

CLAIMS

1. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, wherein:
 - a) the first binding part comprises a heavy chain variable region (VH), which comprises a
 - 5 CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,
 - b) the first binding part comprises a light chain variable region (VL) comprising a CDRL set selected from the group consisting of
 - b1) a CDRL1 of SEQ ID NO: 32, CDRL2 of SEQ ID NO: 33, and CDRL3 of SEQ ID NO: 34,
 - 10 b2) a CDRL1 of SEQ ID NO: 81, CDRL2 of SEQ ID NO: 82, and CDRL3 of SEQ ID NO: 83,
 - b3) a CDRL1 of SEQ ID NO: 84, CDRL2 of SEQ ID NO: 85, and CDRL3 of SEQ ID NO: 86,
 - b4) a CDRL1 of SEQ ID NO: 87, CDRL2 of SEQ ID NO: 88, and CDRL3 of SEQ ID NO: 89,
 - 15 b5) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,
 - b6) a CDRL1 of SEQ ID NO: 93, CDRL2 of SEQ ID NO: 94, and CDRL3 of SEQ ID NO: 95,
 - 20 b7) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,
 - b8) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,
 - b9) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,
 - 25 b10) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,
 - b11) a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110, and
 - 30 b12) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,

c) the second binding part comprises a VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4, and

d) the second binding part comprises a VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

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2. The bispecific antibody according to claim 1, characterized in that the first binding part comprises a light chain variable region comprising a CDRL set selected from the group consisting of

10 a1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

a2) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

a3) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

15 a4) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

a5) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and

20 a6) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113.

3. The bispecific antibody according to claim 1, wherein the first binding part comprises a light chain variable region comprising a CDRL set selected from the group consisting of

25 a1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

a2) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and

a3) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113.

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4. The bispecific antibody according to claim 1, comprising

a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain variable region VL selected from the group consisting of

- b1) a light chain variable region VL of SEQ ID NO: 31,
- b2) a light chain variable region VL of SEQ ID NO: 114,
- 5 b3) a light chain variable region VL of SEQ ID NO: 115,
- b4) a light chain variable region VL of SEQ ID NO: 116,
- b5) a light chain variable region VL of SEQ ID NO: 117,
- b6) a light chain variable region VL of SEQ ID NO: 118,
- b7) a light chain variable region VL of SEQ ID NO: 119,
- 10 b8) a light chain variable region VL of SEQ ID NO: 120,
- b9) a light chain variable region VL of SEQ ID NO: 121,
- b10) a light chain variable region VL of SEQ ID NO: 122,
- b11) a light chain variable region VL of SEQ ID NO: 123, and
- b12) a light chain variable region VL of SEQ ID NO: 124, and
- 15 c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

5. The bispecific antibody according to claim 2, comprising

- a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,
- 20 b) in the first binding part a light chain variable region VL selected from the group consisting of
 - b1) a light chain variable region VL of SEQ ID NO: 117,
 - b2) a light chain variable region VL of SEQ ID NO: 119,
 - b3) a light chain variable region VL of SEQ ID NO: 120,
 - 25 b4) a light chain variable region VL of SEQ ID NO: 121,
 - b5) a light chain variable region VL of SEQ ID NO: 122, and
 - b6) a light chain variable region VL of SEQ ID NO: 124, and
- c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

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6. The bispecific antibody according to claim 3, comprising

- a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain variable region VL selected from the group consisting of

b1) a light chain variable region VL of SEQ ID NO: 117,

b1) a light chain variable region VL of SEQ ID NO: 122, and

5 b4) a light chain variable region VL of SEQ ID NO: 124, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

