

CLAIMS

1. A composition comprising a multispecific protein, a buffer, an excipient and a surfactant, wherein

(a) the multispecific protein is a dimer of two identical polypeptides, wherein each polypeptide comprises, in order from amino-terminus to carboxyl-terminus, or in order from carboxyl-terminus to amino-terminus:

- (i) a first binding domain,
- (ii) a hinge region,
- (iii) an immunoglobulin constant region, and
- (iv) a second binding domain; and

(b) the buffer comprises or consists of succinate or a pharmaceutically acceptable salt or acid thereof.

2. The composition of claim 1, wherein the composition comprises from about 1 mM to about 10 mM succinate or a pharmaceutically acceptable salt or acid thereof.

~~3.~~ ~~The composition of claim 2, and optionally~~ wherein the composition comprises about 5 mM succinate or a pharmaceutically acceptable salt or acid thereof.

~~4.~~ The composition of ~~any one of claims 1-3~~ claim 1 or 2, wherein the excipient comprises or consists of a sugar.

~~5.~~ ~~The composition of claim 4, and optionally~~ wherein the sugar is sucrose.

~~6.~~ The composition of claim ~~4 or 5~~, wherein the composition comprises from about 1% weight/volume (w/v) to about 12% w/v of the sugar.

~~7.~~ ~~The composition of claim 6, and optionally~~ wherein the composition comprises about 6.5% (w/v) of the sugar.

~~8.~~ The composition of any one of claims 1-~~7~~ 4, wherein the surfactant comprises or consists of polysorbate 80.

~~9.~~ ~~The composition of claim 8, and optionally~~ wherein the composition comprises about 0.02% w/v polysorbate 80.

~~106.~~ The composition of any one of claims 1-~~95~~, wherein the composition comprises from about 0.1 mg/ml to about 10 mg/ml of the multispecific protein-

~~11.~~ ~~The composition of claim 10, optionally~~ wherein the composition comprises from about 1 mg/ml to about 5 mg/ml of the multispecific protein-

~~12.~~ ~~The composition of claim 11, and optionally~~ wherein the composition comprises about 2 mg/ml of the multispecific protein.

~~137.~~ The composition of any one of claims 1-~~126~~, wherein the composition comprises about 5 mM succinate, about 6.5% weight/volume (w/v) sucrose and about 0.02% w/v polysorbate 80.

~~148.~~ The composition of any one of claims 1-~~137~~, wherein the composition has a pH from about 4.0 to about 5.5-

~~15.~~ ~~The composition of claim 14, and optionally~~ wherein the composition has a pH of about 4.8.

~~169.~~ The composition of any one of claims 1-~~158~~, wherein the immunoglobulin constant region is a human Fc domain-

~~17.~~ ~~The composition of any one of claims 1-16, and optionally~~ wherein the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgD.

~~18~~10. The composition of any one of claims 1-~~17~~9,

(i) wherein the first binding domain is a CD3 binding domain and the second binding domain is a tumor antigen binding domain-

~~19. The composition of claim 18, and optionally~~ wherein the polypeptide comprises, from N-terminus to C-terminus, the CD3 binding domain, the hinge region, the immunoglobulin constant region, and the tumor antigen binding domain-

~~20. The composition of any one of claims 1-17; or~~

(ii) wherein the first domain is a tumor antigen binding domain, and the second binding domain is a CD3 binding domain-

~~21. The composition of claim 20, and optionally~~ wherein the polypeptide comprises, from N-terminus to C-terminus, the tumor antigen binding domain, the hinge region, the immunoglobulin constant region, and the CD3 binding domain.

~~22~~11. The composition of any one of claims ~~1-17~~9,

(i) wherein the first binding domain is a 4-1-BB binding domain and the second binding domain is a tumor antigen binding domain-

~~23. The composition of claim 22, and optionally~~ wherein the polypeptide comprises, from N-terminus to C-terminus, the 4-1-BB binding domain, the hinge region, the immunoglobulin constant region, and the tumor antigen binding domain-

~~24. The composition of any one of claims 1-17; or~~

(ii) wherein the first binding domain is a tumor antigen binding domain, and the second binding domain is a 4-1-BB binding domain-

~~25. The composition of claim 24, and optionally~~ wherein the polypeptide comprises, from N-terminus to C-terminus, tumor antigen binding domain, the hinge region, the immunoglobulin constant region, and the 4-1-BB binding domain.

~~26~~12. The composition of any one of claims ~~18-25~~10-11, wherein the tumor antigen binding domain binds to CD123, PSMA, CD19, CD33, or HER2.

~~27~~13. The composition of any one of claims ~~1-17~~9,

(i) wherein the first binding domain or the second binding domain is a 4-1BB binding domain-

~~28. The composition of any one of claims 1-17;~~

(ii) wherein the first binding domain or the second binding domain is an OX40 binding domain;

~~29. The composition of any one of claims 1-17;~~

(iii) wherein the first binding domain is a 4-1BB binding domain and wherein the second binding domain is an OX40 binding domain, optionally wherein the 4-1BB binding domain is an scFv and the OX40 binding domain is an scFv.

