyr Pro 370	Ser Asp Ile Ala Val 375	L Glu Trp Glu Ser 380	Asn Gly
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40	Gly Ser Phe Phe Leu 405	Tyr Ser Lys Leu Thr 410		Arg Trp 415
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Gly (145	Суз	Leu	Val	Lys	Asp 150	Tyr	Phe	Pro	Glu	Pro 155	Val	Thr	Val	Ser	Trp 160
Asn :	Ser	Gly	Ala	Leu 165	Thr	Ser	Gly	Val	His 170	Thr	Phe	Pro	Ala	Val 175	Leu
Gln :	Ser	Ser	Gly 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pro	Ser
Ser :	Ser	Leu 195	Gly	Thr	Gln	Thr	Tyr 200	Thr	Cys	Asn	Val	Asp 205	His	Lys	Pro
Ser i	Asn 210	Thr	Lys	Val	Asp	Lys 215	Arg	Val	Glu	Ser	Lys 220	Tyr	Gly	Pro	Pro
Cys 1 225	Pro	Pro	Cys	Pro	Ala 230	Pro	Glu	Phe	Leu	Gly 235	Gly	Pro	Ser	Val	Phe 240
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Pro Leu Ala P r Thr Ala Ala Leu 130 C 35 Gly Cys Leu V l Thr Val Ser Trp 145 160 e Pro Ala Val Leu Asn Ser Gly A 175 40 l Thr Val Pro Ser Gln Ser Ser G 190 1 45 Ser Ser Leu G l Asp His Lys Pro 195 205 Ser Asn Thr I s Tyr Gly Pro Pro 50 210 0 Cys Pro Pro C y Pro Ser Val Phe

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn

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15	Leu Thr Val Leu 305	n His Gln Asp Trp Leu 310	Asn Gly Lys Glu Tyr 315	r Lys Cys 320
20	Lys Val Ser Asn	n Lys Gly Leu Pro Ser 325	Ser Ile Glu Lys Thr 330	Ile Ser 335
	Lys Ala Lys Gly 340	y Gln Pro Arg Glu Pro)		
25	Ser Gln Glu Glu 355	n Met Thr Lys Asn Gln 360	a Val Ser Leu Thr Cys 365	s Leu Val
30	Lys Gly Phe Tyr 370	r Pro Ser Asp Ile Ala 375	N Val Glu Trp Glu Ser 380	Asn Gly
25	Gln Pro Glu Asn 385	n Asn Tyr Lys Thr Thr 390	Pro Pro Val Leu Asp 395	Ser Asp 400
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5	Leu Ala	Т гр Ту 35	: Gln	Gln	Lys	Pro 40	Gly	Gln	Ala	Pro	Arg 45	Leu	Leu	Ile
10	Tyr Arg 50	7 Ala Sei	r Arg	Lys	Glu 55	Ser	Gly	Val	Pro	Asp 60	Arg	Phe	Ser	Gly
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15	Glu Asp	o Ile Ala	1 Thr 85	Tyr	Tyr	Cys	Gln	Gln 90	Tyr	Ser	Ser	Pro	Pro 95	Leu
20	Thr Phe	e Gly Gly 100	_	Thr	Lys	Val	Glu 105	Ile	Lys	Arg	Thr	Val 110	Ala	Ala
25	Pro Ser	Val Phe 115	a Ile	Phe	Pro	Pro 120	Ser	Asp	Glu	Gln	Leu 125	Lys	Ser	Gly
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30	Lys Val 145	. Gln Tr <u>r</u>) Lys	Val 150	Asp	Asn	Ala	Leu	Gln 155	Ser	Gly	Asn	Ser	Gln 160
35	Glu Ser	Val Thi	Glu 165	Gln	Asp	Ser	Lys	Asp 170	Ser	Thr	Tyr	Ser	Leu 175	Ser
40	Ser Thr	: Leu Thi 180		Ser	Lys	Ala	As p 185	Tyr	Glu	Lys	His	Lys 190	Val	Tyr
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	Tyr Arg Ala Asp Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser GJ 50 55 60	L y
15	Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pa 65 70 75 80	
20	Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Pro Pro Le 85 90 95	¥u
25	Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Al 100 105 110	la
	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser G 115 120 125	ЧY
30	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Al 130 135 140	la
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	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Se 165 170 175	er
40	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Ty 180 185 190	ŗr
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15	Tyr	Gln 50	Ala	Ser	Arg	Lys	Glu 55	Ser	Gly	Val	Pro	Asp 60	Arg	Phe	Ser	Gly
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25	Glu	Asp	Ile	Ala	Thr 85	Tyr	Tyr	Cys	Gln	Gln 90	Tyr	Ser	Ser	Pro	Pro 95	Leu
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30	Pro	Ser	Val 115	Phe	Ile	Phe	Pro	Pro 120	Ser	Asp	Glu	Gln	Leu 125	Lys	Ser	Gly
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40	Glu	Ser	Val	Thr	Glu 165	Gln	Asp	Ser	Lys	Asp 170	Ser	Thr	Tyr	Ser	Leu 175	Ser
45	Ser	Thr	Leu	Thr 180	Leu	Ser	Lys	Ala	As p 185	Tyr	Glu	Lys	His	Lys 190	Val	Tyr
50	Ala	Cys	Glu 195	Val	Thr	His	Gln	Gly 200	Leu	Ser	Ser	Pro	Val 205	Thr	Lys	Ser
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20	Tyr Gln Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly 50 55 60
25	Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80
	Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Pro Pro Leu 85 90 95
30	Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala 100 105 110
35	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly 115 120 125
	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala 130 135 140
40	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln 145 150 155 160
45	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175
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	Lys Va 145	l Gln	Trp	Lys	Val 150	Asp	Asn	Ala	Leu	Gln 155	Ser	Gly	Asn	Ser	Gln 160
45	Glu Se	r Val	Thr	Glu 165	Gln	Asp	Ser	Lys	Asp 170	Ser	Thr	Tyr	Ser	Le u 175	Ser
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25	Tyr Arg Ala Asp Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly 50 55 60
30	Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80
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	Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala 100 105 110
40	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly 115 120 125
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	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175
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	Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr 65 70 75 80	
35	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95	
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25	Asp Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45											
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	Arg Leu Thr Val Asp Lys Ser Arg Trp Gln G 290 295	Glu Gly Asn Val Phe Ser 300
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45	Asp Val 145	Ser Gln	Glu Asp 150		Val Gln	Phe Asn 155	Trp Tyr	Val Asp 160
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EP 3 318 633 A1 Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu <210> 69 <211> 325 <212> PRT <213> Artificial <220> <223> artificial sequence <400> 69

