

WHAT IS CLAIMED IS:

1. A protein comprising:
  - (a) a first antigen-binding site that binds NKG2D;
  - (b) a second antigen-binding site that binds CLEC12A; and
  - (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16;wherein the second antigen-binding site that binds CLEC12A comprises:
  - (i) a heavy chain variable domain (VH) comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity-determining region 3 (CDR3) comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 137, 272, and 273, respectively; and a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 140, 141, and 142, respectively;
  - (ii) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 137, 138, and 139, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 140, 141, and 142, respectively;
  - (iii) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 251, 196, and 246, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 198, 199, and 201, respectively;
  - (iv) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 221, 166, and 223, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 240, 226, and 179, respectively;
  - (v) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 206, 166, and 241, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 245, 239, and 179, respectively;
  - (vi) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 221, 236, and 223, respectively; and a VL comprising CDR1,

CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 152, 226, and 179, respectively;

(vii) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 159, 170, and 183, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 186, 188, and 189, respectively;

(viii) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 197, 202, and 207, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 211, 212, and 214, respectively;

(ix) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 220, 222, and 257, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 224, 225, and 227, respectively; or

(x) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 230, 231, and 232, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 233, 234, and 235, respectively.

2. The protein of claim 1, wherein the second antigen-binding site that binds CLEC12A comprises

(i) ~~a~~ the VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 137, 272, and 273, respectively; and ~~a~~ the VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 140, 141, and 142, respectively; or

(ii) ~~a~~ the VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 137, 138, and 139, respectively; and ~~a~~ the VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 140, 141, and 142, respectively.

3. The protein of claim 1 or 2, wherein

(i) the VH comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:335, and the VL comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:336;

(ii) the VH comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:270, and the VL comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:271; ~~or~~

(iii) the VH comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:178, and the VL comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:289;

(iv) the VH comprises an amino acid sequence as set forth in SEQ ID NO:335, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:336;

(v) the VH comprises an amino acid sequence as set forth in SEQ ID NO:270, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:271;

(vi) the VH comprises an amino acid sequence as set forth in SEQ ID NO:178, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:289;

(vii) the VH comprises an amino acid sequence as set forth in SEQ ID NO:143, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:144;

(viii) the VH comprises an amino acid sequence as set forth in SEQ ID NO:147, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:144;

(ix) the VH comprises an amino acid sequence as set forth in SEQ ID NO:244, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:144;

(x) the VH comprises an amino acid sequence as set forth in SEQ ID NO:178, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:144;

(xi) the VH comprises an amino acid sequence as set forth in SEQ ID NO:256, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:144;

(xii) the VH comprises an amino acid sequence as set forth in SEQ ID NO:143, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:163;

(xiii) the VH comprises an amino acid sequence as set forth in SEQ ID NO:143, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:167;

(xiv) the VH comprises an amino acid sequence as set forth in SEQ ID NO:143, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:171; or

(xv) the VH comprises an amino acid sequence as set forth in SEQ ID NO:174, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:175.

4. ~~— The protein of any one of claims 1-3, wherein~~

~~— (i) the VH comprises the amino acid sequence of SEQ ID NO:335, and the VL comprises the amino acid sequence of SEQ ID NO:336;~~

~~— (ii) the VH comprises the amino acid sequence of SEQ ID NO:270, and the VL comprises the amino acid sequence of SEQ ID NO:271; or~~

~~— (iii) the VH comprises the amino acid sequence of SEQ ID NO:178, and the VL comprises the amino acid sequence of SEQ ID NO:289.~~

5. ~~— The protein of claim 1 or 2, wherein the VH and the VL comprise the amino acid sequences of SEQ ID NOs: 143 and 144; 147 and 144; 244 and 144; 178 and 144; 256 and 144; 143 and 163; 143 and 167; 143 and 171; or 174 and 175, respectively.~~

64. The protein of any one of claims 1-53, wherein the second antigen-binding site is present as a single-chain fragment variable (scFv), and wherein the scFv comprises an amino acid sequence selected from SEQ ID NOs: 274, 145, 146, 149, 150, 153, 154, 156, 157, 160, 161, 164, 165, 168, 169, 172, 173, 176, 177, 180, and 181.