~~30. The composition of any one of claims 1-17;~~

(iv) wherein the first binding domain is an OX40 binding domain and wherein the second binding domain is a 4-1BB binding domain optionally wherein the 4-1BB binding domain is an scFv and the OX40 binding domain is an scFv.

~~31. The composition of claim 29 or 30, wherein the 4-1BB binding domain is an scFv and the OX40 binding domain is an scFv.~~

~~32. The composition of any one of claims 1-17;~~

(v) wherein the first binding domain is an OX40 binding domain and the second binding domain is a tumor antigen binding domain;

~~33. The composition of any one of claims 1-17; or~~

(vi) wherein the first binding domain is a tumor antigen binding domain and the second binding domain is an OX40 binding domain.

~~34~~14. The composition of any one of claims 1-~~33~~13, wherein at least one of the first binding domain and the second binding domain comprises:

(i) an immunoglobulin heavy chain variable region (VH) comprising HCDR1, HCDR2, and HCDR3; and

(ii) an immunoglobulin light chain variable region (VL) comprising LCDR1, LCDR2, and LCDR3.

~~35~~15. The composition of any one of claims 1-~~34~~14, wherein at least one of the first binding domain and the second binding domain is a single chain variable fragment (scFv);

~~36.~~ The composition of claim ~~35~~, optionally wherein the light chain variable region of the scFv is carboxy-terminal to the heavy chain variable region of the scFv;

~~37.~~ The composition of claim ~~35~~, or wherein the light chain variable region of the scFv is amino-terminal to the heavy chain variable region of the scFv;

~~38.~~ The composition of any one of claims ~~35-37~~, optionally wherein the scFv comprises a linker polypeptide;

~~39.~~ The composition of claim ~~38~~, optionally wherein the linker polypeptide is between the light chain variable region and the heavy chain variable region of the scFv;

~~40.~~ The composition of any one of claims ~~38-39~~, optionally wherein the linker polypeptide comprises a Gly₄Ser (SEQ ID NO: 128) linker;

~~41.~~ The composition of claim ~~40~~, and optionally wherein the linker polypeptide comprises the formula (Gly₄Ser)_n, wherein n = 1-5 (SEQ ID NO: 129).

~~42~~16. The composition of any one of claims ~~18-26~~10-26,

(i) wherein the tumor antigen binding domain is an anti-CD123 scFv comprising:
a HCDR1 that comprises SEQ ID NO: 10, a HCDR2 that comprises SEQ ID NO: 11, and a HCDR3 that comprises SEQ ID NO: 12; and
a LCDR1 that comprises SEQ ID NO: 13, a LCDR2 that comprises SEQ ID NO: 14, and a LCDR3 that comprises SEQ ID NO: 15;

~~43.~~ The composition of any one of claims ~~18-26~~, and

(ii) wherein the tumor antigen binding domain is an anti-CD123 scFv comprising a VH comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 136, and a VL comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 134.

~~44. The composition of any one of claims 18-26; or~~

(iii) wherein the tumor antigen binding domain is an anti-CD123 scFv, and wherein the scFv comprises a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 27.

~~45~~17. The composition of ~~any one of claims 18 to 24~~claim 10,

(i) wherein the CD3 binding domain is an anti-CD3 scFv comprising:

a HCDR1 that comprises SEQ ID NO: 19, a HCDR2 that comprises SEQ ID NO: 20, and a HCDR3 that comprises SEQ ID NO: 21; and

a LCDR1 that comprises SEQ ID NO: 22, a LCDR2 that comprises SEQ ID NO: 23, and a LCDR3 that comprises SEQ ID NO: 24.

~~46. The composition of any one of claims 18-21; or~~

(ii) wherein the CD3 binding domain is an anti-CD3 scFv that comprises a VH comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 383 or 387, and a VL comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 384.

~~47. The composition of any one of claims 18-21; or~~

(iii) wherein the CD3 binding domain is an anti-CD3 scFv that comprises a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 27.

~~48~~18. The composition of any one of claims ~~18-24~~10 or ~~45-47~~17, wherein each polypeptide comprises a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 31.

~~49~~19. The composition of any one of claims 1-~~48~~18,

(i) wherein the immunoglobulin constant region comprises one, two, three or more amino acid substitutions compared to a wild-type immunoglobulin constant region to reduce or prevent binding to FcγR1, FcγRIIa, FcγRIIb, FcγRIIa, and FcγRIIIb.

~~50. The composition of any one of claims 1-48;~~

(ii) wherein the immunoglobulin constant region comprises one, two, three or more amino acid substitutions compared to a wild-type immunoglobulin constant region to prevent or reduce Fc-mediated T-cell activation.

~~51. The composition of any of claims 1-48;~~

(iii) wherein the immunoglobulin constant region comprises one, two, three or more amino acid substitutions compared to a wild-type immunoglobulin constant region to prevent or reduce CDC activity.

