

CLAIMS

1. A protein comprising:
 - (a) a first antigen-binding site that binds NKG2D;
 - (b) a second antigen-binding site that binds BCMA; and
 - (c) an antibody Fc domain or a portion thereof sufficient to bind CD16.
2. The protein according to claim 1, wherein the first antigen-binding site binds to human and non-human primate NKG2D.
3. The protein according to claim 1 or 2, wherein the first antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.
4. The protein according to claim 3, wherein the heavy chain variable domain and the light chain variable domain are present on the same polypeptide.
5. The protein according to any one of claims 3-4, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.
6. The protein according to claim 5, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.
7. The protein according to claim 5 or 6, wherein the light chain variable domain of the first antigen-binding site has an amino acid sequence identical to the amino acid sequence of the light chain variable domain of the second antigen-binding site.
8. The protein according to any one of claims 1-7, wherein the first antigen-binding site comprises:
 - (i) a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:111, a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:112, a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:113, a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:114, a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:115, and a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:116;

(ii) a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:64, a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:65, and a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:66;

(iii) a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:67, a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:68, a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:69, a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:70, a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:71, and a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:72; or

(iv) a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:73, a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:74, a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:75, a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:76, a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:77, and a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:78.

9. The protein according to claim 8, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1.

10. The protein according to claim 8, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:41 and a light chain variable domain at least 95% identical to the amino acid sequence of SEQ ID NO:42.

11. The protein according to claim 8, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:43 and a light chain variable domain at least 95% identical to the amino acid sequence of SEQ ID NO:44.

12. The protein according to claim 8, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:45 and a light chain variable domain at least 95% identical to the amino acid sequence of SEQ ID NO:46.

13. The protein according to claim 8, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:47 and a light chain variable domain at least 95% identical to the amino acid sequence of SEQ ID NO:48.

14. The protein of claim 1 or 2, wherein the first antigen-binding site is a single-domain antibody.

15. The protein of claim 14, wherein the single-domain antibody is a V_HH fragment or a V_{NAR} fragment.

16. The protein according to any one of claims 1-2 or 14-15, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

17. The protein according to claim 16, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.

18. The protein according to any one of the preceding claims, wherein the second antigen-binding site comprises:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:134;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:135; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:136.

19. The protein according to claim 18, wherein the second antigen-binding site comprises a heavy chain variable domain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:93 and a light chain variable domain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:94.

20. The protein according to any one of claims 1-17, wherein the second antigen-binding site comprises:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:50;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:51; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:52.

21. The protein according to claim 20, wherein the second antigen-binding site comprises:
a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:55;
a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:56; and
a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:57 or SEQ ID NO:58.
22. The protein according to claim 21, wherein the second antigen-binding site comprises
a heavy chain variable domain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:49 and a light chain variable domain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:53 or SEQ ID NO:54.
23. The protein according to any one of claims 1-17, wherein the second antigen-binding site comprises:
a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:79;
a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:80; and
a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:81.
24. The protein according to claim 23, wherein the second antigen-binding site comprises:
a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:82;
a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:83; and
a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:84.
25. The protein according to claim 24, wherein the second antigen-binding site comprises
a heavy chain variable domain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:59 and a light chain variable domain comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:60.
26. The protein according to any one of claims 1-17, wherein the second antigen-binding site comprises:
a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:85;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:86; and
a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:87.

27. The protein according to claim 26, wherein the second antigen-binding site comprises:
a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:88;
a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:89; and
a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:90.

28. The protein according to claim 27, wherein the second antigen-binding site comprises
a heavy chain variable domain comprising an amino acid sequence at least 95% identical to the
amino acid sequence of SEQ ID NO:61 and a light chain variable domain comprising an amino
acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:62.

29. The protein according to any one of claims 1-4 or 8-14, wherein the second antigen-
binding site is a single-domain antibody.

30. The protein of claim 29, wherein the second antigen-binding site is a V_HH fragment or
a V_{NAR} fragment.

31. The protein according to any one of the preceding claims, wherein the protein
comprises a portion of an antibody Fc domain sufficient to bind CD16, wherein the antibody
Fc domain comprises hinge and CH2 domains.

32. The protein according to claim 31, wherein the antibody Fc domain comprises hinge
and CH2 domains of a human IgG1 antibody.

33. The protein according to claim 31 or 32, wherein the Fc domain comprises an amino
acid sequence at least 90% identical to amino acids 234-332 of a human IgG1 antibody.

34. The protein according to any one of claims 31-33, wherein the Fc domain comprises an
amino acid sequence at least 90% identical to the Fc domain of human IgG1 and differs at one
or more positions selected from the group consisting of Q347, Y349, L351, S354, E356, E357,
K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407,
K409, T411, and K439.

35. A formulation comprising a protein according to any one of the preceding claims and a

pharmaceutically acceptable carrier.

36. A host or *in vitro* cell comprising one or more nucleic acids encoding the protein according to any one of claims 1-34.

37. Use of the protein according to any one of claims 1-34 in the manufacture of a medicament for directly and/or indirectly enhancing BCMA-expressing tumor cell death by exposing the tumor cell and a natural killer cell to an effective amount of the protein.

38. Use of the protein according to any one of claims 1-34 or the formulation according to claim 35 in the manufacture of a medicament for treating BCMA-expressing cancer.

39. The use of claim 38, wherein the BCMA-expressing cancer is multiple myeloma, acute myelomonocytic leukemia, T cell lymphoma, acute monocytic leukemia, or follicular lymphoma.