TRISPECIFIC AND/OR TRIVALENT BINDING PROTEINS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application Serial No. 62/322,036, filed April 13, 2016; U.S. Provisional Application Serial No. 62/331,191, filed May 3, 2016; U.S. Provisional Application Serial No. 62/412,187, filed October 24, 2016; and EP Application No. EP17305298.6, filed March 17, 2017; which are incorporated herein by reference in their entirety.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 183952027140SEQLISTING.txt, date recorded: April 11, 2017, size: 200 KB).

FIELD OF THE INVENTION

[0003] The disclosure relates to trispecific and/or trivalent binding proteins comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more target proteins, wherein a first pair of polypeptides forming the binding protein possess dual variable domains having a cross-over orientation and wherein a second pair of polypeptides forming the binding protein possess a single variable domain. The disclosure also relates to methods for making trispecific and/or trivalent binding proteins and uses of such binding proteins.

BACKGROUND

[0004] Monoclonal antibody based biotherapeutics have become an important avenue for new drug development. Monoclonal antibody technology offers specific targeting, precise signaling delivery and/or payload to specific cell population, and provides long lasting biological effect through its Fc functions. Efforts in antibody engineering have allowed developing bispecific antibodies combining the specificities of two monoclonal antibodies for various biological applications, expanding the scope of antibody drug development. Newly discovered neutralizing antibodies with improved breadth and

potency may provide more options for developing biotherapeutics to treat complexed diseases such as cancer, arthritis, and/or inflammatory disorders.

BRIEF SUMMARY

[0005] Provided herein are multispecific binding proteins (*e.g.*, antibodies) that form three antigen binding sites. These binding proteins can specifically bind one, two, or three antigen targets or target proteins.

[0006] In one embodiment, the disclosure provides a binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more antigen targets or target proteins, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain has a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain has a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0007] In some embodiments, the second and/or third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains.

[0008] In another embodiment, the disclosure provides a binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0009] In some embodiments, the binding protein is trispecific and capable of specifically binding three different antigen targets. In some embodiments, the binding protein is trivalent but bispecific and capable of specifically binding three antigen targets, two of them being identical. In some embodiments, the binding protein of the present disclosure is trivalent but monopecific and capable of specifically binding three antigen targets, all of them being identical. In some embodiments, the binding protein is capable of inhibiting the function of one or more target proteins. In some embodiments, the binding protein is trispecific and capable of specifically binding three different antigen targets.

[0010] In some embodiments, a binding protein of the present disclosure comprises one, two, or three antigen binding sites that specifically bind a target protein selected from A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4 (also known as VTCN1), B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2 (also known as MCP-1), CCL3 (also known as MIP-1a), CCL4 (also known as MIP-1b), CCL5 (also known as RANTES), CCL7 (also known as MCP-3), CCL8 (also known as mcp-2), CCL11 (also known as eotaxin), CCL15 (also known as MIP-1d), CCL17 (also known as TARC), CCL19 (also known as MIP-3b), CCL20 (also known as MIP-3a), CCL21 (also known as MIP-2), CCL24 (also known as MPIF-2/eotaxin-2), CCL25 (also known as TECK), CCL26 (also known as eotaxin-3), CCR3, CCR4, CD3, CD19, CD20, CD23 (also known as FCER2, a receptor for IgE), CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80 (also known as B7-1), CD86 (also known as B7-2), CD122, CD137 (also known as 41BB), CD137L, CD152 (also known as CTLA4), CD154 (also known as CD40L), CD160, CD272, CD273 (also known as PDL2), CD274 (also known as PDL1), CD275 (also known as B7H2), CD276 (also known as B7H3), CD278 (also known as ICOS), CD279 (also known as PD-1), CDH1 (also known as E-cadherin), chitinase, CLEC9, CLEC91, CRTH2, CSF-1 (also known as M-CSF), CSF-2 (also known as GM-CSF), CSF-3 (also known as GCSF), CX3CL1 (also known as SCYD1), CXCL12 (also known as SDF1), CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb (also known as a receptor for IL25), IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4 (also known as b4 integrin), ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2 (also known as a receptor for IL33), STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP (also known as a co-receptor for IL7Ra), TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1 (also known as GPR5/CCXCR1). In some embodiments, one or more of the above antigen targets are human antigen targets. In some embodiments, the binding protein of the present disclosure is trispecific and capable of specifically binding three different antigen targets selected from the above list. In some embodiments, the binding protein of the present disclosure is trivalent but bispecific and capable of specifically binding three antigen targets

selected from the above list, two of them being identical. In some embodiments, the binding protein of the present disclosure is trivalent but monopecific and capable of specifically binding three antigen targets selected from the above list, all of them being identical. In some embodiments, the binding protein specifically binds three target proteins that correspond to two target proteins on T cells and to one tumor target protein. In some embodiments, one of said target proteins on T cells is CD3. In some embodiments, one of said target proteins on T cells is CD28. In some embodiments, said tumor target protein is CD38. In some embodiments, the binding protein specifically binds three target proteins that correspond to two target proteins on T cells and to one target protein selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0011] In another embodiment, the disclosure provides a binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain has a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain has a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 2, 4, 10, 14, 18, 22, 115;

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125;

(c) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167;

(d) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; or

(e) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5; and

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 1, 3, 9, 13, 17, 21, 114;

(b) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122;

(c) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166;

(d) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128; or

(e) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5.