7. ~~— The protein of claim 6, wherein the scFv comprises the amino acid sequence of SEQ ID NO:274 or SEQ ID NO:180.~~

85. The protein of claim 1, wherein the second antigen-binding site that binds CLEC12A comprises:

(i) a the VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of as set forth in SEQ ID NOs: 251, 196, and 246, respectively; and a the VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of as set forth in SEQ ID NOs: 198, 199, and 201, respectively;

(ii) the VH comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 195, 196, 187, respectively; and the VL comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 198, 199, 201, respectively;

(iii) the VH comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 192, 196, and 187, respectively; and the VL comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 198, 199, and 201, respectively; or

(iv) the VH comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 192, 196, and 213, respectively; and the VL comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 198, 199, and 201, respectively.

9. ~~The protein of claim 1, wherein the second antigen-binding site that binds CLEC12A comprises:~~

~~—— (i) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 195, 196, 187, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 198, 199, 201, respectively;~~

~~—— (ii) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 192, 196, and 187, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 198, 199, and 201, respectively; or~~

~~—— (iii) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 192, 196, and 213, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 198, 199, and 201, respectively.~~

106. The protein of claim 1 or 5 ~~any one of claims 1 and 8-9~~, wherein

(i) the VH comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:148, and the VL comprises an amino acid sequence at least ~~90%~~ 95% identical to SEQ ID NO:203;

(ii) the VH comprises an amino acid sequence as set forth in SEQ ID NO:148, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:203;

(iii) the VH comprises an amino acid sequence as set forth in SEQ ID NO:162, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:203;

(iv) the VH comprises an amino acid sequence as set forth in SEQ ID NO:210, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:203;

(v) the VH comprises an amino acid sequence as set forth in SEQ ID NO:162, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:218; or

(vi) the VH comprises an amino acid sequence as set forth in SEQ ID NO:210, and the VL comprises an amino acid sequence as set forth in SEQ ID NO:218.

~~11. The protein of any one of claims 1 and 8-10, wherein the VH comprises the amino acid sequence of SEQ ID NO:148, and the VL comprises the amino acid sequence of SEQ ID NO:203.~~

~~12. The protein of claim 11, wherein the VH and the VL comprise the amino acid sequences of SEQ ID NOs: 162 and 203; 210 and 203; 162 and 218; 148 and 218; or 210 and 218, respectively.~~

~~13. The protein of claim 5 or 6 any one of claims 8-12, wherein second the antigen-binding site is present as an scFv, and wherein the scFv comprises an amino acid sequence selected from SEQ ID NOs: 184, 185, 204, 205, 208, 209, 215, 216, 252, 253, 254, and 255.~~

~~14. The protein of claim 13, wherein the scFv comprises the amino acid sequence of SEQ ID NO:204.~~

~~15. The protein of any one of the preceding claims, wherein the second antigen-binding site binds CLEC12A in a glycosylation independent manner.~~

~~16. A protein comprising:~~

~~— (a) a first antigen-binding site that binds NKG2D;~~

~~— (b) a second antigen-binding site that binds CLEC12A; and~~

~~— (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16;~~

~~— wherein the second antigen-binding site binds CLEC12A in a glycosylation independent manner.~~

~~17. The protein of any one of claims 1-16 1-8, wherein the second antigen-binding site binds human CLEC12A with a dissociation constant ( $K_D$ ) smaller than or equal to 20 nM as measured by surface plasmon resonance (SPR).~~

~~18~~10. The protein of any one of claims ~~1-7~~ 1-4 and ~~9-16~~ 1-7, wherein the second antigen-binding site binds human CLEC12A with a  $K_D$  smaller than or equal to 1 nM as measured by SPR.

