

CLAIMS

1. A bispecific antibody that specifically binds NKp46 and CD38, comprising:
 - i) a first heavy chain comprising
a heavy chain complementarity determining region 1 (CDRH1) comprising an amino acid sequence of SEQ ID NO: 17;
a heavy chain complementarity determining region 2 (CDRH2) comprising an amino acid sequence of SEQ ID NO: 18; and
a heavy chain complementarity determining region 3 (CDRH3) comprising an amino acid sequence of SEQ ID NO: 19;
 - ii) a first light chain comprising
a light chain complementarity determining region 1 (CDRL1) comprising an amino acid sequence of SEQ ID NO: 20;
a light chain complementarity determining region 2 (CDRL2) comprising an amino acid sequence of SEQ ID NO: 21; and
a light chain complementarity determining region 3 (CDRL3) comprising an amino acid sequence of SEQ ID NO: 22;
 - iii) a second heavy chain comprising
a CDRH1 comprising an amino acid sequence of SEQ ID NO: 32;
a CDRH2 comprising an amino acid sequence of SEQ ID NO: 33; and
a CDRH3 comprising an amino acid sequence of SEQ ID NO: 34; and
 - iv) a second light chain comprising
a CDRL1 comprising an amino acid sequence of SEQ ID NO: 35;
a CDRL2 comprising an amino acid sequence of SEQ ID NO: 36; and
a CDRL3 comprising an amino acid sequence of SEQ ID NO: 37; andwherein the bispecific antibody comprises a first antigen binding region comprising i) and ii) that specifically binds to NKp46 and a second antigen binding region comprising iii) and iv) that specifically binds to CD38.
2. The bispecific antibody of claim 1, wherein
the first heavy chain comprises a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 23, 25, 27 or 29;
the first light chain comprises a first light chain variable region comprising an amino acid sequence of SEQ ID NO: 24, 26, 28 or 30;

the second heavy chain comprises a second heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38; and
the second light chain comprises a second light chain variable region comprising an amino acid sequence of SEQ ID NO: 39.

3. The bispecific antibody of claim 1, wherein the first antigen binding region comprises

a) a first heavy chain comprising a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 23 and a first light chain comprising a first light chain variable region comprising the amino acid sequence of SEQ ID NO: 24;

b) a first heavy chain comprising a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 25 and a first light chain comprising a first light chain variable region comprising the amino acid sequence of SEQ ID NO: 26;

c) a first heavy chain comprising a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 27 and a first light chain comprising a first light chain variable region comprising the amino acid sequence of SEQ ID NO: 28; or

d) a first heavy chain comprising a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 29 and a first light chain comprising a first light chain variable region comprising the amino acid sequence of SEQ ID NO: 30.

4. The bispecific antibody of claim 1, wherein the second antigen binding region comprises:

a second heavy chain comprising a second heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38 and a second light chain comprising a second light chain variable region comprising the amino acid sequence of SEQ ID NO: 39.

5. The bispecific antibody of claim 1, wherein

a) the first heavy chain comprises a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 23; the first light chain comprises a first light chain variable region comprising an amino acid sequence of SEQ ID NO: 24; the second heavy chain comprises a second heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38; and the second light chain comprises a second light chain variable region comprising an amino acid sequence of SEQ ID NO: 39;

b) the first heavy chain comprises a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 25; the first light chain comprises a first light chain variable region comprising an amino acid sequence of SEQ ID NO: 26; the second heavy chain comprises a second heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38; and the second light chain comprises a second light chain variable region comprising an amino acid sequence of SEQ ID NO: 39;

c) the first heavy chain comprises a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 27; the first light chain comprises a first light chain variable region comprising an amino acid sequence of SEQ ID NO: 28; the second heavy chain comprises a second heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38; and the second light chain comprises a second light chain variable region comprising an amino acid sequence of SEQ ID NO: 39; or

d) the first heavy chain comprises a first heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 29; the first light chain comprises a first light chain variable region comprising an amino acid sequence of SEQ ID NO: 30; the second heavy chain comprises a second heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 38; and the second light chain comprises a second light chain variable region comprising an amino acid sequence of SEQ ID NO: 39.

6. The bispecific antibody of claim 1, wherein the bispecific antibody comprises a fused heavy chain comprising an amino acid sequence of SEQ ID NO: 41, a first light chain comprising an amino acid sequence of SEQ ID NO: 31 and a second light chain comprising an amino acid sequence of SEQ ID NO: 40.

7. The bispecific antibody of claim 1, wherein the bispecific antibody comprises an amino acid sequence of SEQ ID NO: 46, a first light chain comprising an amino acid sequence of SEQ ID NO: 31 and a second light chain comprising an amino acid sequence of SEQ ID NO: 40.