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	Asp	Thr 130	Leu	Met	Ile	Ser	Arg 135	Thr	Pro	Glu	Val	Thr 140	Cys	Val	Val	Val
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25	Asn	Ser	Thr	Tyr 180	Arg	Val	Val	Ser	Val 185	Leu	Thr	Val	Leu	His 190	Gln	Asp
20	Trp	Leu	As n 195	Gly	Lys	Glu	Tyr	Lys 200	Cys	Lys	Val	Ser	Asn 205	Lys	Gly	Leu
30	Pro	Ser 210	Ser	Ile	Glu	Lys	Thr 215	Ile	Ser	Lys	Ala	Lys 220	Gly	Gln	Pro	Arg
35	Glu 225	Pro	Gln	Val	Tyr	Thr 230	Leu	Pro	Pro	Ser	Gln 235	Lys	Glu	Met	Thr	Lys 240
	Asn	Gln	Val	Ser	Leu 245	Thr	Cys	Leu	Val	Lys 250	Gly	Phe	Tyr	Pro	Ser 255	Asp
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	Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser 50 55 60
25	Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr 65 70 75 80
30	Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys 85 90 95
35	Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro 100 105 110
	Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys 115 120 125
40	Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val 130 135 140
45	Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp 145 150 155 160
50	Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 165 170 175
	Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 180 185 190
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EP 3 318 633 A1 Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro <210> 71 <211> 325 <212> PRT <213> Artificial <220> <223> artificial sequence <400> 71 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

⁵⁰ Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser 50
 ⁵⁵ Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr 65
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10	Glu	Phe	Leu 115	Gly	Gly	Pro	Ser	Val 120	Phe	Leu	Phe	Pro	Pro 125	Lys	Pro	Lys
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15	Asp 145	Val	Ser	Gln	Glu	Asp 150	Pro	Glu	Val	Gln	Phe 155	Asn	Trp	Tyr	Val	As p 160
20	Gly	Val	Glu	Val	His 165	Asn	Ala	Lys	Thr	Lys 170	Pro	Arg	Glu	Glu	Gln 175	Phe
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50	Arg	Leu 290	Thr	Val	Asp	Lys	Ser 295	Arg	Trp	Gln	Glu	Gly 300	Asn	Val	Phe	Ser
	Суз 305	Ser	Val	Met	His	Glu 310	Ala	Leu	His	Asn	His 315	Tyr	Thr	Gln	Lys	Ser 320
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	Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser 50 55 60
25	Leu Ser Ser Val Val Thr Val Pro Ser Ser Leu Gly Thr Gln Thr 65 70 75 80
30	Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys 85 90 95
35	Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro 100 105 110
	Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys 115 120 125
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45	Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp 145 150 155 160
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5	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys 225 230 235 240	
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	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 260 265 270	
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~	Asn Ser Thr Tyr 180	Arg Val Val Ser Va 18		His Gln Asp 190
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25	Thr Tyr 65	Ser Leu	Ser	Ser 70	Thr	Leu	Thr	Leu	Ser 75	Lys	Ala	Asp	Tyr	Glu 80
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55	<211> / <212> PRT	
	<213> Artificial	

	<220> <223> artificial sequence
5	<400> 178
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10	<210> 179 <211> 9
	<212> PRT <213> Artificial
15	<220> <223> artificial sequence
	<400> 179
20	Gln Gln Tyr Tyr Ser Pro Pro Leu Thr 1 5

Claims

- A multispecific antibody that functionally substitutes for blood coagulation factor VIII, which comprises a first polypeptide comprising a first antigen-binding site that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX, as well as a second polypeptide comprising a fourth antigen-binding site that recognizes blood coagulation factor X and a fourth polypeptide comprising a fourth antigen-binding site that recognizes blood coagulation factor X, and a fourth polypeptide comprising a fourth antigen-binding site that recognizes blood coagulation factor X, wherein the first polypeptide and the third polypeptide each comprises an antigen-binding site of an H chain or L chain of an antibody against blood coagulation factor X, respectively; and the second polypeptide and the fourth polypeptide each comprises an antigen-binding site of an H chain or L chain of an antibody against blood coagulation factor X, respectively, wherein
- (a) the antigen-binding site of the first polypeptide comprises an antigen-binding site which comprises H chain
 CDRs consisting of any one of the amino acid sequences selected from the following (a1) to (a11) and the
 antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises H chain
 CDRs consisting of any one of the amino acid sequences selected from the following (b1) to (b11):