~~19~~11. The protein of any one of claims ~~1-7~~ 1-4 and ~~8-10~~ 15-18, wherein the second antigen-binding site binds human CLEC12A comprising a K244Q substitution.

~~20~~12. The protein of any one of claims ~~1-19~~ 1-11, wherein the protein comprises an antibody Fc domain or a portion thereof sufficient to bind CD16.

~~21~~13. The protein of any one of claims ~~1-20~~ 1-12, wherein:

- (i) the first antigen-binding site that binds NKG2D is a Fab fragment, and the second antigen-binding site that binds CLEC12A is an scFv; or
- (ii) the first antigen-binding site that binds NKG2D is an scFv, and the second antigen-binding site that binds CLEC12A is a Fab fragment.

~~22. The protein of any one of claims 1-5, 8-12, and 15-20, wherein the first antigen-binding site that binds NKG2D is an scFv, and the second antigen-binding site that binds CLEC12A is a Fab fragment.~~

~~23~~14. The protein of any one of claims ~~1-20~~ 1-12, further comprising an additional antigen-binding site that binds CLEC12A.

~~24~~15. The protein of claim ~~23~~14, wherein:

- (i) the first antigen-binding site that binds NKG2D is an scFv, and
- (ii) the second and the additional antigen-binding sites that bind CLEC12A are either each a Fab fragment or each an scFv.

~~25. The protein of claim 23, wherein the first antigen-binding site that binds NKG2D is an scFv, and the second and the additional antigen-binding sites that bind CLEC12A are each an scFv.~~

~~26~~16. The protein of ~~any one of claims 23-25~~ claim 14 or 15, wherein the amino acid sequences of the second and the additional antigen-binding sites are identical.

27. — A protein comprising:

- (a) a first antigen-binding site that binds NKG2D;
  - (b) a second antigen-binding site that binds CLEC12A; and
  - (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16;
- wherein the first antigen-binding site that binds NKG2D is a Fab fragment, and the second antigen-binding site that binds CLEC12A is an scFv.

2817. The protein of claim 13 or 14 ~~any one of claims 22, 24-26~~, wherein the scFv that binds NKG2D and/or CLEC12A is linked to an antibody constant domain or a portion thereof sufficient to bind CD16, via a hinge comprising:

- (i) Ala-Ser; ~~or~~
- (ii) Gly-Ser;
- (iii) Thr-Lys-Gly-Ala-Ser;
- (iv) Thr-Lys-Gly- Gly-Ser;
- (v) Ala-Ser-Thr-Lys-Gly; or
- (vi) Gly-Ser-Thr-Lys-Gly.

29. — ~~The protein of any one of claims 21 and 25-28, wherein each scFv that binds CLEC12A is linked to an antibody constant domain or a portion thereof sufficient to bind CD16, via a hinge comprising Ala-Ser or Gly-Ser.~~

30. — ~~The protein of claim 28 or 29, wherein the hinge further comprises an amino acid sequence Thr-Lys-Gly.~~

3118. The protein of any one of claims ~~22, 24-26, 28, and 30~~ 13-17, wherein within the scFv that binds NKG2D and/or CLEC12A, the heavy chain variable domain of the scFv forms a disulfide bridge with the light chain variable domain of the scFv.

32. — ~~The protein of any one of claims 21, 25-27, and 30-31, wherein within each scFv that binds CLEC12A, the heavy chain variable domain of the scFv forms a disulfide bridge with the light chain variable domain of the scFv.~~

~~33~~19. The protein of claim ~~31~~18 ~~or 32~~, wherein the disulfide bridge is formed between C44 of the heavy chain variable domain and C100 of the light chain variable domain, numbered under the Kabat numbering scheme.

~~34~~20. The protein of any one of claims ~~22, 24-26, 28, 30-31, and 33~~ 13-19, wherein within the scFv that binds NKG2D and/or CLEC12A, the heavy chain variable domain is linked to the light chain variable domain via a flexible linker.

