Claims

1. A bispecific binding molecule comprising at least one Ang2-binding component and at least one Dll4-binding component.

2. The bispecific binding molecule of claim 1, further comprising at least one serum albumin binding component.

3. The bispecific binding molecule of claim 1 or 2, comprising a Dll4-binding component comprising at least a variable domain with four framework regions and three complementarity determining regions CDR1, CDR2 and CDR3, respectively, wherein said CDR3 has an amino acid sequence selected from amino acid sequences shown in

   a. SEQ IDs NOs: 1 to 166 and 458,

   b. SEQ ID NOs: 333 to 353, or

   c. SEQ ID NOs: 375 to 395.

4. The bispecific binding molecule of claim 3, the Dll4-binding component of which is an isolated immunoglobulin single variable domain or a polypeptide containing one or more of said immunoglobulin single variable domains, wherein said immunoglobulin single variable domain consists of four framework regions and three complementarity determining regions CDR1, CDR2 and CDR3, respectively, and wherein said CDR3 has an amino acid sequence selected from amino acid sequences shown in

   a. SEQ ID NOs: 1 to 166 and 458,

   b. SEQ ID NOs: 333 to 353, or

   c. SEQ ID NOs: 375 to 395.

5. The bispecific binding molecule of claim 4, wherein said one or more immunoglobulin single variable domain contain

   a. a CDR3 with an amino acid sequence selected from a first group of amino acid sequences shown in SEQ ID NOs: 1 to 166;

   b. a CDR1 and a CDR2 with an amino acid sequences that is contained, as indicated in Table 5, as partial sequence in a sequence selected from a second group of amino acid sequences shown SEQ ID NOs: 167 to 332 and 459;

   c. wherein a SEQ ID NO: x of said first group, for SEQ ID NOs: 1 – 166 corresponds to SEQ ID NO: y of said second group in that y = x +166.

6. The bispecific binding molecule of claim 4, wherein said one or more immunoglobulin single variable domains contain

   a. a CDR3 with an amino acid sequence selected a said first group of amino acid sequences shown in SEQ ID NOs: 333 to 353;

   b. a CDR1 and a CDR2 with an amino acid sequence that is contained, as indicated in Table 16-A , as a partial sequence in a sequence selected from a second group of sequences shown SEQ ID NO: 354 to 374;

   c. wherein a SEQ ID NO: x of said first group corresponds with SEQ ID NO: y of said second group in that y = x +21.

7. The bispecific binding molecule of claim 4, wherein said one or more immunoglobulin single variable domains contain

   a. a CDR3 with an amino acid sequence selected a said first group of amino acid sequences shown in SEQ ID NOs:375 to 395;

b. a CDR1 and a CDR2 with an amino acid sequence that is contained, as indicated in Table 16-B, as a partial sequence in a sequence selected from a second group of sequences shown in SEQ ID NOs: 396 to 416;

c. wherein a SEQ ID NO: x of said first group corresponds to SEQ ID NO: y of said second group in that y = x +21.

8. The bispecific binding molecule of any one of claims 4 to 7, wherein said one or more immunoglobulin single variable domains are VHHs.

9. The bispecific binding molecule of claim 8, wherein said one or more VHHs have an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 167 to 332 and 459.

10. The bispecific binding molecule of claim 8, said one or more VHHs have an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 354 to 374.

11. The bispecific binding molecule of claim 8, wherein said one or more VHHs have an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs:396 to 416.

12. An immunoglobulin single variable domain which has been obtained by affinity maturation of an immunoglobulin single variable domain as defined in claim 5.

13. A VHH which has been obtained by affinity maturation of a VHH as defined in claim 9.

14. A Dll4-binding VHH with an amino acid sequence selected from acid sequences shown in SEQ ID NOs: 356 and 358.

15. An immunoglobulin single variable domain which has been obtained by humanization of a VHH defined in claim 14.

16. A Dll4-binding VHH with an amino acid sequence selected from sequences shown in SEQ ID NOs: 402, 407 and 416.

17. An immunoglobulin single variable domain which has been obtained by humanization of a VHH defined in claim 16.

18. An immunoglobulin single variable domain which has been obtained by humanization of an immunoglobulin single variable domain as defined in claim 5.

