Patent Claims

1. A bispecific antibody specifically binding to human vascular endothelial growth factor (VEGF) and human angiopoietin-2 (ANG-2) comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2.

2. The bispecific antibody according to claim 1, characterized in that

   i) said antigen-binding sites are each a pair of an antibody heavy chain variable domain and an antibody light chain variable domain;

   ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO: 17, or SEQ ID NO: 94, a CDR2 region of SEQ ID NO: 2, SEQ ID NO: 10, SEQ ID NO: 18, or SEQ ID NO: 95, and a CDR1 region of SEQ ID NO:3, SEQ ID NO: 11, SEQ ID NO: 19, or SEQ ID NO: 96, and in the light chain variable domain a CDR3 region of SEQ ID NO: 4, SEQ ID NO: 12, SEQ ID NO: 20, or SEQ ID NO: 97, a CDR2 region of SEQ ID NO:5, SEQ ID NO: 13, SEQ ID NO: 21, or SEQ ID NO: 98, and a CDR1 region of SEQ ID NO:6, SEQ ID NO: 14, SEQ ID NO: 22, or SEQ ID NO: 99;

   iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 25, SEQ ID NO: 38, SEQ ID NO: 46, SEQ ID NO: 54, SEQ ID NO: 62, SEQ ID NO: 70, SEQ ID NO: 78, or SEQ ID NO: 86, a CDR2 region of SEQ ID NO: 26, SEQ ID NO: 39, SEQ ID NO: 47, SEQ ID NO: 55, SEQ ID NO: 63, SEQ ID NO: 71, SEQ ID NO: 79, or SEQ ID NO: 87, and a CDR1 region of SEQ ID NO:27, SEQ ID NO: 40, SEQ ID NO: 48, SEQ ID NO: 56, SEQ ID NO: 64, SEQ ID NO: 72, SEQ ID NO: 80, or SEQ ID NO: 88,and in the light chain variable domain a CDR3 region of SEQ ID NO: 28, SEQ ID NO: 28 with the mutations T92L, H93Q andW94T, SEQ ID NO: 41, SEQ ID NO: 49, SEQ ID NO: 57, SEQ ID NO: 65, SEQ ID NO: 73, SEQ ID NO: 81, or SEQ ID NO: 89, a CDR2 region of SEQ ID NO:29, SEQ ID NO: 42, SEQ ID NO: 50, SEQ ID NO: 58, SEQ ID NO: 66, SEQ ID NO: 74, SEQ ID NO: 82 or SEQ ID NO: 90, and a CDR1 region of SEQ ID NO:30, SEQ ID NO: 43, SEQ

ID NO: 51, SEQ ID NO: 59, SEQ ID NO: 67, SEQ ID NO: 75, SEQ ID NO: 83, or SEQ ID NO: 91.

3. The bispecific antibody according to claim 2, characterized in that

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and in the light chain variable domain a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO:5, and a CDR1 region of SEQ ID NO:6; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 46, a CDR2 region of, SEQ ID NO: 47, and a CDR1 region of SEQ ID NO: 48, and in the light chain variable domain a CDR3 region of SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 51.

4. The bispecific antibody according to claim 3, characterized in that

ii) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain SEQ ID NO: 7, and as light chain variable domain SEQ ID NO: 8, and

iii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain SEQ ID NO: 52, and as light chain variable domain a SEQ ID NO: 53.

5. The bispecific antibody according to claim 2, characterized in that

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and in the light chain variable domain a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO:5, and a CDR1 region of SEQ ID NO:6;

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 62, a CDR2 region of SEQ ID NO: 63, and a CDR1 region of SEQ

ID NO: 64, and in the light chain variable domain a CDR3 region of SEQ ID NO: 65, a CDR2 region of SEQ ID NO: 66, and a CDR1 region of SEQ ID NO: 67.

6. The bispecific antibody according to claim 5, characterized in that

ii) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain SEQ ID NO: 7, and as light chain variable domain SEQ ID NO: 8; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain SEQ ID NO: 68, and as light chain variable domain a SEQ ID NO: 69.

7. The bispecific antibody according to claim 2, characterized in that

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and in the light chain variable domain a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO:5, and a CDR1 region of SEQ ID NO:6;

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 78, a CDR2 region of SEQ ID NO: 79, and a CDR1 region of SEQ ID NO: 80, and in the light chain variable domain a CDR3 region of SEQ ID NO: 81, a CDR2 region of SEQ ID NO: 82, and a CDR1 region of SEQ ID NO: 83.

8. The bispecific antibody according to claim 7, characterized in that

ii) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain SEQ ID NO: 7, and as light chain variable domain SEQ ID NO: 8; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain SEQ ID NO: 84, and as light chain variable domain a SEQ ID NO: 85.

9. The bispecific antibody according to any one of claims 1 to 8, characterized in that

the ratio of the binding affinities KD(antigen-binding site specific for VEGF)/KD(antigen-binding site specific for ANG-2) is 1.0- 10.0

10. The bispecific antibody according to any one of claims 1 to 9, characterized in that the second antigen-binding site that specifically binds to human ANG-2 is not specifically binding to human Angiopoetin 1 (ANG-1).