40	(a1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 75, 76, and 77, respectively;
	(a2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 78, 79, and 80, respectively;
	(a3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
45	with amino acid sequences of SEQ ID NOs: 81, 82, and 83, respectively;
	(a4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of zSEQ ID NOs: 84, 85, and 86, respectively;
	(a5) an antigen-binding site comprising the H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of zSEQ ID NOs: 87, 88, and 89, respectively;
50	(a6) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of zSEQ ID NOs: 90, 91, and 92, respectively;
	(a7) an antigen-binding site comprising the H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of zSEQ ID NOs: 93, 94, and 95, respectively;
	(a8) an antigen-binding site comprising the of H chain CDR 1, 2, and 3 having at least 70% sequence
55	identity with amino acid sequences of zSEQ ID NOs: 96, 97, and 98, respectively;
	(a9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of zSEQ ID NOs: 99, 100, and 101, respectively;
	(a10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity

	with amino acid sequences of zSEQ ID NOs: 102, 103, and 104, respectively;
	(a11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 105, 106, and 107, respectively;
	(b1) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
5	with amino acid sequences of SEQ ID NOs: 108, 109, and 110, respectively;
	(b2) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 111, 112, and 113, respectively;
	(b3) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 114, 115, and 116, respectively;
10	(b4) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 117, 118, and 119, respectively;
	(b5) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 120, 121, and 122, respectively;
	(b6) an antigen-binding site comprising the H chain CDR 1, 2, and 3 having at least 70% sequence identity
15	with amino acid sequences of SEQ ID NOs: 123, 124, and 125, respectively;
	(b7) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 126, 127, and 128, respectively;
	(b8) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
00	with amino acid sequences of SEQ ID NOs: 129, 130, and 131, respectively;
20	(b9) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
	with amino acid sequences of SEQ ID NOs: 132, 133, and 134, respectively;
	(b10) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity with amino acid sequences of SEQ ID NOs: 135, 136, and 137, respectively; and
	(b11) an antigen-binding site comprising an H chain CDR 1, 2, and 3 having at least 70% sequence identity
25	with amino acid sequences of SEQ ID NOs: 174, 175, and 176, respectively; or
20	with annual acid sequences of SEQ ID NOS. 174, 175, and 170, respectively, of
	(b) the antigen-binding site of the first polypeptide comprises an antigen-binding site which comprises an H
	(a) are an agent an and a set be the best best best and an an agent and and a set best best and a set best best
	chain variable region consisting of any one of the amino acid sequences selected from the following (a1) to
	chain variable region consisting of any one of the amino acid sequences selected from the following (a1) to (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises
30	chain variable region consisting of any one of the amino acid sequences selected from the following (a1) to (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1)
30	(a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises
30	(a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11):
30	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35;
30 35	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36;
	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36;
35	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37;
	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38;
35	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38;
35	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39;
35	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39;
35	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40;
35 40	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40;
35 40	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41;
35 40	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41;
35 40	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42;
35 40	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41;
35 40 45	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42;
35 40 45	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 43; (a10) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding s
35 40 45	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a10) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a10) an antigen-binding
35 40 45 50	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 43; (a10) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a10) an antigen-binding
35 40 45	 (a11) and the antigen-binding site of the second polypeptide comprises an antigen-binding site which comprises an H chain variable region consisting of any one of the amino acid sequences selected from the following (b1) to (b11): (a1) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 35; (a2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 36; (a3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 37; (a4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 38; (a5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 39; (a6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 40; (a7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 41; (a8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a10) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 42; (a10) an antigen-binding

with the amino acid sequence of SEQ ID NO: 46; (b2) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 47;

	(b3) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 48; (b4) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 49;
5	(b5) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 50;
	(b6) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 51;
10	(b7) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 52; (b8) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
	with the amino acid sequence of SEQ ID NO: 53; (b9) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
15	with the amino acid sequence of SEQ ID NO: 54; (b10) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
	with the amino acid sequence of SEQ ID NO: 55; and (b11) an antigen-binding site comprising an H chain variable region having at least 70% sequence identity
	with the amino acid sequence of SEQ ID NO: 172; and
20	wherein
	(a) the antigen-binding sites included in the third polypeptide and the fourth polypeptide comprise an antigen- binding site which comprises L chain CDRs consisting of any one of the amino acid sequences selected from the following (c1) to (c10):
25	(c1) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity
	with the amino acid sequences of SEQ ID NOs: 138, 139, and 140, respectively;
	(c2) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity
30	with the amino acid sequences of SEQ ID NOs: 141, 142, and 143, respectively; (c3) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity
	with the amino acid sequences of SEQ ID NOs: 144, 145, and 146, respectively;
	(c4) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity with the amino acid sequences of SEQ ID NOs: 147, 148, and 149, respectively;
	(c5) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity
35	with the amino acid sequences of SEQ ID NOs: 150, 151, and 152, respectively; (c6) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity
	with the amino acid sequences of SEQ ID NOs: 153, 154, and 155, respectively;
	(c7) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity with the amino acid sequences of SEQ ID NOs: 156, 157, and 158, respectively;
40	(c8) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity with the amino acid sequences of SEQ ID NOs: 159, 160, and 161, respectively;
	(c9) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity
	with the amino acid sequences of SEQ ID NOs: 137, 138, and 139, respectively; and
45	(c10) an antigen-binding site comprising an L chain CDR1, 2, and 3 having at least 70% sequence identity with the amino acid sequences of SEQ ID NOs: 177, 178, and 179, respectively; or
	(b) the antigen-binding sites included in the third polypeptide and the fourth polypeptide comprise an antigen-
	binding site which comprises an L chain variable region consisting of any one of the amino acid sequences selected from the following (c1) to (c10):
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	(c1) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 56;
	(c2) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity
<i>E E</i>	with the amino acid sequence of SEQ ID NO: 57;
55	(c3) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 58;
	(c4) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity
	with the amino acid sequence of SEQ ID NO: 59;

