

What is claimed is:

1. A multispecific antigen-binding protein comprising:
 - a) two B cell maturation antigen (BCMA) antigen-binding moieties each comprising a Fab fragment and an Fc portion and wherein each Fab fragment comprises: a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:67, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:68, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:69; and a light chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:70, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:71, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:72, and
 - b) two CD16A antigen-binding moieties each in the format of a single chain variable fragment (scFv) comprising: a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:73, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:74, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:75; and a light chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:76, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:77, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:78, wherein the variable region at the N-terminus of each of the two scFvs is the light chain variable region,

wherein the N-terminus of the first of the two scFvs is fused to the C-terminus of the Fc portion of the first of the two BCMA binding moieties and the N-terminus of the second of the two scFvs is fused to the C-terminus of the Fc portion of the second of the two BCMA binding moieties.
2. The multispecific antigen-binding protein of claim 1, comprising an Fc portion mutation selected from the group consisting of (a) C220S, C229S, E233P, L234A, L234V, L234F, L235A, L235E, P238S, D265A, N297A, N297Q, and P331S, or (b) L234A, L234V, L234F, L235A, L235E, P238S, and D265A, according to the Kabat EU numbering.
3. The multispecific antigen-binding protein of claim 1, wherein the two CD16A antigen-binding moieties each comprise:

a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3; and/or a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2.

4. The multispecific antigen-binding protein of claim 1, wherein the protein is a tetramer comprising a first polypeptide chain consisting of the amino acid sequence set forth in SEQ ID NO: 61, and a second polypeptide chain consisting of the amino acid sequence set forth in SEQ ID NO: 62.

5. The multispecific antigen-binding protein of claim 1, wherein the two BCMA antigen-binding moieties each comprise: a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 65 and/or a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 66.

6. A pharmaceutical composition comprising a multispecific antigen-binding protein comprising two CD16A antigen-binding moieties, wherein each CD16A antigen-binding moiety is in the format of a single chain variable fragment (scFv), and two B cell maturation antigen (BCMA) antigen-binding moieties, wherein each BCMA antigen-binding moiety comprises an Fab fragment and an Fc portion, wherein:

(i) the two CD16A antigen-binding moieties each comprise:

(a) a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:73, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:74, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:75; and

(b) a light chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:76, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:77, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:78; wherein the variable region at the N-terminus of each of the two scFvs is the light chain variable region;

(c) wherein the N-terminus of the first of the two scFvs is fused to the C-terminus of the Fc portion of the first of the two BCMA binding moieties and the N-terminus of the second of the two scFvs is fused to the C-terminus of the Fc portion of the second of the two BCMA binding moieties; and

(ii) the two BCMA antigen-binding moieties each comprise:

(a) a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:67, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:68, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:69; and

(b) a light chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:70, a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:71, and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:72;

and a pharmaceutically acceptable carrier.

7. A bispecific antigen-binding protein comprising two CD16A antigen-binding moieties each in the format of a single chain variable fragment (scFv) and two B cell maturation antigen (BCMA)-targeting moieties each comprising an Fab fragment and an Fc portion, wherein the N-terminus of the first of the two scFvs is fused to the C-terminus of the first of the two BCMA-targeting moieties, and the N-terminus of the second of the two scFvs is fused to the C-terminus of the second of the two BCMA-targeting moieties wherein:

(i) the two CD16A antigen-binding moieties each comprise:

(a) a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:73; a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:74; and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:75, and

(b) a light chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:76; a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:77; and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:78; wherein the variable region at the N-terminus of each of the two scFvs is the light chain variable region; and

(ii) the two BCMA antigen-binding moieties each comprise:

(a) a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:67; a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:68; and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:69, and

(ii) a light chain variable region comprising a CDR1 consisting of the amino acid sequence set forth in SEQ ID NO:70; a CDR2 consisting of the amino acid sequence set forth in SEQ ID NO:71; and a CDR3 consisting of the amino acid sequence set forth in SEQ ID NO:72.

8. The bispecific antigen-binding protein of claim 7, wherein:

(i) the two CD16A antigen-binding moieties each comprise a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3;

(ii) the two CD16A antigen-binding moieties each comprise a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2;

(iii) the two BCMA antigen-binding moieties each comprise a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 65;

(iv) the two BCMA antigen-binding moieties each comprise a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 66;

(v) the two CD16A antigen-binding moieties each comprise a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2;

(vi) the two BCMA antigen-binding moieties each comprise a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 65 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 66; and/or

(vii) the two CD16A antigen-binding moieties each comprise a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2; and the two BCMA antigen-binding moieties each comprise a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 65 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 66.