[0012] In some embodiments, the second and/or third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains.

[0013] In another embodiment, the disclosure provides a binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 2, 4, 10, 14, 18, 22, 115;

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125;

(c) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167;

(d) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; or

(e) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5;

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 1, 3, 9, 13, 17, 21, 114;

(b) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122;

(c) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166;

(d) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128; or

(e) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5.

[0014] In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167; and V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166. In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in

any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; and (d) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128.

[0015] In some embodiments of any of the binding proteins described herein, (a) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45; (b) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45; (c)

V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:37, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:38, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:39; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:55, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:56, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:57; (d) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:37, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:38, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:39; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:55, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:56, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:57; (e) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ

ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:42; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:58, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:59; (f) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:42; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:58, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:59; (g) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino

acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:126, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:127, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:128; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:140; (h) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:126, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:127, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:128; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:140; (i) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:120, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:121, and a CDR-

H3 comprising the amino acid sequence of SEQ ID NO:122; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:123, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:124, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:125; or (j) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:120, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:121, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:122; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:123, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:124, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:125. In some embodiments, (a) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45.

[0016] In some embodiments, the binding protein comprises one antigen binding site that specifically binds a T-cell surface protein and another antigen binding site that specifically binds an antigen target, *e.g.*, a tumor target protein. In some embodiments, the binding protein comprises an antigen binding site that specifically binds CD3, an antigen binding site that specifically binds CD28, and an antigen binding site that specifically binds a tumor target protein selected from the group consisting of CD19, CD20, CD38, Her2, and LAMP1. In some embodiments, V_{H1} and V_{L1} form a first antigen binding site that specifically binds human CD3, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human CD28, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds a human tumor target protein. In some embodiments, V_{H1} and V_{L1} form a first antigen binding site that specifically binds human CD28, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human CD3, and V_{H3} and V_{L3} form a third binding site that specifically binds a human tumor target protein. In some embodiments, the antigen binding site specifically binds a human tumor target protein selected from the group consisting of CD19, CD20, CD38, Her2, and LAMP1. In some embodiments, the antigen binding site that specifically binds CD3 comprises: (a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 152 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 153; or (b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 154 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 155. In some embodiments, the antigen binding site that specifically binds CD3 comprises six CDRs, or a heavy chain and a light chain variable domain, shown in Tables 2-5. In some embodiments, the antigen binding site that specifically binds CD28 comprises: (a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 160 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 161; or (b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 162 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 163. In some embodiments, the antigen binding site that specifically binds CD28 comprises six CDRs, or a heavy chain and a light chain variable domain, shown in Tables 2-5. In some embodiments, the antigen binding site that specifically binds a tumor target protein comprises: (a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 156 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 157; (b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 158 and a light chain variable domain comprising the amino acid sequence of

SEQ ID NO: 159; (c) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 164 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 165; (d) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 150 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 151; or (e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 166 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 167. In some embodiments, the antigen binding site that specifically binds a tumor target protein comprises six CDRs, or a heavy chain and a light chain variable domain, shown in Tables 2-5. In some embodiments, the antigen binding site that specifically binds a tumor target protein comprises six CDRs, or a heavy chain and a light chain variable domain, of an anti-Her2, anti-CD19, anti-CD20, anti-CD38, or anti-LAMP1 binding domain shown in Tables 2-5.

[0017] In another embodiment, the disclosure provides a binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain has a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain has a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 61, 63, 69, 71, 74, 76, 82, 86, 88, 94; or

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions of a variable domain of at least one amino acid sequence set forth in any one of SEQ ID NOs: 61, 63, 69, 71, 74, 76, 82, 86, 88, 94;

(c) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173;

(d) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179; or

(e) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5; and

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 60, 62, 68, 73, 75, 81, 85, 87, 93; or

(b) V_{H1}, V_{H2}, and V_{H3} each independently comprise heavy chain complementarity determining regions of a variable domain of at least one amino acid sequence set forth in any one of in any one of SEQ ID NOs: 60, 62, 68, 73, 75, 81, 85, 87, 93;

(c) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172;

(d) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137; or

(e) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5.

[0018] In some embodiments, the second and/or third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains.

[0019] In another embodiment, the disclosure provides a binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \quad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 61, 63, 69, 71, 74, 76, 82, 86, 88, 94;

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions of a variable domain of at least one amino acid sequence set forth in any one of SEQ ID NOs: 61, 63, 69, 71, 74, 76, 82, 86, 88, 94;

(c) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173;

(d) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179; or

(e) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5;

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 60, 62, 68, 73, 75, 81, 85, 87, 93;

(b) V_{H1}, V_{H2}, and V_{H3} each independently comprise heavy chain complementarity determining regions of a variable domain of at least one amino acid sequence set forth in any one of in any one of SEQ ID NOs: 60, 62, 68, 73, 75, 81, 85, 87, 93;

(c) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172;

(d) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137;

(e) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5.