(c5) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 60;

(c6) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 61;

(c7) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 62;

(c8) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 63;

(c9) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 64; and

(c10) an antigen-binding site comprising an L chain variable region having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 173,

wherein the blood coagulation factor X (F.Xa) generation-promoting activity of the multispecific antibody is higher
 than the activity of a bispecific antibody hA69-KQ/hB26-PF/hAL-AQ which comprises an H chain comprising SEQ
 ID NOs: 165 and 166, and a commonly shared L chain comprising SEQ ID NO: 167.

- 2. The multispecific antibody of claim 1, wherein
- (a) the first and second polypeptides further comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region; or

(b) the first and second polypeptides comprise an antibody H chain constant region, and the third and fourth polypeptides comprise an antibody L chain constant region, and wherein the third polypeptide and the fourth polypeptide are a commonly shared L chain.

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3. The multispecific antibody of claim 2, wherein

(a) the first polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from the group consisting of the following (d1) to (d6) or the group consisting of the following (d7) to (d9), and the second polypeptide comprises an antibody H chain constant region consisting of any one of the amino acid sequences selected from a group different from that of the above-mentioned first polypeptide:

(d1) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 65; 35 (d2) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 66; (d3) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 67; (d4) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ 40 ID NO: 68; (d5) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 69; (d6) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 70; 45 (d7) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 71; (d8) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 72; and (d9) an H chain constant region having at least 70% sequence identity with amino acid sequence of SEQ 50 ID NO: 73; and

(b) the third and fourth polypeptides comprise the antibody L chain constant region consisting of the following amino acid sequence of:

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(e) an L chain constant region having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 74; or

(c) the first polypeptide comprises any one antibody H chain selected from the following (a1) to (a14), the second

polypeptide comprises any one antibody H chain selected from the following (b1) to (b12), and the third polypeptide and the fourth polypeptide comprise any one antibody L chain selected from the following (c1) to (c10):

(a1) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with 5 amino acid sequence of SEQ ID NO: 1; (a2) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 2; (a3) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 3; 10 (a4) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 10; (a5) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 11; (a6) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with 15 amino acid sequence of SEQ ID NO: 12; (a7) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 13; (a8) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 14; 20 (a9) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 15; (a10) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 16; (a11) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity 25 with amino acid sequence of SEQ ID NO: 17; (a12) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 18; (a13) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 19; 30 (a14) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 20; (b1) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 4; (b2) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with 35 amino acid sequence of SEQ ID NO: 5; (b3) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 6; (b4) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 7; 40 (b5) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 21; (b6) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 22; (b7) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with 45 amino acid sequence of SEQ ID NO: 23; (b8) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 24; (b9) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 25; 50 (b10) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 26; (b11) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 27; (b12) an antibody H chain consisting of the amino acid sequence having at least 70% sequence identity 55 with amino acid sequence of SEQ ID NO: 170; (c1) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 8; (c2) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with

amino acid sequence of SEQ ID NO: 9; (c3) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 28; (c4) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with 5 amino acid sequence of SEQ ID NO: 29; (c5) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 30; (c6) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 31; 10 (c7) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 32; (c8) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 33; (c9) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with 15 amino acid sequence of SEQ ID NO: 34; and

- (c10) an antibody L chain consisting of the amino acid sequence having at least 70% sequence identity with amino acid sequence of SEQ ID NO: 171.
 - A bispecific antibody of any one of the following (a) to (u): 4.

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(a) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain 25 of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 9; (b) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain 30 of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 9; (c) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 2, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain 35 of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 8; (d) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 3, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain 40 of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 9; (e) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 6, and the third polypeptide and the fourth polypeptide are a commonly shared L chain 45 of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 30; (f) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 10, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 7, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 33; (g) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 4, and the third polypeptide and the fourth polypeptide are a commonly shared L chain 55 of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 33; (h) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 11, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid

sequence of SEQ ID NO: 5, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 30; (i) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence having at least 70% sequence identity with the amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 12, the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 23;

(j) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 13, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 22, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 22, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 29;

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- (k) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 14, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 14, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ
 ID NO: 33;
 - (I) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 15, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 23, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 30;
 - (m) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 16, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 21, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence of SEQ ID NO: 28;
- (n) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 17, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 34;
- (o) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having
 at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 18, the second polypeptide is an
 H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 30;
- (p) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 30;