~~35. The protein of any one of claims 21, 25-27, 29-30, and 32-34, wherein within each scFv that binds CLEC12A, the heavy chain variable domain is linked to the light chain variable domain via a flexible linker.~~

~~36~~21. The protein of claim ~~20~~ 34 ~~or 35~~, wherein the flexible linker comprises (G<sub>4</sub>S)<sub>4</sub>.

~~37. The protein of any one of claims 22, 24-26, 28, 30-31, 33-34, and 36, wherein within the scFv that binds NKG2D, the heavy chain variable domain is positioned at the C-terminus of the light chain variable domain.~~

~~38. The protein of any one of claims 21, 25-27, 29-30, 32-33, and 35-37, wherein within each scFv that binds CLEC12A, the heavy chain variable domain is positioned at the C-terminus of the light chain variable domain.~~

~~39. The protein of any one of claims 22, 24-26, 28, 30-31, 33-34, and 36, wherein within the scFv that binds NKG2D, the heavy chain variable domain is positioned at the N-terminus of the light chain variable domain.~~

~~40. The protein of any one of claims 21, 25-27, 29-30, 32-33, 35-36, and 39, wherein within each scFv that binds CLEC12A, the heavy chain variable domain is positioned at the N-terminus of the light chain variable domain.~~

~~41~~22. The protein of any one of claims ~~21, 27, 29-30, 32-33, 35-36, 38 and 40~~ 13-21, wherein the Fab fragment that binds NKG2D and/or CLEC12A is not positioned between an antigen-binding site and the Fc or the portion thereof.

~~42. The protein of any one of claims 22, 24, 26, 28, 30-31, 33-34, 36-37, and 39, wherein no Fab fragment that binds CLEC12A is positioned between an antigen-binding site and the Fc or the portion thereof.~~

~~43~~23. The protein according to ~~any one of~~ any one of claims ~~1-42~~ 1-22, wherein the first antigen-binding site that binds NKG2D comprises:

(i) a VH comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 81, 82, and 112, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising ~~the~~ amino acid sequences ~~of~~ as set forth in SEQ ID NOs: 86, 77, and 87, respectively;

(ii) ~~a VH comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 81, 82, and 97, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 86, 77, and 87, respectively; or~~

(iii) ~~a VH comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 81, 82, and 84, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising amino acid sequences as set forth in SEQ ID NOs: 86, 77, and 87, respectively.~~

~~44. The protein of any one of claims 1-42, wherein the first antigen-binding site that binds NKG2D comprises:~~

~~—— (i) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 81, 82, and 97, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 86, 77, and 87, respectively; or~~

~~—— (ii) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 81, 82, and 84, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 86, 77, and 87, respectively.~~

~~45~~24. The protein of claim ~~43 or 44~~ 23, wherein:

(i) ~~the~~ the VH of the first antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:95, and the VL of the first antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:85; or

(ii) the VH of the first antigen-binding site comprises an amino acid sequence as set forth in SEQ ID NO:95, and the VL of the first antigen-binding site comprises an amino acid sequence as set forth in SEQ ID NO:85.

~~46. The protein of any one of claims 43-45, wherein the VH of the first antigen-binding site comprises the amino acid sequence of SEQ ID NO:95, and the VL of the first antigen-binding site comprises the amino acid sequence of SEQ ID NO:85.~~

~~4725.~~ The protein of any one of claims ~~1-46~~ 1-24, wherein the antibody Fc domain is a human IgG1 antibody Fc domain.

