

WHAT IS CLAIMED IS:

1. A protein comprising:
 - (a) a first antigen-binding site that binds NKG2D;
 - 5 (b) a second antigen-binding site that binds fibroblast activation protein (FAP); and
 - (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.
2. The protein according to claim 1, wherein the first antigen-binding site binds to
10 NKG2D in humans.
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.
- 15 5. The protein according to claims 3 or 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.
- 20 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. A protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to an amino acid sequence
25 selected from: SEQ ID NO:1, SEQ ID NO:41, SEQ ID NO:49, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:69, SEQ ID NO:77, SEQ ID NO:85, SEQ ID NO:167, SEQ ID NO:171, SEQ ID NO: 175, SEQ ID NO:179, SEQ ID NO:183, SEQ ID NO:187, and SEQ ID NO:93.

9. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:41 and a light chain variable domain at least 90% identical to SEQ ID NO:42.
10. The protein according to any one of claims 1 to 7, wherein the first antigen-binding
5 site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:49 and a light chain variable domain at least 90% identical to SEQ ID NO:50.
11. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:57 and a light chain variable domain at least 90% identical to SEQ ID NO:58.
- 10 12. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:59 and a light chain variable domain at least 90% identical to SEQ ID NO:60.
13. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:61 and a
15 light chain variable domain at least 90% identical to SEQ ID NO:62.
14. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:69 and a light chain variable domain at least 90% identical to SEQ ID NO:70.
15. The protein according to any one of claims 1 to 7, wherein the first antigen-binding
20 site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:77 and a light chain variable domain at least 90% identical to SEQ ID NO:78.
16. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:85, SEQ ID NO:167, SEQ ID NO:171, SEQ ID NO: 175, SEQ ID NO:179, SEQ ID NO:183, or SEQ
25 ID NO:187, and a light chain variable domain at least 90% identical to SEQ ID NO:86.
17. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:93 and a light chain variable domain at least 90% identical to SEQ ID NO:94.

18. The protein according to any one of claims 1 to 7, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:101 and a light chain variable domain at least 90% identical to SEQ ID NO:102.
19. The protein according to any one of claims 1 to 7, wherein the first antigen-binding
5 site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:103 and a light chain variable domain at least 90% identical to SEQ ID NO:104.
20. The protein according to claim 1 or 2, wherein the first antigen-binding site is a single-domain antibody.
21. The protein according to claim 20, wherein the single-domain antibody is a V_HH
10 fragment or a V_{NAR} fragment.
22. The protein according to any one of claims 1 to 2 or 20 to 21, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.
23. The protein according to claim 22, wherein the heavy chain variable domain and the
15 light chain variable domain of the second antigen-binding site are present on the same polypeptide.
24. The protein according to any one of claims 1 to 23, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:114 and the light chain variable domain of the second antigen-
20 binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:118.
25. The protein according to any one of claims 1 to 23, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:131 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:135.
- 25 26. The protein according to any one of claims 1 to 23, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:139 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:143.

27. The protein according to any one of claims 1 to 23, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:122 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:126.
- 5 28. The protein according to any one of claims 1 to 23, wherein the second antigen-binding site comprises CDR1, CDR2, and CDR3 sequences of a heavy chain variable domain and a light chain variable domain selected from the group consisting of SEQ ID NO:114 and 118, 131 and 135, 139 and 143, and 122 and 126, respectively.
29. The protein according to any one of claims 1 to 4 or 8 to 21, wherein the second
10 antigen-binding site is a single-domain antibody.
30. The protein according to 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 claims 1 to 30, wherein the protein comprises a portion of an antibody Fc domain sufficient to bind CD16, wherein the antibody Fc domain
15 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.
- 20 34. The protein according to claim 33, wherein the Fc domain comprises 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, K439.
- 25 35. A formulation comprising a protein according to any one of claims 1 to 34 and a pharmaceutically acceptable carrier.
36. A cell comprising one or more nucleic acids encoding a protein according to any one of claims 1 to 34.

37. A method of enhancing tumor cell death, the method comprising exposing tumor cells and natural killer cells to an effective amount of the protein according to any one of claims 1 to 34.

38. A method of treating cancer, wherein the method comprises administering an effective amount of the protein according to any one of claims 1 to 34 or the formulation according to claim 35 to a patient.

39. The method according to claim 38, wherein the cancer to be treated is selected from the group consisting of infiltrating ductal carcinoma, pancreatic ductal adenocarcinoma, stomach cancer, uterine cancer, cervical cancer, colorectal cancer, breast cancer, ovarian cancer, bladder cancer, lung cancer, mesothelioma, gastric cancer, pancreatic cancer, head and neck cancer, liver cancer, endometrial cancer, neuroendocrine cancer, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, osteosarcoma, chondrosarcoma, liposarcoma, synovial sarcoma, schwannoma, melanoma, and glioma.

40. A method of treating an autoimmune disease, wherein the method comprises administering an effective amount of the protein according to any one of claims 1 to 34 or the formulation according to claim 35 to a patient.

41. The method according to claim 40, wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, Grave's disease, Sjögren's syndrome, primary biliary cirrhosis, primary sclerosis cholangitis, and inflammatory destructive arthritis.

42. A method of treating fibrosis, wherein the method comprises administering an effective amount of the protein according to any one of claims 1 to 34 or the formulation according to claim 35 to a patient.

43. A method according to claim 42, wherein the fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis, renal fibrosis, hepatic fibrosis, and cardiac fibrosis.