(q) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 24, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 31;

(r) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 19, the second polypeptide is an

H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 27, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 28;

(s) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid SEQ ID NO: 25, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 32;

(t) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 20, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 26, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 26, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 31; and

(u) a bispecific antibody, wherein the first polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 12, the second polypeptide is an H chain consisting of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 170, and the third polypeptide and the fourth polypeptide are a commonly shared L chain of an amino acid sequence having at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 171,

- wherein the blood coagulation factor X (F.Xa) generation-promoting activity of the bispecific antibody is higher than
 the activity of a bispecific antibody hA69-KQ/hB26-PF/hAL-AQ which comprises an H chain comprising SEQ ID
 NOs: 165 and 166, and a commonly shared L chain comprising SEQ ID NO: 167.
 - 5. A nucleic acid encoding the multispecific antibody of any one of claims 1 to 3 or the bispecific antibody of claim 4.
- 30 **6.** A vector inserted with the nucleic acid of claim 5.

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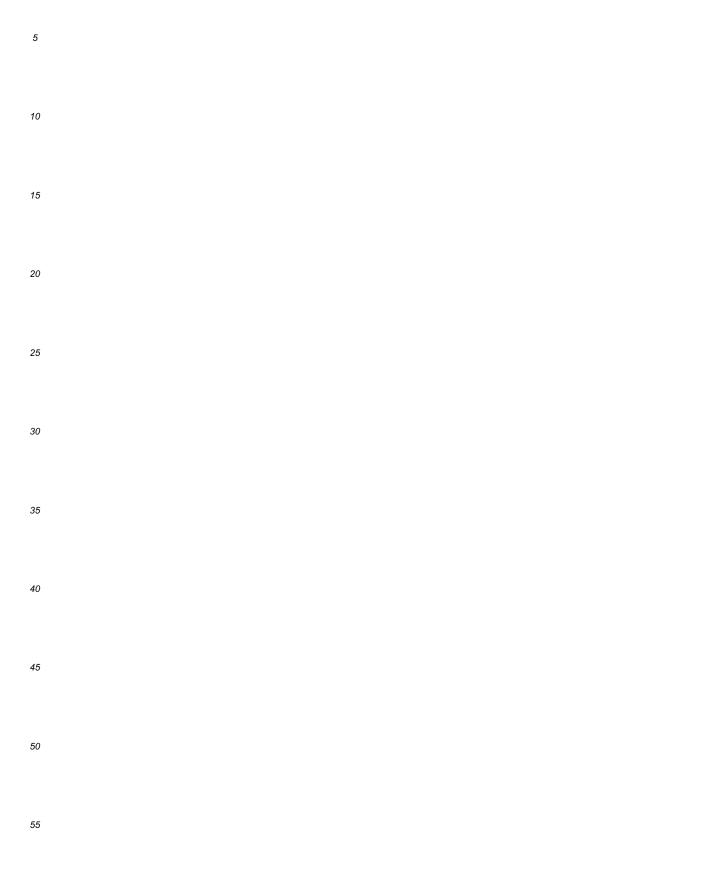
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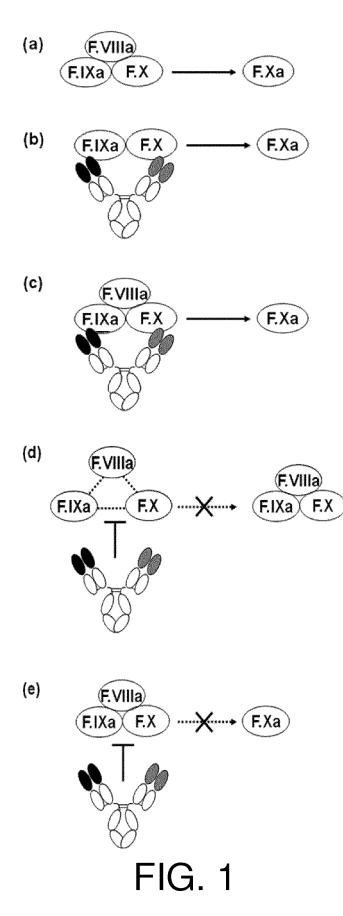
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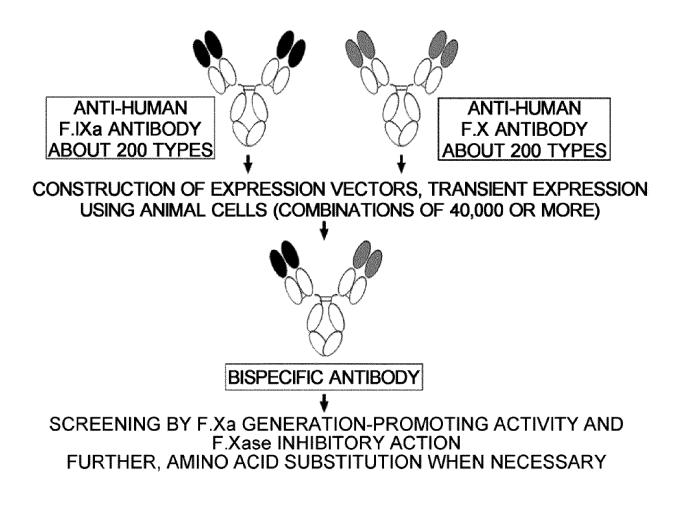
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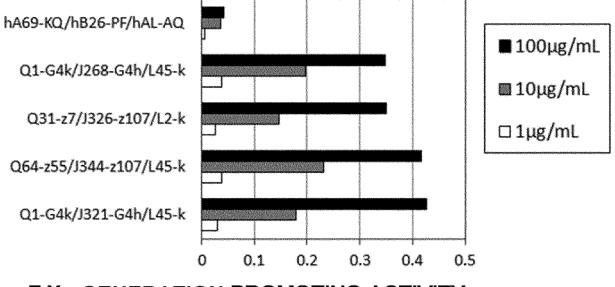
- 7. A cell comprising the nucleic acid of claim 5 or the vector of claim 6.
- 8. A method for producing the multispecific antibody of any one of claims 1 to 3 or the bispecific antibody of claim 4 by culturing the cell of claim 7.
 - **9.** A pharmaceutical composition comprising the multispecific antibody of any one of claims 1 to 3 or the bispecific antibody of claim 4, and a pharmaceutically acceptable carrier.
- **10.** The composition of claim 9, which is a pharmaceutical composition for use in prevention and/or treatment of bleeding, a disease accompanying bleeding, or a disease caused by bleeding.
 - **11.** The composition for use of claim 10, wherein the bleeding, the disease accompanying bleeding, or the disease caused by bleeding is a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII.
 - 12. The composition for use of claim 11, wherein
- (a) the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation
 factor VIII and/or activated blood coagulation factor VIII is hemophilia A;
 (b) the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation
 factor VIII and/or activated blood coagulation factor VIII is a disease showing emergence of an inhibitor against
 blood coagulation factor VIII and/or activated blood coagulation factor VIII;
 (c) the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation
 factor VIII and/or activated blood coagulation factor VIII;
 (c) the disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation
 factor VIII and/or activated blood coagulation factor VIII is acquired hemophilia; or
 (d) the disease that develops and/or progresses due to a decrease in the activity of blood coagulation factor
 VIII and/or activated blood coagulation factor VIII is von Willebrand disease.