[0020] In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173; and V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172. In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179; and V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137.

[0021] In some embodiments of any of the binding proteins described herein, (a) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2

comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; (b) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; (c) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a

CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; (d) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; (e) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; (f) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID

NO:131; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; (g) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; (h) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ

ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; (i) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; or (j) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ

ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144. In some embodiments, one or more of V_{H1}, V_{L1}, V_{H2}, V_{L2}, V_{H3}, and V_{L3} comprises one, two, or three CDR sequences of an antibody shown in Tables 2-5.

[0022] In some embodiments, the binding protein comprises three antigen binding sites, where one, two, or three of the antigen binding site(s) specifically bind(s) a cytokine target protein selected from the group consisting of IL-4, IL-13 and TNFa. In some embodiments, (a)V_{H1} and V_{L1} form a first antigen binding site that specifically binds human TNFa, V_{H2} and V_{L2} form an antigen binding site that specifically binds human IL13, and V_{H3} and V_{L3} form an antigen binding site that specifically binds human IL4; (b) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human TNFa, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL4, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL13; (c) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL4, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human TNFa, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL13; (d) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL4, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL13, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human TNFa; (e) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL13, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL4, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human TNFa; or (f) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL13, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human TNFa, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL4. In some embodiments, the antigen binding site that specifically binds human TNFa comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:168 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:169. In some embodiments, the antigen binding site that specifically binds human IL4 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:170 and a light chain variable domain comprising the

amino acid sequence of SEQ ID NO:171. In some embodiments, the antigen binding site that specifically binds human IL13 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:173.

[0023] In some embodiments of any of the binding proteins described herein, the second and/or third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains. In some embodiments, at least one of L_1, L_2, L_3 or L_4 is independently 0 amino acids in length. In some embodiments, L_1, L_2, L_3 or L_4 are each independently at least one amino acid in length. In some embodiments, the binding protein is trispecific and capable of specifically binding three different antigen targets. In some embodiments, the binding protein is trispecific and capable of specifically binding three different antigen targets. In some embodiments, the binding protein is capable of inhibiting the function of one or more target proteins.

[0024] In some embodiments of any of the binding proteins described herein, at least one of L_1, L_2, L_3 or L_4 is independently 0 amino acids in length. In some embodiments, L_1, L_2, L_3 or L_4 are each independently at least one amino acid in length. In some embodiments, one, two, three, or all four of L_1, L_2, L_3 and L_4 are between 0 and 15 amino acids in length. In some embodiments, at least two of L_1, L_2, L_3 and L_4 are between 1 and 15 amino acids in length. In some embodiments, (a) L_1, L_2, L_3 and L_4 each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148); or (b) L_1, L_2, L_3 and L_4 each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148). In some embodiments, L_1 comprises the sequence GQPKAAP (SEQ ID NO: 175), L_2 comprises the sequence TKGPS (SEQ ID NO:106), L_3 comprises the sequence S, and L_4 comprises the sequence RT; L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; L_1 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_2 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; or L_1 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), L_2 is 0 amino acids in

length, L_3 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), and L_4 is 0 amino acids in length.

[0025] In some embodiments of any of the binding proteins described herein, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, and wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and/or second Fc regions comprise amino acid substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S. In some embodiments, the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4

according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V. In some embodiments, the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W. In some embodiments, the C_{H3} domains of the second and the third polypeptide chains both comprise amino acid substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; and wherein only one of the first and the second Fc regions comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F. In some embodiments, the C_{H3} domains of the second and the third polypeptide chains are human IgG1 C_{H3} domains, and wherein only one of the C_{H3} domains comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and/or second Fc regions are human IgG4 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions

are S228P and R409K. In some embodiments, the C_{H3} domains of the second and the third polypeptide chains are human IgG4 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and/or second Fc regions are human IgG4 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A. In some embodiments, the C_{H3} domains of the second and the third polypeptide chains are human IgG4 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and/or second Fc regions are human IgG1 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A and L235A. In some embodiments, the C_{H3} domains of the second and the third polypeptide chains are human IgG1 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A and L235A. In some embodiments, the first and/or second Fc regions are human IgG1 Fc regions. In some embodiments, the first and/or second Fc regions are human IgG4 Fc regions.

[0026] In some embodiments of any of the binding proteins described herein, the C_L domain of the first polypeptide chain is a human kappa C_L domain, and the C_L domain of the fourth polypeptide chain is a human lambda C_L domain; or the C_L domain of the first

polypeptide chain is a human lambda C_L domain, and the C_L domain of the fourth polypeptide chain is a human kappa C_L domain. In some embodiments, the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain. In some embodiments, the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain. In some embodiments, the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354, 366, 435, and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C, T366W, H435R, and Y436F; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the fourth polypeptide chain comprises a kappa C_L domain. In some embodiments, the first polypeptide chain comprises a kappa C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a lambda C_L domain. In some

embodiments, second and/or third polypeptide chain comprise a human IgG1 or IgG4 Fc region.