~~4826.~~ The protein of claim ~~4725~~, wherein:

(i) the antibody Fc domain or the portion thereof comprises an amino acid sequence at least 90% identical to SEQ ID NO:118;

(ii) at least one polypeptide chain of the antibody Fc domain comprises one or more mutations, relative to SEQ ID NO:118, at one or more positions selected from Q347, Y349, L351, S354, D356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411, and K439, numbered according to the EU numbering system; and/or

(iii) at least one polypeptide chain of the antibody Fc domain comprises one or more mutations, relative to SEQ ID NO:118, selected from Q347E, Q347R, Y349S, Y349K, Y349T, Y349D, Y349E, Y349C, L351K, L351D, L351Y, S354C, D356K, E357Q, E357L, E357W, K360E, K360W, Q362E, S364K, S364E, S364H, S364D, T366V, T366I, T366L, T366M, T366K, T366W, T366S, L368E, L368A, L368D, K370S, N390D, N390E, K392L, K392M, K392V, K392F, K392D, K392E, T394F, D399R, D399K, D399V, S400K, S400R, D401K, F405A, F405T, Y407A, Y407I, Y407V, K409F, K409W, K409D, T411D, T411E, K439D, and K439E, numbered according to the EU numbering system.

~~49. The protein of claim 47 or 48, wherein at least one polypeptide chain of the antibody Fc domain comprises one or more mutations, relative to SEQ ID NO:118, at one or more positions selected from Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411, and K439, numbered according to the EU numbering system.~~

~~50. The protein of any one of claims 47-49, wherein at least one polypeptide chain of the antibody Fc domain comprises one or more mutations, relative to SEQ ID NO:118, selected from Q347E, Q347R, Y349S, Y349K, Y349T, Y349D, Y349E, Y349C, L351K, L351D, L351Y, S354C, E356K, E357Q, E357L, E357W, K360E, K360W, Q362E, S364K, S364E, S364H, S364D, T366V, T366I, T366L, T366M, T366K, T366W, T366S, L368E, L368A, L368D, K370S, N390D, N390E, K392L, K392M, K392V, K392F, K392D, K392E, T394F, D399R, D399K, D399V, S400K, S400R, D401K, F405A, F405T, Y407A, Y407I, Y407V, K409F, K409W, K409D, T411D, T411E, K439D, and K439E, numbered according to the EU numbering system.~~

~~5127.~~ The protein of claim 25 or 26 ~~any one of claims 47-50~~, wherein one polypeptide chain of the antibody heavy chain constant region comprises one or more mutations, relative to SEQ ID NO:118, at one or more positions selected from Q347, Y349, L351, S354, E356D356, E357, K360, Q362, S364, T366, L368, K370, K392, T394, D399, S400, D401, F405, Y407, K409, T411 and K439; and the other polypeptide chain of the antibody heavy chain constant region comprises one or more mutations, relative to SEQ ID NO:118, at one or more positions selected from Q347, Y349, L351, S354, E356D356, E357, S364, T366, L368, K370, N390, K392, T394, D399, D401, F405, Y407, K409, T411, and K439, numbered according to the EU numbering system.

~~5228.~~ The protein of claim ~~5127~~, wherein:

(i) one polypeptide chain of the antibody heavy chain constant region comprises K360E and K409W substitutions relative to SEQ ID NO:118; and the other polypeptide chain of the antibody heavy chain constant region comprises Q347R, D399V and F405T substitutions relative to SEQ ID NO:118, numbered according to the EU numbering system; or

(ii) one polypeptide chain of the antibody heavy chain constant region comprises a Y349C substitution relative to SEQ ID NO:118; and the other polypeptide chain of the antibody heavy chain constant region comprises an S354C substitution relative to SEQ ID NO:118, numbered according to the EU numbering system.

~~53. The protein of claim 51 or 52, wherein one polypeptide chain of the antibody heavy chain constant region comprises a Y349C substitution relative to SEQ ID NO:118; and the other~~

~~polypeptide chain of the antibody heavy chain constant region comprises an S354C substitution relative to SEQ ID NO:118, numbered according to the EU numbering system.~~

5429. A protein comprising:

(a) a first polypeptide comprising ~~the~~ an amino acid sequence ~~of~~ as set forth in SEQ ID NO:259 or SEQ ID NO:276;

(b) a second polypeptide comprising ~~the~~ an amino acid sequence ~~of~~ as set forth in SEQ ID NO:260; and

(c) a third polypeptide comprising ~~the~~ an amino acid sequence ~~of~~ as set forth in SEQ ID NO:261.