13. A kit, which comprises at least the multispecific antigen-binding molecule of any one of claims 1 to 3 or the bispecific antibody of claim 4, or the composition of any one of claims 9 to 12.

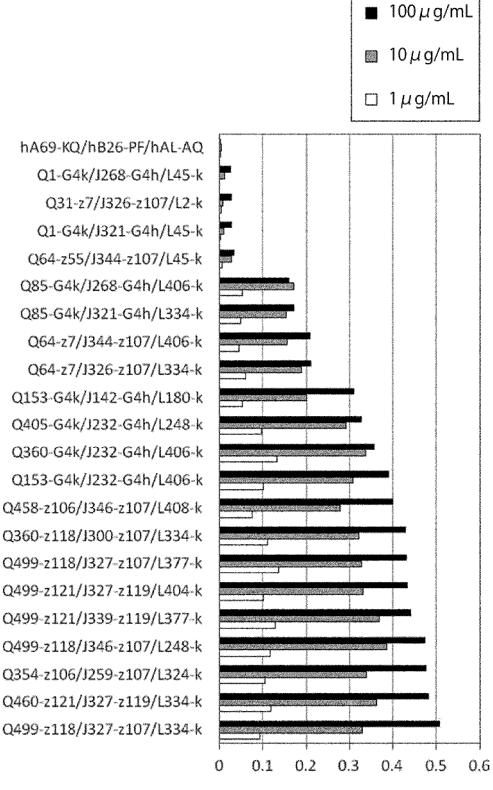




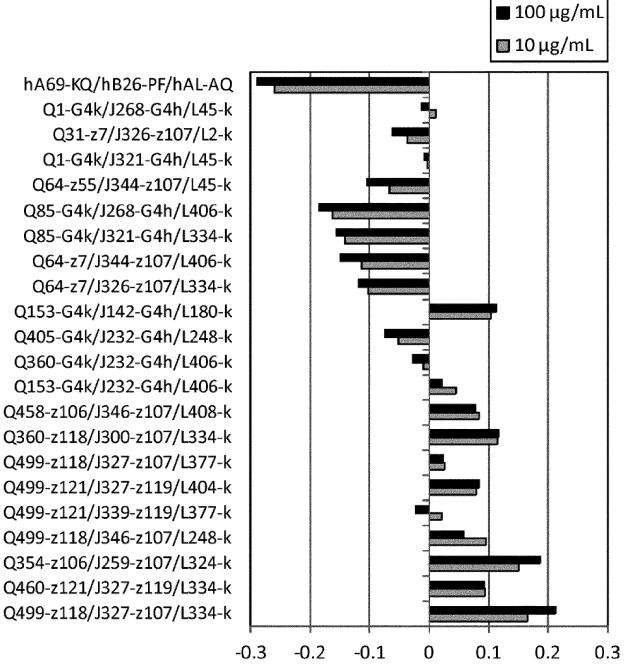




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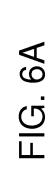


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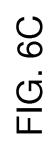
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EUROPEAN SEARCH REPORT