9. The pharmaceutical composition of claim 6, wherein the bispecific antigen-binding protein comprises an Fc portion mutation selected from the group consisting of (a) C220S, C229S, E233P, L234A, L234V, L234F, L235A, L235E, P238S, D265A, N297A, N297Q, and P331S, or (b) L234A, L234V, L234F, L235A, L235E, P238S, and D265A, according to the Kabat EU numbering.

10. The pharmaceutical composition of claim 6, wherein the two CD16A antigen-binding moieties each comprise: a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 3; and/or a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2.
11. The pharmaceutical composition of claim 6, wherein the two BCMA antigen-binding moieties each comprise: a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 65 and/or a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 66.
12. The pharmaceutical composition of claim 6, wherein the bispecific antigen-binding protein is a tetramer comprising a first polypeptide chain consisting of the amino acid sequence set forth in SEQ ID NO: 61, and a second polypeptide chain consisting of the amino acid sequence set forth in SEQ ID NO: 62.
13. The bispecific antigen-binding protein of claim 7, comprising an Fc portion mutation selected from the group consisting of (a) C220S, C229S, E233P, L234A, L234V, L234F, L235A, L235E, P238S, D265A, N297A, N297Q, and P331S, or (b) L234A, L234V, L234F, L235A, L235E, P238S, and D265A, according to the Kabat EU numbering.
14. The bispecific antigen-binding protein of claim 7, wherein the bispecific antigen-binding protein is a tetramer comprising a first polypeptide chain consisting of the amino acid sequence set forth in SEQ ID NO: 61, and a second polypeptide chain consisting of the amino acid sequence set forth in SEQ ID NO: 62.
15. Use of the multispecific antigen-binding protein of any one of claims 1-5, the pharmaceutical composition of any one of claims 6 or 9-12, or the bispecific antigen-binding protein of any one of claims 7, 8, 13 or 14 in the manufacture of a medicament for treating, ameliorating or preventing a disease.
16. The use of claim 15, wherein the disease is cancer.
17. The use of claim 15 or claim 16, wherein the disease is a hematologic cancer.
18. The use of any one of claims 15-17, wherein the disease is multiple myeloma.

19. The use of any one of claims 15-18, wherein the subject is a cancer patient.
20. The use of any one of claims 15-19, wherein the subject is a hematological cancer patient.
21. The use of any one of claims 15-20, wherein the subject is a multiple myeloma patient.
22. The use of any one of claims 15-21, wherein the subject is a relapsed/refractory multiple myeloma patient.
23. The use of any one of claims 15-22, wherein the subject has received an anti-CD38 therapy.
24. The use of any one of claims 15-23, wherein the subject has received daratumumab.
25. The use of any one of claims 15-24, wherein the subject is daratumumab naïve, daratumumab resistant, daratumumab refractory, or daratumumab relapsed.
26. The use of claim 25, wherein the subject is daratumumab resistant, daratumumab refractory, or daratumumab relapsed.
27. The use of any one of claims 15-26, wherein the subject expresses a CD16A polymorphism.
28. The use of claim 27, wherein the CD16A polymorphism is a CD16A-158V/F polymorphism.
29. Use of the multispecific antigen-binding protein of any one of claims 1-5, the pharmaceutical composition of any one of claims 6 or 9-12, or the bispecific antigen-binding protein of any one of claims 7, 8, 13, or 14 in the manufacture of a medicament for treating a subject having a depleted or reduced NK cell population.
30. The use of claim 29, wherein the subject has been previously treated with an anti-CD38 therapy.
31. The use of claim 30, wherein the anti-CD38 therapy is daratumumab therapy.

32. The use of any one of claims 29-31, wherein the multispecific or bispecific antigen-binding protein is administered intravenously.
33. The use of any one of claims 29-31, wherein the multispecific or bispecific antigen-binding protein is administered subcutaneously.
34. The use of any one of claims 29-33, wherein a second therapy is administered with the multispecific antigen-binding protein, pharmaceutical composition, or bispecific antigen-binding protein.
35. The use of claim 34, wherein the second therapy is selected from the group consisting of therapies comprising an anti-PD-1 antibody, therapies comprising an anti-PD-L1 antibodies, therapies comprising a CD3 bispecific antibody, therapies comprising an anti-TIGIT antibody, therapies comprising an anti-VEGF antibody, and therapies comprising an anti-FcRH5 antibody .
36. The use of claim 35, wherein the second therapy is a cytokine therapy.
37. The use of claim 36, wherein the cytokine therapy comprises the administration of a cytokine selected from the group consisting of IL-15, IL-2, IL-12, IL-21, and IL-6.
38. The use of claim 37, wherein the cytokine therapy comprises the administration of IL-2.
39. The use of claim 37, wherein the cytokine therapy comprises the administration of IL-15.
40. The multispecific antigen-binding protein of any one of claims 1-5, the pharmaceutical composition of any one of claims 6 or 9-12, or the bispecific antigen-binding protein of any one of claims 7, 8, 13, or 14 for use in therapy.