

One aspect as reported herein is a bispecific antibody that specifically binds to human IL-1beta, wherein the antibody is a bivalent, bispecific antibody comprising

a) a first light chain and a first heavy chain of an antibody specifically binding to a first antigen, and

5 b) a second light chain and a second heavy chain of an antibody specifically binding to a second antigen, wherein the variable domains VL and VH of the second light chain and the second heavy chain are replaced by each other;

wherein

10 i) in the constant domain CL of the first light chain under a) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and wherein in the constant domain CH1 of the first heavy chain under a) the amino acid at position 147 or the amino acid at position
15 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index),

or wherein

ii) in the constant domain CL of the second light chain under b) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat),
20 and wherein in the constant domain CH1 of the second heavy chain under b) the amino acid at position 147 or the amino acid at position 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index)

25 wherein the bispecific antibody comprises

a) a heavy chain variable domain comprising hypervariable regions selected from the group of

• a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 02, a HVR-H2 comprising the amino acid sequence of SEQ ID
30 NO: 03, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 05,

- a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 07, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 08, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 10,
- 5 • a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 12, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 13, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 15;

and

10 a light chain variable domain comprising

- a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 17; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 18; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 19;

15 or

b) a heavy chain variable domain comprising

- a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 22, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24,

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and a light chain variable domain comprising

- a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 26; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 27; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28,

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wherein the bispecific antibody specifically binds to a second antigen selected from the group consisting of human ANG2 and human VEGF; and

wherein the antibody is of human subclass IgG1 or of human subclass IgG4; and

wherein the antibody comprises the mutations I253A, H310A, and H435A, wherein the numbering is according to the EU index.

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In the disclosure, the antibody specifically binds to human PDGF-B and comprises

- a) a heavy chain variable domain comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 30, (b) a HVR-H2 comprising

the amino acid sequence of SEQ ID NO: 31, and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 33, and a light chain variable domain comprising (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37,

or

b) a heavy chain variable domain comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 39, (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 40, and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain comprising (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 44; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 46,

or

c) a heavy chain variable domain comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 48, (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 49, and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 51, and a light chain variable domain comprising (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 53; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 54; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 55.

One aspect as reported herein is a bispecific antibody that specifically binds to human PDGF-B, wherein the antibody is a bivalent, bispecific antibody comprising

a) a first light chain and a first heavy chain of an antibody specifically binding to a first antigen, and

b) a second light chain and a second heavy chain of an antibody specifically binding to a second antigen, wherein the variable domains VL and VH of the second light chain and the second heavy chain are replaced by each other;

wherein

5 i) in the constant domain CL of the first light chain under a) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and wherein in the constant domain CH1 of the first heavy chain under a) the amino acid at position 147 or the amino acid at position 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index),

or wherein

10 ii) in the constant domain CL of the second light chain under b) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and wherein in the constant domain CH1 of the second heavy chain under b) the amino acid at position 147 or the amino acid at position 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index)

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wherein the antibody comprises

a) a heavy chain variable domain comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 30, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 31, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 33, and a light chain variable domain comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37;

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or

25 b) a heavy chain variable domain comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 39, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 40, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 44; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 46;

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or

5 c) a heavy chain variable domain comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 48, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 49, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 51, and a light chain variable domain comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 53; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 54; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 55;

wherein the bispecific antibody specifically binds to a second antigen selected from the group consisting of human ANG2, human VEGF and human IL-1beta;

10 wherein the antibody is of human subclass IgG1 or of human subclass IgG4; and

wherein the antibody comprises the mutations I253A, H310A, and H435A, wherein the numbering is according to the EU index of Kabat.

In one embodiment the antibody specifically binds to human ANG2 and comprises

15 a) a heavy chain variable domain comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 57, (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58, and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 60, and a light chain variable domain comprising (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 62; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 63; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 64,

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- ii) H310A, H433A, and Y436A, or
- iii) L251D, L314D, and L432D, or
- iv) combinations of i) to iii)

in the first Fc-region polypeptide and in the second Fc-region polypeptide.

5 One aspect as reported herein is a pharmaceutical formulation comprising an antibody as reported herein and optionally a pharmaceutically acceptable carrier.

One aspect as reported herein is the antibody as reported herein for use as a medicament.

10 One aspect as reported herein is the antibody as reported herein for use in the treatment of an ocular vascular disease.

One aspect as reported herein is the antibody as reported herein for use in the treatment of an eye disease.

15 One aspect as reported herein is the use of the antibody as reported herein in the manufacture of a medicament for the treatment of an ocular vascular disease or an eye disease.

In one embodiment the medicament is for the treatment of an ocular vascular disease, preferably for the treatment of macular degeneration.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

I. DEFINITIONS

20 An "acceptor human framework" for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework "derived from" a human immunoglobulin
25 framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human
30 immunoglobulin framework sequence or human consensus framework sequence.