11. The bispecific antibody according to any one of claims 1 to 10, characterized in that said antibody is bivalent, trivalent or tetravalent

12. A pharmaceutical composition comprising an antibody according to claims 1 to 11

13. The pharmaceutical composition according to claims 12 for the treatment of cancer.

14. The pharmaceutical composition according to claims 12 for the treatment of vascular diseases.

15. The bispecific antibody according to any one of claims 1 to 10 for the treatment of cancer.

16. The use of an antibody according to any one of claims 1 to 10 for the manufacture of a medicament for the treatment of cancer.

17. A method of treatment of patient suffering from cancer by administering an antibody according to any one of claims 1 to 10 to a patient in the need of such treatment.

19. The bispecific antibody according to any one of claims 1 to 10 for the treatment of vascular diseases.

20. The use of an antibody according to any one of claims 1 to 10 for the manufacture of a medicament for the treatment of vascular diseases.

21. A method of treatment of patient suffering from vascular diseases by administering an antibody according to any one of claims 1 to 10 to a patient in the need of such treatment.

22. A nucleic acid encoding a bispecific antibody according to claims 1 to 10 .

23. An expression vectors containing the nucleic acid according claim 22 capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell.

24. A prokaryotic or eukaryotic host cell comprising a vector according to claim 23.

25. A method for the production of a bispecific antibody according to claims 1 to 10, characterized by expressing a nucleic acid according to claim 22 in a prokaryotic or eukaryotic host cell and recovering said bispecific antibody from said cell or the cell culture supernatant.

26. An antibody obtained by the recombinant method of claim 25.

Claims

1. A bispecific antibody specifically binding to human vascular endothelial growth factor (VEGF) and human angiopoietin-2 (ANG-2) comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2,

a) wherein

i) said antigen-binding sites are each a pair of an antibody heavy chain variable domain and an antibody light chain variable domain;

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 9, a CDR2 region of SEQ ID NO: 10, and a CDR1 region of SEQ ID NO: 11, and in the light chain variable domain a CDR3 region of SEQ ID NO: 12, a CDR2 region of SEQ ID NO: 13, and a CDR1 region of SEQ ID NO: 14; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 78, a CDR2 region of SEQ ID NO: 79, and a CDR1 region of SEQ ID NO: 80, and in the light chain variable domain a CDR3 region of SEQ ID NO: 81, a CDR2 region of SEQ ID NO: 82, and a CDR1 region of SEQ ID NO: 83;

or

b) wherein

i) said antigen-binding sites are each a pair of an antibody heavy chain variable domain and an antibody light chain variable domain;

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO: 3, and in the light chain variable domain a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO: 5, and a CDR1 region of SEQ ID NO: 6; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 46, a CDR2 region of SEQ ID NO: 47, and a CDR1 region of SEQ ID NO: 48, and in the light chain variable domain a CDR3 region of SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 51.

2. The bispecific antibody according to claim 1, wherein

i) said antigen-binding sites are each a pair of an antibody heavy chain variable domain and an antibody light chain variable domain;

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 9, a CDR2 region of SEQ ID NO: 10, and a CDR1 region of SEQ ID NO: 11, and in the light chain variable domain a CDR3 region of SEQ ID NO: 12, a CDR2 region of SEQ ID NO: 13, and a CDR1 region of SEQ ID NO: 14; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 78, a CDR2 region of SEQ ID NO: 79, and a CDR1 region of SEQ ID NO: 80, and in the light chain variable domain a CDR3 region of SEQ ID NO: 81, a CDR2 region of SEQ ID NO: 82, and a CDR1 region of SEQ ID NO: 83.

3. The bispecific antibody according to claim 1, wherein

i) said antigen-binding sites are each a pair of an antibody heavy chain variable domain and an antibody light chain variable domain;

ii) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO: 3, and in the light chain variable domain a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO: 5, and a CDR1 region of SEQ ID NO: 6; and

iii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3 region of SEQ ID NO: 46, a CDR2 region of SEQ ID NO: 47, and a CDR1 region of SEQ ID NO: 48, and in the light chain variable domain a CDR3 region of SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 51.

4. The bispecific antibody according to any one of claims 1 to 3, wherein

the ratio of the binding affinities KD of the antigen-binding site specific for VEGF/KD of the antigen-binding site specific for ANG-2 is 1.0- 10.0.

5. The bispecific antibody according to any one of claims 1 to 4, wherein the second antigen-binding site that specifically binds to human ANG-2 is not specifically binding to human Angiopoetin 1 (ANG-1).

6. A pharmaceutical composition comprising an antibody according to claims 1 to 5.

7. The pharmaceutical composition according to claim 6 for the treatment of cancer.

8. The pharmaceutical composition according to claim 6 for the treatment of vascular diseases.

9. The bispecific antibody according to any one of claims 1 to 5 for use in the treatment of cancer.

10. The bispecific antibody according to any one of claims 1 to 5 for use in the treatment of vascular diseases.

11. A nucleic acid encoding a bispecific antibody according to any one of claims 1 to 5.

12. An expression vectors containing the nucleic acid according to claim 11 capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell.

13. A prokaryotic or eukaryotic host cell comprising a vector according to claim 12.

14. A method for the production of a bispecific antibody according to any one of claims 1 to 5, characterized by expressing a nucleic acid according to claim 11 in a prokaryotic or eukaryotic host cell and recovering said bispecific antibody from said cell or the cell culture supernatant.

15. An antibody obtained by the recombinant method of claim 14.