[0027] In another embodiment, the disclosure provides a binding protein comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 13; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 14;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ

ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 13; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 14;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 17; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 18

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 17; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 18;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 21; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 22;

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 21; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 22;

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 61;

(j) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 61;

(k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ

ID NO: 71 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 71;

(l) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 76 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 76; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 75 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 75; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 82; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 81 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:81; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(n) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:88; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 87; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(o) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 94 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 94; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 93 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 93; the third polypeptide chain comprises the amino acid sequence of SEQ ID

NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(q) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(r) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(s) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:

62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(t) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 115 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 115; or

(u) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 115 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 115.

[0028] In another embodiment, the disclosure provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding the binding protein or polypeptide thereof according to any of the above embodiments. In another embodiment, the disclosure provides an expression vector comprising the nucleic acid molecule according to one of the above embodiments. In another embodiment, the disclosure provides an isolated host cell comprising the nucleic acid molecule according to any of the above embodiments. In another embodiment, the disclosure provides an isolated host cell comprising the expression vector according to any of the above embodiments. In some embodiments, the isolated host cell is a mammalian cell or an insect cell. In one embodiment, the disclosure provides a vector system comprising one or more vectors encoding a first, second, third, and fourth

polypeptide chain of a binding protein according to any of the above embodiments. In some embodiments, the vector system comprises a first vector encoding the first polypeptide chain of the binding protein, a second vector encoding the second polypeptide chain of the binding protein, a third vector encoding the third polypeptide chain of the binding protein, and a fourth vector encoding the fourth polypeptide chain of the binding protein. In some embodiments, the vector system comprises a first vector encoding the first and second polypeptide chains of the binding protein, and a second vector encoding the third and fourth polypeptide chains of the binding protein. In some embodiments, the one or more vectors are expression vectors. In one embodiment, the disclosure provides an isolated host cell comprising the vector system according to any of the above embodiments. In one embodiment, the disclosure provides a method of producing a binding protein, the method comprising: a) culturing a host cell according to any of the above embodiments under conditions such that the host cell expresses the binding protein; and b) isolating the binding protein from the host cell. In one embodiment, the disclosure provides a pharmaceutical composition comprising the binding protein according to any of the above embodiments and a pharmaceutically acceptable carrier.

[0029] In another embodiment, the disclosure provides a method of preventing and/or treating cancer in a patient comprising administering to the patient a therapeutically effective amount of at least one binding protein or pharmaceutical composition according to any of the above embodiments. In another embodiment, the disclosure provides a binding protein or pharmaceutical composition according to any of the above embodiments for use in preventing and/or treating cancer in a patient. In another embodiment, the disclosure provides a binding protein according to any of the above embodiments for the manufacture of a medicament for preventing and/or treating cancer in a patient. In some embodiments, the binding protein comprises one antigen binding site that specifically binds a T-cell surface protein and another antigen binding site that specifically binds a tumor target protein. In some embodiments, the binding protein comprises an antigen binding site that specifically binds CD3, an antigen binding site that specifically binds CD28, and an antigen binding site that specifically binds a tumor target protein selected from the group consisting of CD19, CD20, CD38, Her2, and LAMP1. In some embodiments, the at least one binding protein is co-administered with a chemotherapeutic agent. In some embodiments, the patient is a human. In some embodiments, the binding protein is capable of inhibiting the function of one or more target proteins selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4,

B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0030] In another embodiment, the disclosure provides a method of preventing and/or treating an inflammatory disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of at least one binding protein or pharmaceutical composition according to any of the above embodiments. In another embodiment, the disclosure provides a binding protein or pharmaceutical composition according to any of the above embodiments for use in preventing and/or treating an inflammatory disease or disorder in a patient. In another embodiment, the disclosure provides a binding protein according to any of the above embodiments for the manufacture of a medicament for preventing and/or treating an inflammatory disease or disorder in a patient. In some embodiments, the binding protein comprises three antigen binding sites that each specifically bind a cytokine target protein selected from the group consisting of IL-4, IL-13 and TNFa. In some embodiments, two of the three binding sites specifically bind a cytokine target protein selected from the group consisting of IL-4, IL-13 and TNFa. In some embodiments, the at least one binding protein is co-administered with an anti-inflammatory agent. In some embodiments, the patient is a human. In some embodiments, the binding protein is capable of inhibiting the function of one or more target proteins selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20,

CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0031] In another embodiment, the disclosure provides a method of purifying a binding protein produced by a host cell, comprising:

(a) producing in a host cell a binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more antigen targets or target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair; wherein only one of the C_{H3} domain of the second polypeptide chain and the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F;

(b) contacting the binding protein produced in (a) with Protein A; and

(c) eluting the binding protein from Protein A under conditions suitable for isolating the binding protein away from binding proteins comprising either 0 or 2 C_{H3} domains comprising the amino acid substitutions are H435R and Y436F.