Patent Claims

1. A bispecific antibody that specifically binds to human IL-1beta, wherein the antibody is a bivalent, bispecific antibody comprising
 - a) a first light chain and a first heavy chain of an antibody specifically binding to a first antigen, and
 - 5 b) a second light chain and a second heavy chain of an antibody specifically binding to a second antigen, wherein the variable domains VL and VH of the second light chain and the second heavy chain are replaced by each other;wherein
 - 10 i) in the constant domain CL of the first light chain under a) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and wherein in the constant domain CH1 of the first heavy chain under a) the amino acid at position 147 or the amino acid at position
15 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index),
 - or wherein
 - 20 ii) in the constant domain CL of the second light chain under b) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and wherein in the constant domain CH1 of the second heavy chain under b) the amino acid at position 147 or the amino acid at position 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index)wherein the bispecific antibody comprises
 - a) a heavy chain variable domain comprising hypervariable regions selected from the group of
 - a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 02, a HVR-H2 comprising the amino acid sequence of SEQ ID
30 NO: 03, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 05,

- a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 07, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 08, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 10,
- 5 • a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 12, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 13, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 15;

and

10 a light chain variable domain comprising

- a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 17; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 18; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 19;

15 or

b) a heavy chain variable domain comprising

20 a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 22, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24,

and a light chain variable domain comprising

- a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 26; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 27; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28,

25 wherein the bispecific antibody specifically binds to a second antigen selected from the group consisting of human ANG2 and human VEGF; and

wherein the antibody is of human subclass IgG1 or of human subclass IgG4; and

30 wherein the antibody comprises the mutations I253A, H310A, and H435A, wherein the numbering is according to the EU index.

2. A bispecific antibody that specifically binds to human PDGF-B, wherein the antibody is a bivalent, bispecific antibody comprising
- a) a first light chain and a first heavy chain of an antibody specifically binding to a first antigen, and
- 5 b) a second light chain and a second heavy chain of an antibody specifically binding to a second antigen, wherein the variable domains VL and VH of the second light chain and the second heavy chain are replaced by each other;
- wherein
- 10 i) in the constant domain CL of the first light chain under a) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat), and wherein in the constant domain CH1 of the first heavy chain under a) the amino acid at position 147 or the amino acid at position
- 15 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index),
- or wherein
- ii) in the constant domain CL of the second light chain under b) the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat),
- 20 and wherein in the constant domain CH1 of the second heavy chain under b) the amino acid at position 147 or the amino acid at position 213 is substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to EU index)
- 25 wherein the antibody comprises
- a) a heavy chain variable domain comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 30, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 31, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 33, and a light chain variable
- 30 domain comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37;

or

5 b) a heavy chain variable domain comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 39, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 40, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable domain comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 44; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 45; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 46;

10 or

15 c) a heavy chain variable domain comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 48, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 49, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 51, and a light chain variable domain comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 53; a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 54; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 55;

20 wherein the bispecific antibody specifically binds to a second antigen selected from the group consisting of human ANG2, human VEGF and human IL-1beta;

wherein the antibody is of human subclass IgG1 or of human subclass IgG4; and

25 wherein the antibody comprises the mutations I253A, H310A, and H435A, wherein the numbering is according to the EU index of Kabat.

3. The bispecific antibody according to any one of claims 1 or 2, wherein the antibody specifically binds to human ANG-2, wherein the antibody comprises

acid sequence of SEQ ID NO: 90; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 91.

4. The bispecific antibody according to any one of claims 1 or 2 that further specifically binds to human VEGF and further comprises

- 5 a) the HVR-H1, HVR-H2 and HVR-H3 as contained in the heavy chain variable domain of SEQ ID NO: 107 and the HVR-L1, HVR-L2 and HVR-L3 as contained in the heavy chain variable domain of SEQ ID NO: 108,

or

- 10 b) the HVR-H1, HVR-H2 and HVR-H3 as contained in the heavy chain variable domain of SEQ ID NO: 109 and the HVR-L1, HVR-L2 and HVR-L3 as contained in the heavy chain variable domain of SEQ ID NO: 110.

5. The antibody according to any one of claims 1 to 4, wherein the antibody comprises a first Fc-region polypeptide and a second Fc-region polypeptide, and

wherein

- 5 i) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide, or
- 10 ii) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, or
- 15 iii) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, or
- iv) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, S354C, T366W and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, Y349C, T366S, L368A, Y407V, or

- 5 v) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, S354C, T366W and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, Y349C, T366S, L368A, Y407V, or
- 10 vii) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, or
- 15 viii) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, or
- 20 ix) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, S354C, T366W and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, Y349C, T366S, L368A, Y407V, or
- 25 x) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, S354C, T366W and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, Y349C, T366S, L368A, Y407V.

6. A pharmaceutical formulation comprising an antibody according to any one of claims 1 to 5 and optionally a pharmaceutically acceptable carrier.
7. The antibody according to any one of claims 1 to 5 for use as a medicament.
8. The antibody according to any one of claims 1 to 5 for use in the treatment of
5 an ocular vascular disease.
9. The antibody according to any one of claims 1 to 5 for use in the treatment of an eye disease.
10. Use of the antibody according to any one of claims 1 to 5 in the manufacture
10 of a medicament for the treatment of an ocular vascular disease or an eye disease.