19. An immunoglobulin single variable domain which has been obtained by humanization of an immunoglobulin single variable domain as defined in claim 12.

20. The bispecific binding molecule of claim 1, which binds to an epitope of Dll4 that is totally or partially contained within the EGF-2 domain that corresponds to amino acid residues 252-282 of SEQ ID NO: 417.

21. The bispecific binding molecule of claim 20, which is a immunoglobulin single variable domain or a polypeptide containing same.

22. The bispecific binding molecule of any one of claims 1 to 20, comprising an Ang2-binding component comprising at least a variable domain with four framework regions and three complementarity determining regions CDR1, CDR2 and CDR3, respectively, wherein said CDR3 has an amino acid sequence selected from amino acid sequences shown in SEQ IDs NOs: 491, 494, 497, 500, 503, 506, 509, 512, 515, or 518.

23. The bispecific binding molecule of claim 22, the Ang2-binding component of which is an isolated immunoglobulin single variable domain or a polypeptide containing one or more of said immunoglobulin single variable domains, wherein said immunoglobulin single variable domain consists of four framework regions and three complementarity determining regions CDR1, CDR2 and CDR3, respectively, and wherein said CDR3 has an amino acid

sequence selected from amino acid sequences shown in SEQ IDs NOs: 491, 494, 497, 500, 503, 506, 509, 512, 515, or 518.

24. The bispecific binding molecule of claim 23, wherein said one or more immunoglobulin single variable domain contain

a. a CDR3 with an amino acid sequence selected from a first group of amino acid sequences shown in SEQ ID NOs: SEQ IDs NOs: 491, 494, 497, 500, 503, 506, 509, 512, 515, or 518 (Table 36);

b. a CDR1 with an amino acid sequences that is contained, as indicated in Table 22-A or 28, as partial sequence in a sequence selected from a second group of amino acid sequences shown SEQ ID NOs: 489, 492, 495, 498, 501, 504, 507, 510, 513, or 516 (Table 36);

c. a CDR2 with an amino acid sequences that is contained, as indicated in Table 22-A or 28, as partial sequence in a sequence selected from a second group of amino acid sequences shown SEQ ID NOs: 490, 493, 496, 499, 502, 505, 508, 511, 514, or 517 (Table 36).

25. The bispecific binding molecule of any one of claims 22 to 24, wherein said one or more immunoglobulin single variable domains are VHHs.

26. The bispecific binding molecule of claim 25, wherein said one or more VHHs have an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 479, 480, 481, 482, 483, 484, 485, 486, 487, or 488.

27. An immunoglobulin single variable domain which has been obtained by affinity maturation of an immunoglobulin single variable domain as defined in claim 24.

28. A VHH which has been obtained by affinity maturation of a VHH as defined in claim 26.

29. An Ang2-binding VHH with an amino acid sequence selected from acid sequences shown in SEQ ID NOs: 479, 480, 481, 482, 483, 484, 485, 486, 487, or 488.

30. An immunoglobulin single variable domain which has been obtained by humanization of a VHH defined in claim 29.

31. An immunoglobulin single variable domain which has been obtained by humanization of an immunoglobulin single variable domain as defined in claim 24.

32. The binding molecule of any one of claim 2 to 31, the serum albumin binding component of which is an isolated immunoglobulin single variable domain or a polypeptide containing one or more of said immunoglobulin single variable domains, wherein said immunoglobulin single variable domain consists of four framework regions and three complementarity determining regions CDR1, CDR2 and CDR3, respectively, and wherein said CDR3 has an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 522, 525, 528, 531, 534, 537, or 540.

33. The binding molecule of claim 32, wherein said one or more immunoglobulin single variable domain contain

a. a CDR3 with an amino acid sequence selected from a first group of amino acid sequences shown in SEQ ID NOs: SEQ IDs NOs: 522, 525, 528, 531, 534, 537, or 540;

b. a CDR1 with an amino acid sequences selected from a second group of amino acid sequences shown SEQ ID NOs: 520, 523, 526; 529, 532, 535, or 538;

c. a CDR2 with an amino acid sequences selected from a second group of amino acid sequences shown SEQ ID NOs: 521, 524, 527, 530, 533, 536, or 539.

34. The bispecific binding molecule of claim 32 to 33, wherein said one or more immunoglobulin single variable domains are VHHs.