[0032] In some embodiments, the C_L domain of the first polypeptide chain is a human kappa C_L domain, and the C_L domain of the fourth polypeptide chain is a human lambda C_L domain; or the C_L domain of the first polypeptide chain is a human lambda C_L domain, and the C_L domain of the fourth polypeptide chain is a human kappa C_L domain, and the method further comprises: (d) contacting the binding protein eluted in (c) with a kappa light chain affinity medium; and (e) eluting the binding protein from the kappa light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only lambda C_L domains. In some embodiments, the method further comprises, after (e), (f) contacting the binding protein eluted in (e) with a lambda light chain affinity medium; and (g) eluting the binding protein from the lambda light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only kappa C_L domains. In some embodiments, the C_L domain of the first polypeptide chain is a human kappa C_L domain, and the C_L domain of the fourth polypeptide chain is a human lambda C_L domain; or the C_L domain of the first polypeptide chain is a human lambda C_L domain, and the C_L domain of the fourth polypeptide chain is a human kappa C_L domain, and the method further comprises: (d) contacting the binding protein eluted in (c) with a lambda light chain affinity medium; and (e) eluting the binding protein from the lambda light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only kappa C_L domains. In some embodiments, the method further comprises, after (e), (f) contacting the binding

protein eluted in (e) with a kappa light chain affinity medium; and (g) eluting the binding protein from the kappa light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only lambda C_L domains. In some embodiments, the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain. In some embodiments, the binding protein is detected in one or more of (c) and (e) using hydrophobic interaction chromatography (HIC). In some embodiments, the C_{H3} domains and/or Fc regions of the second and the third polypeptide chains are human IgG1 or IgG4 C_{H3} domains and/or Fc regions.

[0033] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the invention are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] **FIGS. 1A-1C** show schematic representations of trispecific binding proteins comprising four polypeptide chains that form three antigen binding sites that specifically binds three target proteins, wherein a first pair of polypeptides possess dual variable domains having a cross-over orientation (VH1-VH2 and VL2-VL1) forming two antigen binding sites, and wherein a second pair of polypeptides possess a single variable domain (VH3 and VL3) forming a single antigen binding site. **FIG. 1A** shows a trispecific binding protein comprising a "knobs-into-holes" mutation, where the knob is on the second pair of polypeptides with a single variable domain. **FIG. 1B** shows a trispecific binding protein comprising a "knobs-into-holes" mutation, where the knob is on the first pair of polypeptides having the cross-over orientation. **FIG. 1C** shows the orientation of variable domains on the polypeptide chains, and the knob/hole orientation for the binding proteins shown in Tables 1-3. "Heavy chain A" (*e.g.*, a third polypeptide chain of the present

disclosure) indicates the variable domain of heavy chain A. "Light chain A" (*e.g.*, a fourth polypeptide chain of the present disclosure) indicates the variable domain of light chain A. "Heavy chain B" (*e.g.*, a second polypeptide chain of the present disclosure) indicates variable domain 1 and variable domain 2 of heavy chain B. "Light chain B" (*e.g.*, a first polypeptide chain of the present disclosure) indicates variable domain 1 and variable domain 2 of light chain B.

[0035] **FIG. 2** shows the results of an ELISA assay determining the binding of an anti-Her2 x CD28 x CD3 IgG4 trispecific antibody (Binding Protein 1), or isotype control antibody, to human CD3, CD28 and Her2. The bound antibodies were detected using a horseradish peroxidase (HRP)-conjugated anti-Fab secondary antibody.

[0036] **FIGS. 3A-3C** show the results of antibody-mediated specific killing of $Her2^+$ breast cancer cells using an anti-Her2 x CD28 x CD3 IgG4 trispecific antibody (referred to herein as "Binding protein 1"), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-Her2 IgG1 antibody, or a control antibody (human-IgG1), using human PBMC at the E:T=10. **FIG. 3A** shows the results of trispecific antibody-mediated specific killing of ZR-75-1 cells. **FIG. 3B** shows the results of trispecific antibody-mediated specific killing of AU565 cells. **FIG. 3C** shows the results of FACS analysis determining the cell surface expression of the indicated markers on ZR-75-1 and AU565 cells.

[0037] **FIGS. 4 & 5** show the results of antibody-mediated specific killing of $Her2^+$ breast cancer cells using an anti-Her2 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 1), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-Her2 IgG1 antibody, or a control antibody (human-IgG1). **FIG. 4** shows the results of antibody-mediated specific killing of ZR-75-1 cells using human peripheral blood mononuclear cells (PBMCs) from donor KP45926 at E:T=10. **FIG. 5** shows the results of antibody-mediated specific killing of AU565 cells using human PBMCs from donor KP45944 at E:T=10. **FIGS. 4 & 5** confirm similar cell killing results as shown in **FIGS. 3A-3C** using PBMCs from a different donor.