Application Number EP 17 20 0495

		DOCUMENTS CONSIDI	ERED TO BE RELEVANT		
	Category	Citation of document with in of relevant passa	dication, where appropriate, lges	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
10 15	A	R. J. KERSCHBAUMER: for Coagulation Fac Activity of the Int X-activating Comple JOURNAL OF BIOLOGIC vol. 279, no. 39, 1 January 2004 (200 40445-40450, XP0550	rinsic Factor x", AL CHEMISTRY, 4-01-01), pages	1-13	INV. C12N15/09 A61K39/395 A61P7/04 C07K16/36 C12N5/10 C12P21/02
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REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2005035754 A [0005]
- WO 2005035756 A [0005] [0085]
- WO 2006109592 A [0005] [0014] [0017] [0041] [0085] [0111] [0115] [0128]
- WO 2002032925 A [0015]
- WO 1995001937 A [0015]
- WO 2004044011 A [0015]
- WO 2005040229 A [0015]
- WO 2002020565 A [0015]
- EP 404097 A [0025]
- WO 9311161 A [0025]
- WO 2006106905 A [0028] [0032] [0058] [0085] [0116]
- WO 9312227 A [0038]
- WO 9203918 A [0038]
- WO 9402602 A [0038]
- WO 9425585 A [0038]
- WO 9634096 A **[0038]**

Non-patent literature cited in the description

- Blood, 1981, vol. 58, 1-13 [0006]
- Nature, 1984, vol. 312, 330-337 [0006]
- Nature, 1984, vol. 312, 337-342 [0006]
- *Biochim.Biophys.Acta*, 1986, vol. 871, 268-278 [0006]
- NYGREN et al. Current Opinion in Structural Biology, 1997, vol. 7, 463-469 [0015]
- Journal of Immunol Methods, 2004, vol. 290, 3-28
 [0015]
- BINZ et al. Nature Biotech, 2005, vol. 23, 1257-1266
 [0015]
- HOSSE et al. Protein Science, 2006, vol. 15, 14-27 [0015]
- *Curr Opin Mol Ther.,* August 2010, vol. 12 (4), 487-95 [0015]
- Drugs, 2008, vol. 68 (7), 901-12 [0015]
- BORREBAECK CAK ; LARRICK JW. THERAPEU-TIC MONOCLONAL ANTIBODIES. MACMILLAN PUBLISHERS LTD, 1990 [0020]
- HOLLIGER, P. et al. Proc. Natl. Acad. Sci. USA, 1993, vol. 90, 6444-6448 [0025]
- PLUCKTHUN. The Pharmacology of Monoclonal Antibodies. Springer Verlag, 1994, vol. 113, 269-315
 [0026]
- MILSTEIN C et al. Nature, 1983, vol. 305, 537-540
 [0027]

- WO 9633735 A [0038]
- EP 239400 A [0040]
- WO 9602576 A [0040]
- WO 9951743 A [0040]
- WO 9954342 A [0058]
- WO 0061739 A [0058]
- WO 0231140 A [0058]
- WO 2006067847 A [0058]
- WO 2006067913 A [0058]
- WO 0279255 A [0058]
- WO 2009041613 A [0058]
- WO 2007114325 A [0085]
- US 3773919 A [0102]
- EP 58481 A [0102]
- EP 133988 A [0102]
- WO 9317706 A [0104]
- US 4945050 A [0104]
- WO 1996027011 A [0116]
- RIDGWAY JB et al. Protein Engineering, 1996, vol. 9, 617-621 [0028] [0032]
- MERCHANT AM et al. Nature Biotechnology, 1998, vol. 16, 677-681 [0028] [0032]
- DAVIS JH et al. Protein Eng Des Sel., 2010, vol. 4, 195-202 [0028]
- KELER T et al. Cancer Research, 1997, vol. 57, 4008-4014 [0030]
- BRENNAN M et al. Science, 1985, vol. 229, 81-83 [0030]
- KOSTELNY SA et al. J. of Immunology, 1992, vol. 148, 1547-53 [0031]
- Protein Eng Des Sel, April 2010, vol. 23 (4), 221-8
 [0032]
- Drug Discov Today, 15 September 2005, vol. 10 (18), 1237-44 [0032]
- Nat Biotechnol., November 2007, vol. 25 (11), 1290-7
 [0032]
- MAbs, July 2009, vol. 1 (4), 339-47 [0032]
- *IDrugs,* 2010, vol. 13, 698-700 **[0032]**
- Science, 20 March 2009, vol. 323 (5921), 1610-4
 [0032]
- Immunotherapy, September 2009, vol. 1 (5), 749-51
 [0032]
- MAbs, November 2009, vol. 1 (6), 539-547 [0032]
- DAVIS JH et al. Protein Eng Des Sel, 2010, vol. 4, 195-202 [0032]