~~52. The composition of any one of claims 1-48; or~~

(iv) wherein the immunoglobulin constant region comprises one, two, three or more amino acid substitutions compared to a wild-type immunoglobulin constant region to prevent or reduce ADCC activity.

~~53~~20. The composition of any one of claims 1-~~52~~19, wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain with one, two, three or more amino acid substitutions compared to a wild-type human IgG1 CH2 domain.

~~54~~21. The composition of any one of claims 1-~~53~~20,

(i) wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions L234A, L235A, G237A, and K322A, according to the EU numbering system.

~~55. The composition of any one of claim 54,~~ optionally wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the

substitutions L234A, L235A, G237A, E318A, K320A and K322A, according to the EU numbering system-

~~56. The composition of any one of claims 1-53; or~~

(ii) wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions E233P, L234A, L235A, G237A, and K322A and a deletion of G236, according to the EU numbering system.

~~57~~22. The composition of any one of claims 1-~~56~~21, wherein the hinge region is derived from an immunoglobulin hinge region.

~~58~~23. The composition of any one of claims 1-~~57~~22, wherein each polypeptide comprises and Fc-binding domain linker between the immunoglobulin constant region, and the second binding domain-

~~59. The composition of claim 58; optionally~~ wherein the Fc-binding domain linker comprises a Gly₄Ser (SEQ ID NO: 128) sequence-

~~60. The composition of claim 59; and optionally~~ wherein the Fc-binding domain linker comprises the formula (Gly₄Ser)_n, wherein n = 1-5 (SEQ ID NO: 129).

~~61. The composition of any one of claims 1-60, wherein the composition is for intravenous or subcutaneous administration.~~

~~62. The composition of any one of claims 1 to 61, wherein the composition substantially prevents degradation of the multispecific protein.~~

~~63. The composition of any one of claims 1-62, wherein the composition slows or reduces the degradation of the multispecific protein as compared to an identical multispecific protein stored in histidine buffer under identical storage conditions.~~

~~64. The composition of any one of claims 1 to 63, wherein the composition is substantially stable for at least 1 year at 4°C.~~

~~65. The composition of any one of claims 1 to 64, wherein the composition is substantially resistant to formation of aggregates of multispecific protein.~~

~~66. The composition of any one of claims 1-65, wherein the composition forms fewer aggregates as compared to an identical multispecific protein stored in histidine buffer under identical storage conditions.~~

~~67~~24. A composition comprising a fusion protein, a buffer, an excipient and a surfactant, wherein:

(a) the fusion protein is a dimer of two identical polypeptides, wherein each polypeptide comprises, in order from amino-terminus to carboxyl-terminus:

(i) a first binding domain that specifically binds to CD123,

(ii) a hinge region,

(iii) an immunoglobulin constant region, and

(iv) a second binding domain that specifically binds to CD3; and

(b) the buffer comprises or consists of succinate or a pharmaceutically acceptable salt or acid thereof.

~~68~~25. The composition of claim ~~67~~24, wherein the composition comprises about 5 mM succinate, about 6.5% weight/volume (w/v) sucrose and about 0.02% w/v polysorbate 80.

~~69~~26. The composition of claim ~~67-24~~ or ~~68~~25, wherein the composition comprises from about 0.1 mg/ml to about 10 mg/ml of the multispecific protein.

~~70. The composition of claim 69; optionally~~ wherein the composition comprises from about 1 mg/ml to about 5 mg/ml of the multispecific protein.

~~71. The composition of claim 70; and optionally~~ wherein the composition comprises about 2 mg/ml of the multispecific protein.

~~72~~27. The composition of any one of claims ~~67-24-71-26~~, wherein the composition has a pH from about 4.0 to about 5.5.

~~73. The composition of claim 72,; and optionally~~ wherein the composition has a pH of about 4.8.

~~7428.~~ The composition of any one of claims ~~6724-7327~~, wherein the immunoglobulin constant region is a human Fc domain.

~~75. The composition of any one of claims 67-74,; and optionally~~ wherein the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgD.

~~7629.~~ The composition of any one of claims 1-~~7528~~, wherein the CH2 domain is a human IgG1 CH2 domain with one, two, three or more amino acid substitutions compared to a wild-type human IgG1 CH2 domain.

~~7730.~~ The composition of any one of claims ~~6724-7629~~,

(i) wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions L234A, L235A, G237A, and K322A, according to the EU numbering system.

~~78. The composition of any one of claims 67-77, optionally~~ wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions L234A, L235A, G237A, E318A, K320A and K322A, according to the EU numbering system.

~~79. The composition of any one of claims 67-76,; or~~

(ii) wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions E233P, L234A, L235A, G237A, and K322A and a deletion of G236, according to the EU numbering system.

~~8031.~~ The composition of any one of claims ~~6724-7930~~, wherein the hinge region is derived from an immunoglobulin hinge region.