[0038] **FIGS. 6A & 6B** show the activation ($CD69^+$) and proliferation of human T cells treated with anti-Her2 x CD28 x CD3 IgG4 trispecific binding protein ($HER2/CD28_{sup}xCD3_{mid}$; referred to herein as "Binding Protein 1"), anti-Her2 x CD28 x CD3 IgG4 trispecific binding protein lacking the anti-CD28 binding domain ($HER2/\Delta CD28_{sup}xCD3_{mid}$), anti-Her2 x CD28 x CD3 IgG4 trispecific binding protein lacking the anti-CD3 binding domain ($HER2/CD28_{sup}x\Delta CD3_{mid}$), anti-Her2 x CD28 x CD3 IgG4 trispecific binding protein lacking both anti-CD28 and anti-CD3 binding domains

(HER2/Δ($CD28_{sup}$x$\Delta CD3_{mid}$)), control anti-CD3 monoclonal antibody, or control IgG4 antibody. **FIG. 6A** shows the activation ($CD69^+$) of human $CD4^+$ T cells from three donors. **FIG. 6B** shows the activation ($CD69^+$) of human $CD8^+$ T cells from three donors. $CD28_{sup}$: anti-CD28 superagonist antibody. $CD3_{mid}$: anti-CD3 antibody.

[0039] **FIGS. 7A-C** show IL-2, NFκB, and nuclear factor of activated T-cells (NFAT) pathway activation via anti-CD3 and anti-CD28 signaling, as measured by luciferase assay using human Jurkat T cells with an IL-2 promoter-luciferase construct (**FIG. 7A**), an NFκB promoter-luciferase construct (**FIG. 7B**), or an NFAT promoter-luciferase construct (**FIG. 7C**). Antibodies tested were those described above in reference to **FIGS. 6A-6D**.

[0040] **FIG. 8** shows the results of an ELISA assay determining binding of an anti-CD19 x CD28 x CD3 IgG4 trispecific antibody (referred to herein as "Binding Protein 3"), or isotype control antibody, to CD3, CD28, and CD19. The bound antibodies were detected using a horseradish peroxidase (HRP)-conjugated anti-Fab secondary antibody.

[0041] **FIGS. 9A-9N** show the results of antibody-mediated specific killing of $CD19^+$ human GCB lymphoma cells using an anti-CD19 x CD28 x CD3 IgG4 trispecific antibody (referred to herein as "Binding Protein 3"), or the indicated controls, using human PBMC as effector cells at E:T=10. **FIG. 9A** shows the results of antibody-mediated specific killing of OCI-LY19 cells. **FIG. 9B** shows the results of FACS analysis determining the cell surface expression of the indicated markers on OCI-LY19 cells. **FIG. 9C** shows the results of antibody-mediated specific killing of OCI-LY19 cells using PBMCs from donor KP48572 at E:T=10. **FIG. 9D** shows the results of antibody-mediated specific killing of OCI-LY19 cells using PBMCs from donor KP48573 at E:T=10. **FIG. 9E** shows the results of antibody-mediated specific killing of human lymphoma KARPASS-422 cells using PBMCs from donor KP48572 at E:T=10. **FIG. 9F** shows the results of antibody-mediated specific killing of KARPASS-422 cells using PBMCs from donor KP48573 at E:T=10. **FIG. 9G** shows the results of antibody-mediated specific killing of human chronic B cell leukemia MeC1 cells using PBMCs from donor KP48572 at E:T=10. **FIG. 9H** shows the results of antibody-mediated specific killing of human multiple myeloma RPMI8226 cells using PBMCs from donor KP48775 at E:T=10. **FIG. 9I** shows the results of antibody-mediated specific killing of human Burkitt's lymphoma Raji cells using PBMCs from donor KP48572 at E:T=10. **FIG. 9J** shows the results of antibody-mediated specific killing of Human diffuse large B-cell lymphoma HBL1 cells using PBMCs from donor KP48775 at E:T=10. **FIG. 9K** shows the results of antibody-mediated specific killing of Large cell lymphoma SUDHL8 cells using PBMCs from donor KP48572 at E:T=10. **FIG.**

9L shows the results of antibody-mediated specific killing of SUDHL8 cells using PBMCs from donor KP48573 at E:T=10. **FIG. 9M** shows the results of antibody-mediated specific killing of human B cell lymphoma ARH77 cells using PBMCs from donor KP48775 at E:T=10. **FIG. 9N** shows the results of antibody-mediated specific killing of OCI-Ly3 cells using PBMCs from donor KP48775 at E:T=10.

[0042] **FIG. 10** shows the results of an ELISA assay determining binding of an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding Protein 5), or isotype control antibody, to CD3, CD28 and CD38. The bound antibodies were detected using a horseradish peroxidase (HRP)-conjugated anti-Fab secondary antibody.

[0043] **FIGS. 11A-11D** show the results of antibody-mediated specific killing of $CD38^+$ human multiple myeloma cancer cells using an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-CD38 IgG1 antibody, or a control antibody (human-IgG1). **FIG. 11A** shows the results of antibody-mediated specific killing of MOLP-8 cells using human PBMC as effector cells at E:T=10. **FIG. 11B** shows the results of antibody-mediated specific killing of RPMI-8226 cells using human PBMC as effector cells at E:T=10. **FIG. 11C** shows the results of antibody-mediated specific killing of KMS-12-BM cells using human PBMC as effector cells at E:T=10. **FIG. 11D** shows the results of FACS analysis determining the cell surface expression of the indicated markers on MOLP-8, RPMI-8226, and KMS-12-BM cells.