35. The bispecific binding molecule of claim 34, wherein said one or more VHHs have an amino acid sequence shown in SEQ ID NOs: 98 or 519.

36. The bispecific binding molecule of any one of claims 2 to 35 having the amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 460 to 478.

37. A nucleic acid molecule encoding a binding molecule of any one of claims 1 to 36 or a vector containing same.

38. A host cell containing a nucleic acid molecule of claim 37.

39. A pharmaceutical composition containing at least one bispecific binding molecule of any one of claims 1 to 36 as the active ingredient.

40. The pharmaceutical composition of claim 39 for the treatment of a disease that is associated with Dll4-mediated and/or Ang2-mediated effects on angiogenesis.

41. The pharmaceutical composition of claim 40 for the treatment of cancer and cancerous diseases.

42. The pharmaceutical composition of claim 39 for the treatment of eye diseases.

Claims

1. A bispecific binding molecule comprising
- at least one Ang2-binding component,
- at least one Dll4-binding component, and
- at least one serum albumin binding component,

wherein said Ang2-, Dll4- and serum albumin binding components are immunoglobulin single variable domains, each immunoglobulin single variable domain consisting of four framework regions and three complementarity determining regions (CDRs), and

wherein said bispecific binding molecule is selected from the group consisting of bispecific binding molecules having
(i) the CDR sequences as present in DLLANGBII00017 (SEQ ID NO: 476),
(ii) the CDR sequences as present in DLLANGBII00018 (SEQ ID NO: 477), and
(iii) the CDR sequences as present in DLLANGBII00019 (SEQ ID NO: 478).

2. The bispecific binding molecule of claim 1, wherein said immunoglobulin single variable domains are VHHs.

3. The bispecific binding molecule of claim 2, selected from the group consisting of bispecific binding molecules (i) to (iii),
the molecules (i) comprising
- the DLLBII00018 VHH domain as the Dll4-binding component,
- the Alb11 domain (SEQ ID NO: 519) as the serum albumin binding component,
and
- two ANGBII000921 VHH domains (SEQ ID NO: 485) as the Ang2-binding domains,
in this order;
the molecules (ii) comprising
- one Ang2-binding domain, having a CDR1 having the sequence DYAIG (= SEQ ID NOs: 495, 498, 513, 516), a CDR2 having the sequence AIRSSGGSTYYADSVKG (= SEQ ID NOs: 514, 517), and a CDR3 having the sequence VPAGRLRYGEQWYPIYEYDA (= SEQ ID NO: 515),
- the DLLBII00018 domain as the Dll4-binding component, and
- the Alb11 domain (SEQ ID NO: 519) as the serum albumin binding component,
in this order;

and

the molecules (iii) comprising

- two Ang2-binding domains, each having a CDR1 having the sequence DYAIG (= SEQ ID NOs: 495, 498, 513, 516), a CDR2 having the sequence AIRSSGGSTYYADSVKG (= SEQ ID NOs: 514, 517), and a CDR3 having the sequence VPAGRLRFGEQWYPLYEYDA (= SEQ ID NO: 518),
- the DLL00018 domain as the Dll4-binding component, and
- the Alb11 domain (SEQ ID NO: 519) as the serum albumin binding component, in this order.

4. The bispecific binding molecule of claim 3, selected from the group consisting of
(i) DLLANGBII00017 (SEQ ID NO: 476),
(ii) DLLANGBII00018 (SEQ ID NO: 477), and
(iii) DLLANGBII00019 (SEQ ID NO: 478).

5. A nucleic acid molecule encoding a bispecific binding molecule of any one of claims 1 to 4.

6. A vector containing a nucleic acid molecule of claim 5.

7. A host cell containing a nucleic acid molecule of claim 5 or a vector of claim 6.

8. A pharmaceutical composition containing at least one bispecific binding molecule of any one of claims 1 to 4 as the active ingredient.

9. The pharmaceutical composition of claim 8 for the treatment of a disease that is associated with Dll4-mediated and/or Ang2-mediated effects on angiogenesis.

10. The pharmaceutical composition of claim 8 or 9 for the treatment of cancer and cancerous diseases.

11. The pharmaceutical composition of claim 8 or 9 for the treatment of eye diseases.