~~8432.~~ The composition of any one of claims ~~6724-8031~~, wherein each polypeptide comprises an Fc-binding domain linker between the immunoglobulin constant region and the second binding domain.

~~82.~~ ~~The composition of claim 81;~~ optionally wherein the Fc-binding domain linker comprises a Gly₄Ser (SEQ ID NO: 128) sequence.

~~83.~~ ~~The composition of claim 82;~~ and optionally wherein the Fc-binding domain linker comprises the formula (Gly₄Ser)_n, wherein n = 1-5 (SEQ ID NO: 129).

~~84.~~ ~~The composition of any one of claims 67-83, wherein the composition is for intravenous or subcutaneous administration.~~

~~8533.~~ The composition of any one of claims ~~6724-8432~~, wherein at least one of the first binding domain and the second binding domain comprises:

(i) an immunoglobulin heavy chain variable region (VH) comprising HCDR1, HCDR2, and HCDR3; and

(ii) an immunoglobulin light chain variable region (VL) comprising LCDR1, LCDR2, and LCDR3.

~~8634.~~ The composition of any one of claims ~~6724-8533~~, wherein at least one of the first binding domain and the second binding domain is a single chain variable fragment (scFv).

~~87.~~ ~~The composition of claim 86;~~ optionally wherein the light chain variable region of the scFv is carboxy-terminal to the heavy chain variable region of the scFv.

~~88.~~ ~~The composition of claim 86,~~ or wherein the light chain variable region of the scFv is amino-terminal to the heavy chain variable region of the scFv.

~~89.~~ ~~The composition of any one of claims 86-88;~~ optionally wherein the scFv comprises a linker polypeptide.

~~90. The composition of claim 89,; optionally~~ wherein the linker polypeptide is between the light chain variable region and the heavy chain variable region of the scFv.

~~91. The composition of claim 89 or 90,; optionally~~ wherein the linker polypeptide comprises a Gly₄Ser (SEQ ID NO: 128) linker.

~~92. The composition of claim 91,; and optionally~~ wherein the linker polypeptide comprises the formula (Gly₄Ser)_n, wherein n = 1-5 (SEQ ID NO: 129).

~~93~~35. The composition of any one of claims ~~67~~24-~~92~~34,

(i) wherein the first binding domain is an anti-CD123 scFv comprising:

a HCDR1 comprising the sequence of SEQ ID NO: 10, a HCDR2 comprising the sequence of SEQ ID NO: 11, and a HCDR3 comprising the sequence of SEQ ID NO: 12; and

a LCDR1 comprising the sequence of SEQ ID NO: 13, a LCDR2 comprising the sequence of SEQ ID NO: 14, and a LCDR3 comprising the sequence of SEQ ID NO: 15.

~~94. The composition of any one of claims 67-92,; or~~

(ii) wherein the first binding domain is an anti-CD123 scFv comprising a VH comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 136, and a VL comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 134.

~~95. The composition of any one of claims 67-92,; or~~

(iii) wherein the first binding domain is an anti-CD123 scFv comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 18.

~~96~~36. The composition of any one of claims ~~67~~24-~~95~~35,

(i) wherein the second binding domain is an anti-CD3 scFv comprising:

a HCDR1 comprising the sequence of SEQ ID NO: 19, a HCDR2 comprising the sequence of SEQ ID NO: 20, and a HCDR3 comprising the sequence of SEQ ID NO: 21; and

a LCDR1 comprising the sequence of SEQ ID NO: 22, a LCDR2 comprising the sequence of SEQ ID NO: 23, and a LCDR3 comprising the sequence of SEQ ID NO: 24;

~~97. The composition of any one of claims 67-95;~~

(ii) wherein the second binding domain is an anti-CD3 scFv comprising a VH that comprises a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 383 or 387, and a VL that comprises a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 384;

~~98. The composition of any one of claims 67-95; or~~

(iii) wherein the second binding domain is an anti-CD3 scFv comprising a sequence at least 90%, at least 95%, or 100% identical to SEQ ID NO: 27.

~~99~~37. The composition of any one of claims ~~67-95~~67-95~~35~~, wherein each polypeptide comprises the sequence of SEQ ID NO: 31, or comprises a sequence at least 90%, at least 95%, or at least 98% identical to SEQ ID NO: 31.

~~400~~38. The composition of any one of claims ~~67-95~~67-95~~35~~, wherein:

the first binding domain is an anti-CD123 scFv comprising an immunoglobulin heavy chain variable region (VH) comprising a HCDR1 of SEQ ID NO: 10, a HCDR2 of SEQ ID NO: 11, and a HCDR3 of SEQ ID NO: 12, and an immunoglobulin light chain variable region (VL) comprising a LCDR1 of SEQ ID NO: 13, a LCDR2 of SEQ ID NO: 14, and a LCDR3 of SEQ ID NO: 15, and

the second binding domain is an anti-CD3 scFv comprising an immunoglobulin heavy chain variable region (VH) comprising a HCDR1 of SEQ ID NO: 19, a HCDR2 of SEQ ID NO: 20, and a HCDR3 of SEQ ID NO: 21, and an immunoglobulin light chain variable region (VL) comprising a LCDR1 of SEQ ID NO: 22, a LCDR2 of SEQ ID NO: 23, and a LCDR3 of SEQ ID NO: 24.