[0044] **FIGS. 12A-12D** show the results of antibody-mediated specific killing of $CD38^+$ human multiple myeloma cancer cells using an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-CD38 IgG1 antibody, or a control antibody (human-IgG1), using human PBMC as effector cells at E:T=10 . **FIG. 12A** shows the results of antibody-mediated specific killing of NCI-H929 cells. **FIG. 12B** shows the results of antibody-mediated specific killing of MM.1S cells. **FIG. 12C** shows the results of antibody-mediated specific killing of MM.1R cells. **FIG. 12D** shows the results of FACS analysis determining the cell surface expression of the indicated markers on NCI-H929, MM.1S, and MM.1R cells.

[0045] **FIGS. 13A-13D** show the results of antibody-mediated specific killing of $CD38^+$ human multiple myeloma cancer cells using an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-CD38 IgG1 antibody, or a control antibody (human-IgG1), using

human PBMC as effector cells at E:T=10. **FIG. 13A** shows the results of antibody-mediated specific killing of OPM-2 cells. **FIG. 13B** shows the results of antibody-mediated specific killing of KMS-26 cells. **FIG. 13C** shows the results of antibody-mediated specific killing of U266 cells. **FIG. 13D** shows the results of FACS analysis determining the cell surface expression of the indicated markers on OPM-2, KMS-26, and U226 cells.

[0046] **FIGS. 14A-14C** show the results of antibody-mediated specific killing of $CD38^+$ human lymphoma cancer cells using an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-CD38 IgG1 antibody, or a control antibody (human-IgG1), using human PBMC as effector cells at E:T=10. **FIG. 14A** shows the results of antibody-mediated specific killing of SUDHL-8 cells. **FIG. 14B** shows the results of antibody-mediated specific killing of OCI-LY19 cells. **FIG. 14C** shows the results of FACS analysis determining the cell surface expression of the indicated markers on SUDHL-8 and OCI-LY19 cells.

[0047] **FIGS. 15A-15D** show the results of antibody-mediated specific killing of $CD38^+$ ALL cancer cells using an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-CD38 IgG1 antibody, or a control antibody (human-IgG1), using human PBMC as effector cells at E:T=10. **FIG. 15A** shows the results of antibody-mediated specific killing of KOPN-8 cells. **FIG. 15B** shows the results of antibody-mediated specific killing of HAL-1 cells. **FIG. 15C** shows the results of antibody-mediated specific killing of CCRF-SB cells. **FIG. 15D** shows the results of FACS analysis determining the cell surface expression of the indicated markers on KOPN-8, HAL-1, and CCRF-SB cells.

[0048] **FIG. 16** shows the results of antibody-mediated specific killing of $CD38^+$ myeloma cancer cells using anti-CD38 x CD28 x CD3 IgG4 trispecific antibodies (referred to herein as "Binding protein 5" and "Binding Protein 6," depending on the specific anti-CD28 binding domain used), an anti-CD28 x CD3 IgG4 bispecific antibody (huCD28 x CD3), an anti-CD38 IgG1 antibody, a control anti-CD38 IgG1 antibody, or a control antibody (human-IgG1), using PBMCs from donor PK45926 at E:T=10.

[0049] **FIGS. 17A & 17B** show IL-2, NFκB, and nuclear factor of activated T-cells (NFAT) pathway activation via anti-CD3 and anti-CD28 signaling, as measured by luciferase assay using human Jurkat T cells with an IL-2 promoter-luciferase construct (**FIG. 17A**) or an NFAT promoter-luciferase construct (**FIG. 17B**). Antibodies tested were anti-CD38 x CD28 x CD3 IgG4 trispecific IgG4 antibody (Binding Protein 5, labeled as

"Tri-Ab"), anti-CD38 x CD28 x CD3 IgG4 trispecific IgG4 antibody lacking the CD28 binding domain (labeled as "Tri-Ab (ΔCD28)), anti-CD38 x CD28 x CD3 IgG4 trispecific IgG4 antibody lacking the CD3 binding domain (labeled as "Tri-Ab (ΔCD3)), and anti-CD38 x CD28 x CD3 IgG4 trispecific IgG4 antibody lacking the CD3 and CD28 binding domains (labeled as "Tri-Ab (ΔCD28x ΔCD3)). Luciferase assays were performed in duplicate for each of the indicated Tri-Abs.

[0050] **FIGS. 18A-18E** show the results of a dose escalation toxicity study using the anti-Her2 x CD28 x CD3 IgG4 trispecific antibody (referred to herein as "Binding protein 1") in non-human primates (dose escalating from 0.1, 0.5, 2.5, 5, 10, to 100 μg/kg; animals labeled as "409" and "410"). **FIG. 18A** shows the results of circulating $CD4^+$ T cells percentage in each animal, 6 hours post administering the anti-Her2 x CD28 x CD3 trispecific antibody. **FIG. 18B** shows the results of circulating $CD8^+$ T cells percentage in each animal, 6 hours post administering the anti-Her2 x CD28 x CD3 trispecific antibody. **FIG. 18C** shows the results of the activation ($CD69^+$) of circulating $CD4^+$ T cells 6 hours post dosing. **FIG. 18D** shows the results of the activation ($CD69^+$) of circulating $CD8^+$ T cells 6 hours post dosing. **FIG. 18E** shows the inflammatory cytokine release observed 6 hours post administering the anti-Her2 x CD28 x CD3 trispecific antibody at each dosing.