5530. A pharmaceutical composition comprising the protein of any one of claims 1-54 1-29 and a pharmaceutically acceptable carrier.

~~56. A pharmaceutical formulation comprising the protein of any one of claims 1-54 and a buffer at pH 7.0 or higher.~~

~~57. The pharmaceutical formulation of claim 56, wherein the pH of the formulation is between 7.0 and 8.0.~~

~~58. The pharmaceutical formulation of claim 56 or 57, wherein the buffer comprises citrate.~~

~~59. The pharmaceutical formulation of claim 58, wherein the concentration of citrate is 10 to 20 mM.~~

~~60. The pharmaceutical formulation of any one of claims 56-59, wherein the buffer further comprises phosphate.~~

~~61. The pharmaceutical formulation of any one of claims 56-59, further comprising a sugar or sugar alcohol in the pharmaceutical formulation.~~

~~62. The pharmaceutical formulation of claim 61, wherein the sugar or sugar alcohol is a disaccharide.~~

~~63. The pharmaceutical formulation of claim 62, wherein the disaccharide is sucrose.~~

64.—The pharmaceutical formulation of any one of claims 61-63, wherein the concentration of the sugar or sugar alcohol in the pharmaceutical formulation is 200 to 300 mM.

65.—The pharmaceutical formulation of claim 64, wherein the concentration of the sugar or sugar alcohol in the pharmaceutical formulation is about 250 mM.

66.—The pharmaceutical formulation of any one of claims 56-65, further comprising a nonionic surfactant.

67.—The pharmaceutical formulation of claim 66, wherein the nonionic surfactant comprises a polysorbate.

68.—The pharmaceutical formulation of claim 67, wherein the polysorbate is polysorbate 80.

69.—The pharmaceutical formulation of claim 68, wherein the concentration of polysorbate 80 in the pharmaceutical formulation is 0.005% to 0.05%.

70.—The pharmaceutical formulation of claim 69, wherein the concentration of polysorbate 80 in the pharmaceutical formulation is about 0.01%.

71.—The pharmaceutical formulation of any one of claims 56-70, wherein the concentration of NaCl, if any, is about 1 mM or lower in the pharmaceutical formulation.

72.—The pharmaceutical formulation of any one of claims 56-71, wherein the concentration of the protein is 10 to 200 mg/mL.

73.—The pharmaceutical formulation of claim 72, wherein the concentration of the protein is about 20 mg/mL.

74.—The pharmaceutical formulation of any one of claims 56-59 and 61-73, comprising about 20 mM citrate, about 250 mM sucrose, and about 0.01% polysorbate 80, at pH 7.0.

75.—The pharmaceutical formulation of any one of claims 56-60 and 72-73, comprising about 20 mg/mL of the protein, about 20 mM potassium phosphate, about 10 mM sodium citrate, and about 125 mM sodium chloride, at pH 7.8.

~~7631.~~ A ~~An isolated~~ cell comprising one or more nucleic acids encoding a the protein of any one of claims ~~1-54~~ 1-29.

~~7732.~~ Use of ~~A method of enhancing tumor cell death, the method comprising exposing the tumor cell and a natural killer cell to an effective amount of the protein of any one of claims 1-54~~ 1-29, or the pharmaceutical composition of claim 55 ~~30, or the pharmaceutical formulation of any one of claims 56-75~~ in the manufacture of a medicament for enhancing tumor cell death or treating a cancer.

~~78.~~ ~~A method of treating cancer, the method comprising administering to a subject in need thereof an effective amount of the protein of any one of claims 1-54, the pharmaceutical composition of claim 55, or the pharmaceutical formulation of any one of claims 56-75.~~

~~7933.~~ The ~~method~~ use of claim ~~7832~~, wherein the cancer is a hematologic malignancy.

~~8034.~~ The ~~method~~ use of claim ~~7933~~, wherein the hematologic malignancy is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPNs), lymphoma, non-Hodgkin lymphomas, and classical Hodgkin lymphoma.