39. The composition of any one of claims 1 to 38, wherein the composition is for intravenous or subcutaneous administration.

~~40140.~~ The composition of any one of claims ~~67-1~~ to ~~40039~~, wherein the composition substantially prevents degradation of the multispecific protein-

~~102. The composition of any one of claims 67 to 101,; optionally~~ wherein the composition slows or reduces the degradation of the multispecific protein as compared to an identical multispecific protein stored in histidine buffer under identical storage conditions-

~~103. The composition of any one of claims 67 to 102,; and optionally~~ wherein the composition is substantially stable for at least 1 year at 4°C.

~~40441.~~ The composition of any one of claims ~~67-1~~ to ~~40340~~, wherein the composition is substantially resistant to formation of aggregates of multispecific protein-

~~105. The composition of any one of claims 67 to 104,; and optionally~~ wherein the composition forms fewer aggregates as compared to an identical multispecific protein stored in histidine buffer under identical storage conditions.

~~40642.~~ A composition comprising a fusion protein, a buffer, an excipient and a surfactant, wherein

(a) the fusion protein comprises:

(i) a first binding domain that specifically binds to CD123,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 10, HCDR2 of SEQ ID NO: 11, and HCDR3 of SEQ ID NO: 12; and an immunoglobulin light chain variable region (VL) comprising LCDR1 of SEQ ID NO: 13, LCDR2 of SEQ ID NO: 14, and LCDR3 of SEQ ID NO: 15; and

(ii) a second binding domain that specifically binds to CD3, wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 19, HCDR2 of SEQ ID NO: 20, and HCDR3 of SEQ ID NO: 21; and an immunoglobulin light chain variable region (VL)

comprising LCDR1 of SEQ ID NO: 22, LCDR2 of SEQ ID NO: 23, and LCDR3 of SEQ ID NO: 24; and

(b) the buffer comprises or consists of succinate or a pharmaceutically acceptable salt or acid thereof.

~~407~~43. A composition comprising a fusion protein, about 5 mM succinate, about 6.5% weight/volume (w/v) sucrose and about 0.02% w/v polysorbate 80, wherein the fusion protein comprises a Fab, Fab', F(ab')₂, scFv, disulfide linked Fv, scFv x scFv (BiTE), scFv-Fc (SMIP), scFv-Fc-scFv, quadroma, K λ -body, dAbs, diabody, nanobody, DOCK-AND-LOCKS® (DNLs®), CrossMab Fabs, CrossMab VH-VL, strand-exchange engineered domain bodies (SEEDbodies), Affibodies, Fynomers, Kunitz Domains, Albu-dabs, two engineered Fv fragments with exchanged VHs (e.g., a dual-affinity re-targeting molecules (D.A.R.T.s)), DVD-IG, Covx-body, peptibody, SVD-Igs, dAb-Igs, Knobs-in-Holes, IgG1 antibodies comprising matched mutations in the CH3 domain (e.g., DuoBody antibody) and triomAb.

~~408~~44. A composition comprising a fusion protein, about 5 mM succinate, about 6.5% weight/volume (w/v) sucrose and about 0.02% w/v polysorbate 80, wherein

(a) the fusion protein comprises:

(i) a first binding domain that specifically binds to CD123,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 10, HCDR2 of SEQ ID NO: 11, and HCDR3 of SEQ ID NO: 12; and an immunoglobulin light chain variable region (VL) comprising LCDR1 of SEQ ID NO: 13, LCDR2 of SEQ ID NO: 14, and LCDR3 of SEQ ID NO: 15; and

(ii) a second binding domain that specifically binds to CD3,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 19, HCDR2 of SEQ ID NO: 20, and HCDR3 of SEQ ID NO: 21; and an immunoglobulin light chain variable region (VL) comprising LCDR1 of SEQ ID NO: 22, LCDR2 of SEQ ID NO: 23, and LCDR3 of SEQ ID NO: 24.

~~409~~45. A composition comprising a fusion protein, a buffer, an excipient and a surfactant, wherein

(a) the fusion protein comprises:

(i) a first binding domain that specifically binds to CD123,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising SEQ ID NO: 136; and an immunoglobulin light chain variable region (VL) comprising SEQ ID NO: 134; and

(ii) a second binding domain that specifically binds to CD3,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising SEQ ID NO: 383 or 387; and an immunoglobulin light chain variable region (VL) comprising SEQ ID NO: 384; and

and

(b) the buffer comprises or consists of succinate or a pharmaceutically acceptable salt or acid thereof.