7. A bispecific antibody comprising a first binding part, specifically binding to human
10 CEACAM5 and a second binding part, specifically binding to human CD3ε, said antibody comprising

a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain selected from the group consisting of

b1) the light chain of SEQ ID NO: 40

15 b2) the light chain of SEQ ID NO: 125,

b3) the light chain of SEQ ID NO: 126,

b4) the light chain of SEQ ID NO: 127,

b5) the light chain of SEQ ID NO: 128,

b6) the light chain of SEQ ID NO: 129,

20 b7) the light chain of SEQ ID NO: 130,

b8) the light chain of SEQ ID NO: 131

b9) the light chain of SEQ ID NO: 132,

b10) the light chain of SEQ ID NO: 133,

b11) the light chain of SEQ ID NO: 134, and

25 b12) the light chain of SEQ ID NO: 135, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain of SEQ ID NO: 28.

8. The bispecific antibody according to any one of claims 1 to 7, characterized in comprising a
30 common heavy chain selected from the group consisting of

a) the heavy chain of SEQ ID NO: 43,

b) the heavy chain of SEQ ID NO: 44, and

c) the heavy chain of SEQ ID NO: 45.

9. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, said antibody
5 comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 128.

10. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, said antibody
10 comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 133.

11. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, said antibody
15 comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 135.

12. A bispecific antibody for use in the treatment of cancer, characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically
20 binding to human CD3ε, and characterized in
a) binding to MKN-45 cells with an EC50 value of 0.5 nM to 50 nM,
b) killing MKN-45, HPAF-II, or LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM,
c) binding to CEACAM5 expressing PEAK cells, but not cross reacting with CEACAM8
25 expressing PEAK cells,
d) that the EC50 value for killing in a TDCC assay using LS174T tumor cells as target cells is not increased by more than a factor 5 in presence of 1 µg/mL of sCEA.

13. The bispecific antibody for use according to claim 12, wherein said antibody
30 a) inhibits tumor growth in a HPAF-II model by 25% or more compared to the vehicle control group, and

b) competes with an anti-CEA antibody, comprising as VL and VH domains VL and VH of SEQ ID NOs: 48 and 49, respectively (MEDI).

14. The bispecific antibody for use according to claim 12 or 13, wherein each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329A (Kabat EU index numbering).

15. The bispecific antibody according to any one of claims 1 to 14 for use in the treatment of colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, pancreatic cancer and/or breast cancer.

16. The bispecific antibody according to any one of claims 1 to 14 for use in treating carcinomas in vivo.

17. The bispecific antibody according to any one of claims 1 to 14 for use in administering to a human subject suffering from cancer a pharmaceutically effective amount of a composition containing a bispecific antibody of the invention.

18. The bispecific antibody according to any one of claims 1 to 14 for use in the treatment of colorectal carcinoma, esophageal cancer, pancreatic adenocarcinoma, gastric cancer, non-small cell lung cancer, breast cancer, head and neck carcinoma, uterine and bladder cancers.

19. The bispecific antibody according to any one of claims 1 to 14 for use in monotherapy for the treatment of CEA expressing solid tumors

20. The bispecific antibody according to any one of claims 1 to 14 for use in the treatment of cancer in combination with a bispecific anti-CEAxCD47 antibody in simultaneous, separate, or sequential combination.

21. The bispecific antibody according to any one of claims 1 to 14 for use in the treatment of cancer in combination with a bispecific anti-CEAxCD47 antibody and/or a PD-1 axis antagonist in simultaneous, separate, or sequential combination.

22. The bispecific antibody according to any one of claims 1 to 14 for use in the treatment of cancer in combination with a PD-1 axis antagonist in simultaneous, separate, or sequential combination.

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23. The bispecific antibody according to any one of claims 1 to 14 and a bispecific anti-CEAxCD47 antibody for use in administering in alternating administration, in intervals of 6 to 15 days between administration of the antibody of the invention and the bispecific anti-CEAxCD47 antibody in the treatment of cancer.

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24. The bispecific antibody for use according to any one of claims 15 to 23, wherein the antibody of the invention is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

15 25. The bispecific antibody for use according to claim 23, characterized in that the antibody of the invention is administered to a patient in doses ranging from 1 to 20 mg/kg.