8. The bispecific antibody of any one of claims 1-7, wherein the bispecific antibody comprises at least two Fab fragments with different CH1 and CL domains, wherein said Fab fragments comprise:

a) a first Fab fragment consisting of:

- i. the VH region and VL region that specifically binds NKp46;
 - ii. a CH1 domain of a human immunoglobulin comprising substitution of the threonine residue at position 192 of said CH1 domain with a glutamic acid residue ; and
 - iii. a CL-kappa domain of a human immunoglobulin comprising substitution of the asparagine residue at position 137 of said CL domain with a lysine residue and substitution of the serine residue at position 114 of said CL domain with an alanine residue,
- b) a second Fab fragment consisting of wild-type human CH1 and wild-type human CL domains of an immunoglobulin, and the VH region and VL region that specifically binds CD38; and

wherein the sequence position numbers used for the CH1 and CL domains refer to Kabat numbering and Fab fragments are tandemly arranged in any order, and

wherein the C-terminal end of the CH1 domain of the first Fab fragment being linked to the N-terminal end of the VH domain of the following Fab fragment is through a polypeptide linker.

9. The bispecific antibody of claim 8, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO: 9 or 44.

10. The bispecific antibody of claim 8, further comprising

- c) a dimerized CH2 domain and CH3 domain of an immunoglobulin; and
- d) a hinge region of an IgA, IgG, or IgD, linking the C-terminal ends of the CH1 domains of the antigen binding region to the N-terminal ends of the CH2 domains.

11. The bispecific antibody of claim 8, further comprising an Fc domain derived from an IgG1 Fc domain or an IgG4 Fc domain.

12. The bispecific antibody of claim 11, wherein the Fc domain region comprises an amino acid sequence of SEQ ID NO: 15.

13. The bispecific antibody of claim 11, wherein the Fc domain region comprises an amino acid sequence of SEQ ID NO: 16.

14. The bispecific antibody of any one of claims 1-13, wherein the bispecific antibody is a human antibody, a humanized antibody or a chimeric antibody.

15. The bispecific antibody of any one of claims 1-14, wherein the IgG antibody is an IgG1 or an IgG4 antibody.
16. A nucleic acid sequence encoding any one of claims 1-15.
17. A multispecific antibody comprising the antigen binding regions of the bispecific antibody of any one of claims 1-15.
18. Use of the bispecific antibody of any one of claims 1-15 or the multispecific antibody of claim 17 in the manufacture of a medicament for treating, preventing, or delaying the progression of pathologies associated with aberrant CD38 expression or activity in a subject in need thereof.
19. The use of claim 18, wherein the pathology is cancer.
20. The use of claim 19, wherein the cancer is a multiple myeloma.
21. The use of claim 19, wherein the cancer is lymphoma.
22. The use of claim 19, wherein the cancer is leukemia.
23. Use of the bispecific antibody of any one of claims 1-15 or the multispecific antibody of claim 17 in the manufacture of a medicament for redirecting a NK cell response in a subject in need thereof.
24. The use of claim 23, wherein the NK cell response is NK-mediated cytotoxicity or antibody-dependent cellular cytotoxicity (ADCC).
25. Use of the bispecific antibody according to any one of claims 1-15 in the manufacture of a medicament for promoting specific lysis of cells expressing CD38 (CD38⁺ cells) by natural killer (NK) cells, wherein the CD38⁺ cells is to be contacted with an effective amount of the bispecific antibody according to any one of claims 1-15,
wherein the effective amount is an amount sufficient to promote the specific lysis of the CD38⁺ cells by NK cells.

26. The use of claim 25, wherein the CD38⁺ cells are multiple myeloma cells or lymphoma cells.
27. The use of claim 25, wherein the bispecific antibody is to be administered to a subject suffering from or a risk for multiple myeloma or lymphoma.
28. Use of a natural killer (NK) cell in the manufacture of a medicament for inhibiting proliferation of multiple myeloma cells, lymphoma cells or CD38⁺ cancer cells in a subject treated with a bispecific antibody according to any one of claims 1-15.
29. The use of any one of claims 18-24, wherein the subject is to be administered an effective amount of natural killer (NK) cells.
30. A combination therapy or a kit for treatment of multiple myeloma, lymphoma or a CD38⁺ cancer, comprising NK cells and a bispecific antibody according to any one of claims 1-15.
31. The bispecific antibody according to any one of claims 1-15 for use in combination with NK cells.
31. Use of natural killer (NK) cells and a bispecific antibody according to any one of claims 1-15 in the manufacture of a medicament for the treatment of multiple myeloma, a leukemia (e.g., acute myeloid leukemia), lymphoma or a CD38⁺ cancer.
32. A kit comprising a bispecific antibody of any one of claims 1-15.
33. The use of any one of claims 25-29 or claim 31, wherein the NK cells are induced pluripotent stem cell-derived natural killer (iPSC-NK) cells.
34. The use of any one of claims 25-29 or claim 31, wherein the NK cells are donor-derived NK cells.
35. The use of any one of claims 25-29 or claim 31, wherein, the NK cells are irradiated immortalized NK cells.

36. The use of any one of claims 25-29 or claim 31, wherein the CD38⁺ cancer is a hematological malignancy or a solid tumor.