

CLAIMS

1. An anti-Ang2 VHH antibody, comprising 3 CDRs, HCDR1, HCDR2, and HCDR3 as follows, wherein the HCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 16; the HCDR2 comprises or consists of a sequence set forth in SEQ ID NO: 17 or 20; and the HCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 18.
2. The anti-Ang2 VHH antibody according to claim 1, comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 19 or 21, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 19 or 21.
3. A bispecific binding molecule binding to VEGF A and Ang2, comprising a first target-binding region specifically binding to VEGF A and a second target-binding region specifically binding to Ang2, wherein the second target-binding region is the VHH antibody according to claim 1 or 2.
4. The bispecific binding molecule according to claim 3, wherein the first target-binding region is selected from:
 - a VHH specifically binding to VEGF A;
 - an antigen-binding fragment of an antibody, e.g., an scFv, specifically binding to VEGF A, for example, the antibody is a fully human or humanized antibody; or
 - a VEGF receptor (VEGF R) specifically binding to VEGF A or an extracellular domain thereof or a fusion protein comprising the extracellular domain thereof, e.g., a fusion protein of the extracellular domain thereof with Fc;preferably, the bispecific binding molecule is divalent, trivalent, or tetravalent; preferably, the binding region is linked with linker, e.g., the linker comprises or consists of an amino acid sequence set forth in SEQ ID NO: 23.
5. The bispecific binding molecule according to claim 3 or 4, wherein the bispecific binding molecule is a bispecific antibody.
6. The bispecific binding molecule according to any one of claims 3 to 5, having the following structure:
 - light chain variable region VL of the anti-VEGF antibody-linker-heavy chain variable region VH of the anti-VEGF antibody-linker-anti-Ang2 VHH or
 - heavy chain variable region VH of the anti-VEGF antibody-linker-light chain variable region VL of the anti-VEGF antibody-linker-anti-Ang2 VHH.
7. The bispecific binding molecule according to claim 6, wherein:
 - the light chain variable region VL of the anti-VEGF antibody comprises LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 31; the LCDR2 comprises or consists of a sequence set forth in SEQ ID NO: 32; and the LCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 33; and
 - the heavy chain variable region VH of the anti-VEGF antibody comprises HCDR1, HCDR2, and HCDR3, wherein the HCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 35; the HCDR2

comprises or consists of a sequence set forth in SEQ ID NO: 36; and the HCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 37.

8. The bispecific binding molecule according to claim 7, wherein

the heavy chain variable region VH of the anti-VEGF antibody comprises or consists of an amino acid sequence set forth in SEQ ID NO: 34, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 34; and the light chain variable region VL of the anti-VEGF antibody comprises or consists of an amino acid sequence set forth in SEQ ID NO: 30, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 30.

9. The bispecific binding molecule according to claim 7 or 8, wherein

the binding molecule comprises or consists of an amino acid sequence set forth in SEQ ID NO: 28, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 28.

10. The bispecific binding molecule according to any one of claims 3 to 5, having the following structure:

first anti-VEGF VHH-linker-second anti-VEGF VHH-linker-anti-Ang2 VHH,

wherein the first anti-VEGF VHH is the same as or different from the second anti-VEGF VHH.

11. The bispecific binding molecule according to claim 10, wherein the first anti-VEGF VHH or the second anti-VEGF VHH comprises HCDR1, HCDR2, and HCDR3, wherein

the HCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 1; the HCDR2 comprises or consists of a sequence set forth in SEQ ID NO: 2; and the HCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 3;

or

the HCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 6; the HCDR2 comprises or consists of a sequence set forth in SEQ ID NO: 7 or 10; and the HCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 8.

12. The bispecific binding molecule according to claim 11, wherein the first anti-VEGF VHH or the second anti-VEGF VHH comprises or consists of an amino acid sequence set forth in SEQ ID NO 4, 5, 9, or 11, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO 4, 5, 9, or 11;

optionally, the first anti-VEGF VHH and the second anti-VEGF VHH are the same.

13. The bispecific binding molecule according to claim 11 or 12, wherein the binding molecule comprises or consists of an amino acid sequence set forth in SEQ ID NO: 22, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 22.