26. The bispecific antibody for use according to any one of claims 20 or 21, characterized in that the anti-CEAxCD47 antibody is administered to a patient in doses ranging from 0.1 to 100 mg/kg
20 of body weight per day or per week in single or divided doses, or by continuous infusion.

27. The bispecific antibody for use according to claim 22, wherein the PD-1 axis antagonist is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

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28. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier.

29. A bispecific antibody, comprising a first binding part, specifically binding to human
30 CEACAM5, and a second binding part, specifically binding to human CD3ε, wherein:

- a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain which comprises a variable region comprising a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,
- b) the first binding part comprises
- 5 i) a lambda light chain constant region, and
 - ii) a light chain variable region comprising a CDRL1 derived from SEQ ID NO: 32 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, a CDRL2, derived from SEQ ID NO: 33 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, and a CDRL3, derived from SEQ ID NO: 34 by
 - 10 oligonucleotide-directed mutagenesis using degenerated oligonucleotides, and
- c) the second binding part comprises a light chain variable region, comprising a CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and
- d) the second binding part comprises a light chain constant region of SEQ ID NO: 41.
- 15 30. The bispecific antibody according to claim 29, wherein the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29.
31. A bispecific antibody, comprising a first binding part, specifically binding to human
- 20 CEACAM5, and a second binding part, specifically binding to human CD3ε, comprising
- a) in the first binding part a heavy chain variable region VH having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 1, comprising a CDR1 of SEQ ID NO: 2, a CDR2 of SEQ ID NO: 3, and a CDR3 of SEQ ID NO: 4, and
 - b) a light chain variable region VL selected from the group consisting of
- 25 b1) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 31 and comprising a CDRL1 of SEQ ID NO: 32, CDRL2 of SEQ ID NO: 33, and CDRL3 of SEQ ID NO: 34,
 - b2) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 114 and comprising a CDRL1 of SEQ ID NO: 81, CDRL2 of SEQ ID
 - 30 NO: 82, and CDRL3 of SEQ ID NO: 83,
 - b3) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 115 and a CDRL1 of SEQ ID NO: 84, CDRL2 of SEQ ID NO: 85, and CDRL3 of SEQ ID NO: 86,

- b4) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 116 and a CDRL1 of SEQ ID NO: 87, CDRL2 of SEQ ID NO: 88, and CDRL3 of SEQ ID NO: 89,
- 5 b5) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 117 and a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,
- b6) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 118 and a CDRL1 of SEQ ID NO: 93, CDRL2 of SEQ ID NO: 94, and CDRL3 of SEQ ID NO: 95,
- 10 b7) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 119 and a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,
- b8) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 120 and a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,
- 15 b9) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 121 and a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,
- b10) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 122 and a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and
- 20 b11) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 123 and a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110, and
- 25 b12) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 124 and a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,
- 30 c) the second binding part a heavy chain variable region VH having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 1, comprising a CDR1 of SEQ ID NO: 2, a CDR2 of SEQ ID NO: 3, and a CDR3 of SEQ ID NO: 4, and a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 17, comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