~~410~~46. A composition comprising a fusion protein, a buffer, an excipient and a surfactant, wherein

(a) the fusion protein comprises:

(i) a first binding domain that specifically binds to CD123, wherein the first binding domain comprises SEQ ID NO: 18; and

(ii) a second binding domain that specifically binds to CD3, wherein the second binding domain comprises SEQ ID NO: 27; and

(b) the buffer comprises or consists of succinate or a pharmaceutically acceptable salt or acid thereof.

~~411~~47. A composition comprising a fusion protein, a buffer, an excipient and a surfactant, wherein

(a) the fusion protein is a dimer of two identical polypeptides, wherein each polypeptide comprises, in order from amino-terminus to carboxyl-terminus, or in order from carboxyl-terminus to amino-terminus:

(i) a first binding domain that specifically binds to CD123,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 10, HCDR2 of SEQ ID NO: 11, and HCDR3 of SEQ ID NO: 12; and an immunoglobulin light chain

variable region (VL) comprising LCDR1 of SEQ ID NO: 13, LCDR2 of SEQ ID NO: 14, and LCDR3 of SEQ ID NO: 15,

(ii) a hinge region of SEQ ID NO: 47,

(iii) an immunoglobulin constant region of SEQ ID NO: 131,

(iv) a Fc-binding domain linker of SEQ ID NO: 132, and

(v) a second binding domain that specifically binds to CD3,

wherein the second binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 19, HCDR2 of SEQ ID NO: 20, and HCDR3 of SEQ ID NO: 21; and an immunoglobulin light chain variable region (VL) comprising LCDR1 of SEQ ID NO: 22, LCDR2 of SEQ ID NO: 23, and LCDR3 of SEQ ID NO: 24; and

(b) the buffer comprises or consists of succinate or a pharmaceutically acceptable salt or acid thereof.

41248. A composition comprising a fusion protein, about 5 mM succinate, about 6.5% weight/volume (w/v) sucrose and about 0.02% w/v polysorbate 80, wherein:

the fusion protein is a dimer of two identical polypeptides, wherein each polypeptide comprises, in order from amino-terminus to carboxyl-terminus:

(i) a first binding domain that specifically binds to CD123,

wherein the binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 10, HCDR2 of SEQ ID NO: 11, and HCDR3 of SEQ ID NO: 12; and an immunoglobulin light chain variable region (VL) comprising LCDR1 of SEQ ID NO: 13, LCDR2 of SEQ ID NO: 14, and LCDR3 of SEQ ID NO: 15,

(ii) a hinge region of SEQ ID NO: 47,

(iii) an immunoglobulin constant region of SEQ ID NO: 131,

(iv) a Fc-binding domain linker of SEQ ID NO: 132, and

(v) a second binding domain that specifically binds to CD3,

wherein the second binding domain comprises an immunoglobulin heavy chain variable region (VH) comprising HCDR1 of SEQ ID NO: 19, HCDR2 of SEQ ID NO: 20, and HCDR3 of SEQ ID NO: 21; and an immunoglobulin light chain variable region (VL) comprising LCDR1 of SEQ ID NO: 22, LCDR2 of SEQ ID NO: 23, and LCDR3 of SEQ ID NO: 24.

~~113~~49. A composition comprising a fusion protein, about 5 mM succinate, about 6.5% weight/volume (w/v) sucrose and about 0.02% w/v polysorbate 80, wherein the fusion protein comprises or consists of SEQ ID NO: 31; wherein the composition comprises about 2 mg/ml of the fusion protein; and wherein the composition has a pH of about 4.8.

~~114~~50. Use of the composition of any one of claims 1-49 in the manufacture of a medicament ~~A method for treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition of any one of claims 1-113.~~

~~115~~51. The ~~method~~ use of claim ~~114~~50, wherein the autoimmune disorder is irritable bowel syndrome, inflammatory bowel disease, psoriasis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, asthma, multiple sclerosis, dermatomyositis, polymyositis, pernicious anaemia, primary biliary cirrhosis, acute disseminated encephalomyelitis (ADEM), Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (aPL), autoimmune hepatitis, diabetes mellitus type 1, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, pemphigus vulgaris, Sjögren's syndrome, temporal arteritis, autoimmune hemolytic anemia, bullous pemphigoid, vasculitis, celiac disease, endometriosis, hidradenitis suppurativa, interstitial cystitis, morphea, scleroderma, narcolepsy, neuromyotonia, vitiligo, autoimmune inner ear disease or myasthenia gravis.

~~116~~52. Use of the composition of any one of claims 1 to 49 in the manufacture of a medicament ~~A method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition of any one of claims 1-113.~~

~~117~~53. The ~~method~~ use of claim ~~116~~52, wherein the cancer is selected from a carcinoma or sarcoma.

~~118~~. ~~The method of claim 116;~~ optionally wherein the cancer is selected from a melanoma, kidney cancer, pancreatic cancer, lung cancer, intestinal cancer, prostate

cancer, breast cancer, liver cancer, brain cancer, colon cancer, ovarian cancer, or a hematological cancer.