- HOLLIGER P et al. Proc Natl. Acad. Sci. USA, 1993, vol. 90, 6444-6448 [0033]
- KIPRIYANOV SM et al. J. of Molecular Biology, 1999, vol. 293, 41-56 [0034]
- ZHU Z et al. Protein Science, 1997, vol. 6, 781-788 [0034]
- IGAWA T et al. Protein Eng Des Sel, 2010, vol. 8, 667-77 [0034]
- MALLENDER WD et al. J. of Biological Chemistry, 1994, vol. 269, 199-206 [0035]
- SATO K et al. Cancer Research, 1993, vol. 53, 851-856 [0040]
- Sequences of proteins of immunological interest.
 U.S. Department of Health and Human Services, 1991 [0058]
- An efficient route to human bispecific IgG. Nature Biotechnology. Public Health Service National Institutes of Health, 1998, vol. 16, 677-681 [0058]
- Proc Natl Acad Sci USA., 14 March 2006, vol. 103 (11), 4005-10 [0058]
- MAbs, November 2009, vol. 1 (6), 572-9 [0058]
- *J Biol Chem.*, 02 March 2001, vol. 276 (9), 6591-604 **[0058]**
- Int Immunol., December 2006, vol. 18 (12), 1759-69
 [0058]
- J Biol Chem., 18 August 2006, vol. 281 (33), 23514-24 [0058]
- J Immunol Methods, 01 February 2001, vol. 248 (1-2), 7-15 [0058]
- J Biol Chem., 02 July 2010, vol. 285 (27), 20850-9
 [0058]
- Protein Eng Des Sel, April 2010, vol. 23 (4), 195-202
 [0058]
- J Clin Pharmacol., May 2010, vol. 50 (5), 494-506
 [0058]
- J Immunol Methods, 01 May 2002, vol. 263 (1-2), 133-47 [0058]
- ROSEN S; ANDERSSON M; BLOMBA[•]CK M et al. Clinical applications of a chromogenic substrate method for determination of FVIII activity. *Thromb Haemost*, 1985, vol. 54, 811-23 [0063]
- HASHIMOTO-GOTOH, T; MIZUNO, T; OGASA-HARA, Y; NAKAGAWA, M. An oligodeoxyribonucleotide-directed dual amber method for site-directed mutagenesis. *Gene*, 1995, vol. 152, 271-275 [0069]
- ZOLLER, MJ; SMITH, M. Oligonucleotide-directed mutagenesis of DNA fragments cloned into M13 vectors. *Methods Enzymol.*, 1983, vol. 100, 468-500 [0069]
- KRAMER, W; DRUTSA, V; JANSEN, HW; KRAM-ER, B; PFLUGFELDER, M; FRITZ, HJ. The gapped duplex DNA approach to oligonucleotide-directed mutation construction. *Nucleic Acids Res.*, 1984, vol. 12, 9441-9456 [0069]
- KRAMER W; FRITZ HJ. Oligonucleotide-directed construction of mutations via gapped duplex DNA Methods. *Enzymol*, 1987, vol. 154, 350-367 [0069]

- KUNKEL, TA. Rapid and efficient site-specific mutagenesis without phenotypic selection. *Proc Natl Acad Sci USA.,* 1985, vol. 82, 488-492 [0069]
- MARK, D. F. et al. *Proc. Natl. Acad. Sci. USA*, 1984, vol. 81, 5662-6 [0071]
- ZOLLER, M. J.; SMITH, M. Nucleic Acids Res., 1982, vol. 10, 6487-500 [0071]
- WANG, A. et al. Science, 1984, vol. 224, 1431-3 [0071]
- DALBADIE-MCFARLAND, G. et al. Proc. Natl. Acad. Sci. USA, 1982, vol. 79, 6409-13 [0071]
- KARLIN ; ALTSCHUL. Proc. Natl. Acad. Sci. USA, 1993, vol. 90, 5873-7 [0074]
- ALTSCHUL et al. J. Mol. Biol., 1990, vol. 215, 403-10
 [0074]
- CO, M. S. et al. J. Immunol., 1994, vol. 152, 2968-2976 [0089]
- BETTER, M.; HORWITZ, A. H. Methods Enzymol., 1989, vol. 178, 476-496 [0089]
- PLUCKTHUN, A. ; SKERRA, A. Methods Enzymol., 1989, vol. 178, 497-515 [0089]
- LAMOYI, E. Methods Enzymol., 1986, vol. 121, 652-663 [0089]
- ROUSSEAUX, J. et al. *Methods Enzymol.*, 1986, vol. 121, 663-669 [0089]
- BIRD, R. E.; WALKER, B. W. Trends Biotechnol, 1991, vol. 9, 132-137 [0089]
- WARD et al. Nature, 1989, vol. 341, 544-546 [0090]
- FASEB J., 1992, vol. 6, 2422-2427 [0090]
- BETTER et al. Science, 1988, vol. 240, 1041-1043 [0090]
- LEI, S. P. et al. J. Bacteriol., 1987, vol. 169, 4379 [0091]
- Nucleic Acids. Res., 1990, vol. 18 (17), 5322 [0092]
- MULLIGAN et al. Nature, 1979, vol. 277, 108 [0093]
- MIZUSHIMA et al. Nucleic Acids Res., 1990, vol. 18, 5322 [0093]
- Molecular Cloning. Cold Spring Harbor Laboratory Press, 1989 [0094]
- Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Cold Spring Harbor Laboratory Press, 1996 [0096]
- Antibodies : A Laboratory Manual. Cold Spring Harbor Laboratory, 1988 [0097]
- Expert Opin Drug Deliv, July 2007, vol. 4 (4), 427-40
 [0101]
- Remington's Pharmaceutical Science. 1980 [0102]
- LANGER et al. J. Biomed. Mater. Res., 1981, vol. 15, 267-277 [0102]
- LANGER. Chemtech, 1982, vol. 12, 98-105 [0102]
- SIDMAN et al. *Biopolymers*, 1983, vol. 22, 547-556
 [0102]
- ADOLPH. Viral Genome Methods. CRC Press, 1996
 [0104]
- KABAT EA et al. Sequences of Proteins of Immunological Interest. NIH, 1991 [0140]