32. The bispecific antibody according to any one of claims 29 to 31, wherein the common heavy chain is of SEQ ID NO: 43.
33. The bispecific antibody according to any one of claims 29 to 31, wherein the common heavy
5 chain is of SEQ ID NO: 44.
34. The bispecific antibody according to any one of claims 29 to 31, wherein the common heavy chain is of SEQ ID NO: 45.
- 10 35. A method of treating cancer, comprising administering an effective amount of the bispecific antibody of any one of claims 1 to 11 or 29 to 34, or the pharmaceutical composition of claim 28, to a subject in need thereof.
36. The method of claim 35, wherein the bispecific antibody binds to MKN-45 cells with an
15 EC50 value of 0.5 nM to 50 nM.
37. The method of claim 35 or 36, wherein the bispecific antibody kills MKN-45, HPAF-II, or LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM.
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38. The method of any one of claims 35 to 37, wherein the bispecific antibody binds to CEACAM5 expressing PEAK cells, but does not cross react with CEACAM8 expressing PEAK cells.
- 25 39. The method of any one of claims 35 to 38, wherein the bispecific antibody's EC50 value for killing in a TDCC assay using LS174T tumor cells as target cells is not increased by more than a factor 5 in the presence of 1 µg/mL of sCEA relative to the EC50 in the absence of sCEA.
- 30 40. The method of any one of claims 35 to 39, wherein the bispecific antibody inhibits tumor growth in a HPAF-II model by 25% or more compared to the vehicle control group.

41. The method of any one of claims 35 to 40, wherein the bispecific antibody competes with an anti-CEA antibody comprising as VL and VH the VL and VH of sequences SEQ ID NOs: 48 and 49.
- 5 42. The method of any one of claims 35 to 41, wherein the bispecific antibody comprises the amino acid substitutions L234A, L235A and P329A in each subunit of the Fc domain, as numbered according to Kabat EU index numbering.
43. The method of any one of claims 35 to 42, wherein the subject is a human.
- 10 44. The method of any one of claims 35 to 43, wherein the subject has colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, pancreatic cancer or breast cancer.
45. The method of any one of claims 35 to 43, wherein the subject has a carcinoma.
- 15 46. The method of any one of claims 35 to 43, wherein the subject has colorectal carcinoma, esophageal cancer, pancreatic adenocarcinoma, gastric cancer, non-small cell lung cancer, breast cancer, head and neck carcinoma, uterine cancer, or bladder cancer.
- 20 47. The method of any one of claims 35 to 46, wherein the bispecific antibody is administered as a monotherapy
48. The method of claim 47, wherein the bispecific antibody is administered as a treatment of CEA-expressing solid tumors.
- 25 49. The method of any one of claims 35 to 46, wherein the bispecific antibody is administered in combination with a bispecific anti-CEAxCD47 antibody in simultaneous, separate, or sequential combination.
- 30 50. The method of claim 49, wherein the bispecific antibody is administered in a alternating manner with a bispecific anti-CEAxCD47 antibody with intervals of 6 to 15 days between

administration of the bispecific antibody of the invention and the bispecific anti-CEA $\times$ CD47 antibody.

51. The method of any one of claims 35 to 46, 49, or 50, wherein the bispecific antibody is administered in combination with a PD-1 axis antagonist in simultaneous, separate, or sequential combination.

52. The method of any one of claims 35 to 51, wherein the bispecific antibody is administered in a dose between 0.1 to 100 mg/kg of body weight per day or per week.

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53. The method of any one of claims 35 to 52, wherein the bispecific antibody is administered in a dose between 1 to 20 mg/kg.

54. The method of claim 52 or 53, wherein the bispecific antibody is administered in a divided dose.

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55. The method of claim 52 or 53, wherein the bispecific antibody is administered by continuous infusion.

56. The method of any one of claims 49-55, wherein the bispecific anti-CEA $\times$ CD47 antibody is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

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57. The method of any one of claims 51 to 56, wherein the PD-1 axis antagonist is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

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58. An isolated polynucleotide that encodes the antibody of any one of claims 1 to 34, or a binding part thereof.

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59. A vector comprising the isolated polynucleotide of claim 58.

60. A cell comprising the isolated polynucleotide of claim 58 or the vector of claim 59.

61. The cell of claim 60, which is selected from the group consisting of Streptomyces, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.

62. A method of making a bispecific antibody, comprising expressing the bispecific antibody in the cell of claim claim 60 or 61.

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63. A method of making a bispecific antibody, comprising culturing the cell of claim 60 or 61 and isolating the antibody expressed therein.