~~119. The method of claim 118;~~ and optionally wherein the hematological cancer is an acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm, B-cell acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML).

~~12054. Use of the~~ The composition of any one of claims 1-113-49 for use in treating an autoimmune disorder in a subject.

~~121. Use of the composition of any one of claims 1-113 in the manufacture of a medicament for treating an autoimmune disorder.~~

~~12255. Use of the~~ The composition of any one of claims 1-113-49 for use in treating cancer in a subject.

~~123. Use of the composition of any one of claims 1-113 in the manufacture of a medicament for treating cancer.~~

~~12456. A method of treating a cancer in a subject comprising administering~~ Use of a composition comprising a multispecific protein comprising a CD123 binding domain and a CD3 binding domain in the manufacture of a medicament for treating a cancer, wherein the composition is to be administered to the subject by IV infusion at a dose of 0.3, 1, 3, 6, 9, 12, 18, 20, 24, 30, 36, 48, 50, 60, 75, or 100 µg.

~~12557. A method of treating a cancer in a subject comprising administering~~ Use of a composition of any one of claims 42-4816-18, 93-10035-38, and 108-11144-47 in the manufacture of a medicament for treating a cancer, wherein the composition is to be administered to a patient by IV infusion at a dose of 0.3, 1, 3, 6, 9, 12, 18, 20, 24, 30, 36, 48, 60, 50, 75, or 100 µg.

~~12658. The method-use of claim 124-56 or 12557,~~ wherein the first dose of the composition is to be administered to the patient by IV infusion over a 20-24 hour period of time.

~~127. The method of claim 126,; optionally~~ wherein a second dose of the composition is to be administered to the patient by IV infusion over an 8 hour period of time, wherein the second dose is the same as the first dose.

~~128. The method of claim 127,; optionally~~ wherein a third dose of the composition is to be administered to the patient by IV infusion over a 6 hour period of time, wherein the third dose is the same as the first and the second dose.

~~129. The method of any one of claims 124-128,; and optionally~~ wherein the fourth dose and subsequent doses of the composition are to be administered to the patient by IV infusion over about a 2 to about a 4 hour period of time.

~~13059. The method-use of any one of claims 12456-12557,~~ wherein the composition is to be administered to the patient by continuous IV infusion up to 72 hours.

~~13160. The method-use of any one of claims 12456-13059,~~ wherein the composition is to be administered on days 1, 8, 15, and 22.

~~132. The method of claim 131,; and optionally~~

(i) wherein 6 μg is to be administered on day 1, 9 μg is to be administered on day 8, 12 μg is to be administered on day 15, and 12 μg is to be administered on day 22.

~~133. The method of claim 131,;~~

(ii) wherein 6 μg is to be administered on day 1, 9 μg is to be administered on day 8, 12 μg is to be administered on day 15, and 18 μg is to be administered on day 22.

~~134. The method of claim 131,;~~

(iii) wherein 6 μg is to be administered on day 1, 9 μg is to be administered on day 8, 9 μg is to be administered on day 15, and 9 μg is to be administered on day 22.

~~135. The method of claim 131;~~

(iv) wherein 9 µg is to be administered on day 1, 12 µg is to be administered on day 8, 12 µg is to be administered on day 15, and 12 µg is to be administered on day 22.

~~136. The method of claim 131; or~~

(v) wherein 12 µg is to be administered on day 1, 18 µg is to be administered on day 8, 18 µg is to be administered on day 15, and 18 µg is to be administered on day 22.

~~137~~61. The ~~method use~~ of any one of claims ~~124~~~~56~~-~~130~~~~59~~, wherein the composition is to be administered to a patient by IV according to the following weekly treatment schedule:

(i)

Week 1 dosage: 6 µg;

Week 2 dosage: 9 µg;

Week 3 dosage: 12 µg; and

Week 4 dosage and subsequent week dosages: 12 µg.

~~138. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(ii)

Week 1 dosage: 6 µg;

Week 2 dosage: 9 µg;

Week 3 dosage: 12 µg; and

Week 4 dosage and subsequent week dosages: 18 µg.

~~139. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(iii)

Week 1 dosage: 6 µg;

Week 2 dosage: 12 µg;

Week 3 dosage: 12 µg; and

Week 4 dosage and subsequent week dosages: 12 µg.

~~140. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(iv)

Week 1 dosage: 6 µg;

Week 2 dosage: 12 µg;

Week 3 dosage: 18 µg; and

Week 4 dosage and subsequent week dosages: 24 µg.

~~141. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(v)

Week 1 dosage: 6 µg;

Week 2 dosage: 12 µg;

Week 3 dosage: 18 µg; and

Week 4 dosage and subsequent week dosages: 36 µg.

~~142. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(vi)

Week 1 dosage: 6 µg;

Week 2 dosage: 12 µg;

Week 3 dosage: 18 µg; and

Week 4 dosage and subsequent week dosages: 48 µg.