~~8135.~~ The ~~method~~ use of claim ~~8034~~, wherein

(a) the AML is:

(i) selected from undifferentiated acute myeloblastic leukemia, acute myeloblastic leukemia with minimal maturation, acute myeloblastic leukemia with maturation, acute promyelocytic leukemia (APL), acute myelomonocytic leukemia, acute myelomonocytic leukemia with eosinophilia, acute monocytic leukemia, acute erythroid leukemia, acute megakaryoblastic leukemia (AMKL), acute basophilic leukemia, acute panmyelosis with fibrosis, and blastic plasmacytoid dendritic cell neoplasm (BPDCN);

(ii) characterized by expression of CLL-1 on the AML leukemia stem cells (LSCs); and/or

(iii) a minimal residual disease (MRD);

(b) the MDS is selected from MDS with multilineage dysplasia (MDS-MLD), MDS with single lineage dysplasia (MDS-SLD), MDS with ring sideroblasts (MDS-RS), MDS with excess blasts (MDS-EB), MDS with isolated del(5q), and MDS, unclassified (MDS-U);

(c) the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL);

(d) the MPN is selected from polycythaemia vera, essential thrombocythemia (ET), and myelofibrosis;

(e) the non-Hodgkin lymphoma is selected from B-cell lymphoma and T-cell lymphoma; and/or

(f) the lymphoma is selected from chronic lymphocytic leukemia (CLL), lymphoblastic lymphoma (LPL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), primary mediastinal large B-cell lymphoma (PMBL), follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, plasma cell myeloma (PCM) or multiple myeloma (MM), mature T/NK neoplasms, and histiocytic neoplasms.

~~82. The method of claim 80 or 81, wherein the AML is characterized by expression of CLL-1 on the AML leukemia stem cells (LSCs).~~

~~8336. The method use of claim 8235, wherein~~

~~(a) the LSCs further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96; and/or~~

~~(b) the MRD is characterized by the presence or absence of a mutation selected from *FLT3-ITD* ((Fms-like tyrosine kinase 3)-internal tandem duplications (ITD)), *NPM1* (Nucleophosmin 1), *DNMT3A* (DNA methyltransferase gene *DNMT3A*), and *IDH* (Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2)).~~

~~84. The method of any one of claims 80-83, wherein the AML is a minimal residual disease (MRD).~~

~~85. The method of claim 84, wherein the MRD is characterized by the presence or absence of a mutation selected from *FLT3-ITD* ((Fms-like tyrosine kinase 3)-internal tandem duplications (ITD)), *NPM1* (Nucleophosmin 1), *DNMT3A* (DNA methyltransferase gene *DNMT3A*), and *IDH* (Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2)).~~

86. — The method of claim 80, wherein the MDS is selected from ~~MDS with multilineage dysplasia (MDS-MLD), MDS with single lineage dysplasia (MDS-SLD), MDS with ring sideroblasts (MDS-RS), MDS with excess blasts (MDS-EB), MDS with isolated del(5q), and MDS, unclassified (MDS-U).~~

87. — The method of claim 80, wherein the MDS is a primary MDS or a secondary MDS.

88. — The method of claim 80, wherein the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL).

89. — The method of claim 80, wherein the MPN is selected from ~~polycythaemia vera, essential thrombocythemia (ET), and myelofibrosis.~~

90. — The method of claim 80, wherein the non-Hodgkin lymphoma is selected from ~~B-cell lymphoma and T-cell lymphoma.~~

91. — The method of claim 80, wherein the lymphoma is selected from ~~chronic lymphocytic leukemia (CLL), lymphoblastic lymphoma (LPL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), primary mediastinal large B-cell lymphoma (PMBL), follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, plasma cell myeloma (PCM) or multiple myeloma (MM), mature T/NK neoplasms, and histiocytic neoplasms.~~

9237. The ~~method-use~~ of any one of claims 78-91 ~~32-36~~, wherein the cancer expresses CLEC12A.