14. The bispecific binding molecule according to any one of claims 3 to 5, comprising one or two of the following chains:

VEGF R extracellular domain-Fc-linker-anti-Ang2 VHH;

preferably, wherein the VEGFR extracellular domain is an extracellular domain of VEGFR from a human; preferably, the VEGFR extracellular domain comprises a second antibody-like domain of VEGFR1 and a third antibody-like domain of VEGFR2; more preferably, the VEGFR extracellular domain comprises a second antibody-like domain of human VEGFR1 and a third antibody-like domain of human VEGFR2.

15. The bispecific binding molecule according to claim 14, wherein the VEGFR extracellular domain comprises or consists of an amino acid sequence set forth in SEQ ID NO: 26.

16. The bispecific binding molecule according to claim 14 or 15, wherein the Fc is an Fc derived from human IgG1, IgG2, IgG3, or IgG4, preferably the Fc comprises or consists of an amino acid sequence set forth in SEQ ID NO: 27, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 27.

17. The bispecific binding molecule according to claim 14 or 15, wherein the VEGF R extracellular domain-Fc is a fusion protein of the VEGFR extracellular domain and the Fc, such as aflibercept or a derivative thereof.

18. The bispecific binding molecule according to claim 15, wherein the VEGF R extracellular domain-Fc comprises or consists of an amino acid sequence set forth in SEQ ID NO: 25, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 25.

19. The bispecific binding molecule according to claim 15 or 18, wherein the binding molecule comprises or consists of an amino acid sequence set forth in SEQ ID NO: 24, or comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 24.

20. An anti-VEGF A VHH antibody, comprising 3 CDRs, HCDR1, HCDR2, and HCDR3, as follows, wherein

the HCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 1;

the HCDR2 comprises or consists of a sequence set forth in SEQ ID NO: 2; and

the HCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 3;

or

the HCDR1 comprises or consists of a sequence set forth in SEQ ID NO: 6;

the HCDR2 comprises or consists of a sequence set forth in SEQ ID NO: 7 or 10; and

the HCDR3 comprises or consists of a sequence set forth in SEQ ID NO: 8.

21. The anti-VEGF A VHH antibody according to claim 20, wherein

the VHH antibody comprising or consisting of an amino acid sequence set forth in SEQ ID NO: 4, 5, 9, or 11, or comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the amino acid sequence set forth in SEQ ID NO: 4, 5, 9, or 11.

22. A nucleic acid molecule encoding the VHH antibody according to claim 1, 2, 20 or 21, or the bispecific binding molecule according to any one of claims 3 to 19.

23. An expression vector comprising the nucleic acid molecule according to claim 22.

24. A host cell comprising the nucleic acid molecule according to claim 22 or the expression vector according to claim 23, wherein preferably, the host cell is prokaryotic or eukaryotic, for example, a bacterium such as an *E.coli* cell, e.g., TG1, or a 293 cell such as a 293F or Expi-293 cell.
25. A method for preparing the VHH antibody according to claim 1, 2, 20 or 21, or the bispecific binding molecule according to any one of claims 3 to 19, comprising culturing the host cell according to claim 24 under conditions suitable for expressing the VHH antibody or bispecific binding molecule or the chain thereof, and optionally recovering the VHH or bispecific binding molecule from the host cell or the host cell medium.
26. An immunoconjugate comprising the VHH antibody according to claim 1, 2, 20 or 21, or the bispecific binding molecule according to any one of claims 3 to 19.
27. A pharmaceutical composition or formulation comprising the VHH antibody according to claim 1, 2, 20 or 21, or the bispecific binding molecule according to any one of claims 3 to 19, and optionally one or more additional therapeutic agents and optionally a pharmaceutical supplementary material.
28. Use of the VHH antibody according to claim 1, 2, 20 or 21, or the bispecific binding molecule according to any one of claims 3 to 19, the immunoconjugate according to claim 26, or the pharmaceutical composition or formulation according to claim 27 in the manufacture of a medicament for preventing or treating an ocular disease in a subject, wherein the ocular disease is an ocular disease associated with angiogenesis.
29. The use according to claim 28, wherein the ocular disease is an ocular disease associated with corneal neovascularization.
30. The use according to claim 28 or claim 29, wherein the subject has VEGF, e.g., VEGF A, and/or Ang2 or has VEGF, e.g., VEGF A, and/or Ang2 at an elevated level, e.g., at a nucleic acid or protein level.
31. The use according to claim 28 or claim 29, wherein the VHH antibody or the bispecific binding molecule is to be administered to the subject in combination with one or more therapies, such as therapeutic modalities and/or additional therapeutic agents.