~~143. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(vii)

Week 1 dosage: 6 µg;

Week 2 dosage: 12 µg;

Week 3 dosage: 18 µg; and

Week 4 dosage and subsequent week dosages: 60 µg.

~~144. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(viii)

Week 1 dosage: 6 µg; and

Week 2 and subsequent week dosages: 9 µg.

~~145. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

~~:~~

(ix)

Week 1 dosage: 9 µg; and

Week 2 and subsequent week dosages: 12 µg.

~~146. The method of any one of claims 124-130, wherein the composition is administered to a patient by IV according to the following weekly treatment schedule:~~

or

(x)

Week 1 dosage: 12 µg; and

Week 2 and subsequent week dosages: 18 µg.

~~147~~62. The ~~method~~use of any one of claims ~~124~~56-~~130~~59, wherein the composition is to be administered to a patient during a first 28-day cycle, wherein 6 µg of the multispecific protein is to be administered on day 1, 9 µg of the multispecific protein is to be administered on day 2, 12 µg of the multispecific protein is to be

administered on day 3, 18 µg of the multispecific protein is to be administered on day 4, 18 µg of the multispecific protein is to be administered on day 8, 18 µg of the multispecific protein is to be administered on day 11, 36 µg of the multispecific protein is to be administered on day 15, and 36 µg of the multispecific protein is to be administered on day 22 of the first 28-day cycle.

~~148. The method of claim 147;~~ and optionally wherein the method further comprises administering the multispecific protein is to be further administered to the patient during at least one additional 28-day cycle, wherein 36 µg of the multispecific protein is to be administered on each of days 1, 8, 15, and 22 of the at least one additional 28-day cycle.

~~149~~63. The ~~method~~ use of any one of claims ~~124-130~~56-59, wherein the composition is to be administered to a patient during a first 28-day cycle, wherein 6 µg of the multispecific protein is to be administered on day 1, 12 µg of the multispecific protein is to be administered on day 2, 18 µg of the multispecific protein is to be administered on day 3, 24 µg of the multispecific protein is to be administered on day 4, 24 µg of the multispecific protein is to be administered on day 8, 24 µg of the multispecific protein is to be administered on day 11, 48 µg of the multispecific protein is to be administered on day 15, and 48 µg of the multispecific protein is to be administered on day 22 of the first 28-day cycle.

~~150. The method of claim 149;~~ and optionally wherein the method further comprises administering the multispecific protein is to be further administered to the patient during at least one additional 28-day cycle, wherein 48 µg of the multispecific protein is to be administered on each of days 1, 8, 15, and 22 of the at least one additional 28-day cycle.

~~151~~64. The ~~method~~ use of any one of claims ~~124-130~~56-59, wherein the composition is to be administered to a patient during a first 28-day cycle, wherein 6 µg of the multispecific protein is to be administered on day 1, 12 µg of the multispecific protein is to be administered on day 2, 24 µg of the multispecific protein is to be administered on day 3, 36 µg of the multispecific protein is to be administered on day 4, 36 µg of the multispecific protein is to be administered on day 8, 36 µg of the

multispecific protein is to be administered on day 11, 60 µg of the multispecific protein is to be administered on day 15, and 60 µg of the multispecific protein is to be administered on day 22 of the first 28-day cycle.

~~152. The method of claim 151,; and optionally wherein the method further comprises administering the multispecific protein~~ is to be further administered to the patient during at least one additional 28-day cycle, wherein 60 µg of the multispecific protein is to be administered on each of days 1, 8, 15, and 22 of the at least one additional 28-day cycle.

~~153~~65. The ~~method-use~~ of any one of claims ~~12456-13059~~, wherein the composition is to be administered to a patient during a first 28-day cycle, wherein 6 µg of the multispecific protein is to be administered on day 1, 12 µg of the multispecific protein is to be administered on day 2, 24 µg of the multispecific protein is to be administered on day 3, 36 µg of the multispecific protein is to be administered on day 4, 48 µg of the multispecific protein is to be administered on day 8, 48 µg of the multispecific protein is to be administered on day 11, 100 µg of the multispecific protein is to be administered on day 15, and 100 µg of the multispecific protein is to be administered on day 22 of the first 28-day cycle.

~~154. The method of claim 153,; and optionally wherein the method further comprises administering the multispecific protein~~ is to be further administered to the patient during at least one additional 28-day cycle, wherein 100 µg of the multispecific protein is to be administered on each of days 1, 8, 15, and 22 of the at least one additional 28-day cycle.

~~155~~66. The ~~method-use~~ of any one of claims ~~12456-13059~~, (i) wherein the composition is to be administered to a patient by IV and the dosage is increased each week for the first weeks.

~~156. The method of any one of claims 124-130,; or (ii)~~ wherein the patient is to be administered the composition once, twice, three, or four times each week.

15767. The ~~method~~ use of any one of claims 12456-15666, wherein the composition is to be administered to the patient with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).