[0051] **FIGS. 19A-B** show the *in vivo* anti-tumor activity of the anti-Her2 x CD28 x CD3 IgG4 trispecific antibody (referred to herein as "Binding protein 1") in the $CD34^+$ umbilical cord blood cell humanized NSG mouse model implanted with BT474 cells. **FIG. 19A** shows the change in body weight of mice treated with the indicated concentrations of the anti-Her2 x CD28 x CD3 trispecific binding protein or PBS control. **FIG. 19B** shows the change in tumor volume in mice treated with the indicated concentrations of the anti-Her2 x CD28 x CD3 trispecific binding protein or PBS control.

[0052] **FIGS. 20A-20H** show the *in vivo* anti-tumor activity of the anti-Her2 x CD28 x CD3 IgG4 trispecific antibody (referred to herein as "Binding protein 1") in the human PBMCs humanized NSG mouse model implanted with BT474 cells. **FIG. 20A** shows the effect of administering the indicated concentrations of the anti-Her2 x CD28 x CD3 trispecific binding protein, the indicated concentrations of Herceptin, or vehicle control, on the body weight of the mice. **FIG. 20B** shows the dose-dependent anti-tumor activity of the anti-Her2 x CD28 x CD3 trispecific binding protein, Herceptin or indicated controls, as in individual mice. **FIG. 20C** shows the average tumor volume in the mice after administration of the indicated concentrations of the anti-Her2 x CD28 x CD3 trispecific binding protein or PBS control. **FIG. 20D** shows the average tumor volume in the mice

after administration of the indicated concentrations of Herceptin or PBS control. **FIG. 20E** shows bar graphs of the average tumor volume at day 34 in the mice after administration of the indicated concentrations of the anti-Her2 x CD28 x CD3 trispecific binding protein, the indicated concentrations of Herceptin, or PBS control. **FIG. 20F** shows the average tumor weight at day 34 in the mice after administration of the indicated concentrations of the anti-Her2 x CD28 x CD3 trispecific binding protein, the indicated concentrations of Herceptin, or PBS control. **FIG. 20G** shows the human CD45+, CD3+, CD4+, CD8+ cells in the blood of the mice at the end of the study. **FIG. 20H** shows the human CD45+, CD3+, CD4+, CD8+ cells in the spleens of the mice at the end of the study.

[0053] **FIGS. 21A-F** show the results of a dose escalation toxicity study using the anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5) in non-human primates (dose escalating from 0.1, 0.5, 2.5, 5, 10, to 100 μg/kg). **FIG. 21A** shows T cell activation ($CD69^+$) (line graph) and proliferation (bar graph) of circulating $CD4^+$ T cells after administration of the anti-CD38 x CD28 x CD3 trispecific antibody. **FIG. 21B** shows T cell activation ($CD69^+$) (line graph) and proliferation (bar graph) of circulating $CD8^+$ T cells after administration of the anti-CD38 x CD28 x CD3 trispecific antibody. **FIG. 21C** shows IL6 release in animals receiving the anti-CD38 x CD28 x CD3 trispecific antibody 6 hours post each dosing by individual animal. **FIG. 21D** shows IL10 release in animals receiving the anti-CD38 x CD28 x CD3 trispecific antibody 6 hours post each dosing by individual animal. **FIG. 21E** shows TNFα release in animals receiving the anti-CD38 x CD28 x CD3 trispecific antibody. **FIG. 21F** shows IFNγ release in animals receiving the anti-CD38 x CD28 x CD3 trispecific antibody 6 hours post each dosing by individual animal.

[0054] **FIGS. 22A-22C** show the *in vivo* anti-tumor activity of the anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5) in the CD34+ umbilical cord blood cells humanized NSG mouse model implanted with RPMI-8226 multiple myeloma cells transduced with CD38 and PD-L1. As a pilot study, this experiment determined the working dose range for the Binding protein 5. **FIG. 22A** shows the *in vivo* tumor growth curve in groups of the indicated concentrations of the anti-CD38 x CD28 x CD3 trispecific binding protein or controls. **FIG. 22B** shows tumor infiltrating human $CD8^+$ T cells in mice administered the anti-CD38 x CD28 x CD3 trispecific binding protein or the indicated controls. **FIG. 22C** shows tumor infiltrating human $CD4^+$ T cells in mice administered the anti-CD38 x CD28 x CD3 trispecific binding protein or the indicated controls.

[0055] **FIGS. 23A-23D** show the *in vivo* activity of the anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5) in the CD34+ umbilical cord blood cells humanized

NSG mouse model implanted with RPMI-8226 cells transduced with CD38 and PD-L1. **FIG. 23A** shows the change in body weight of mice treated with the indicated concentrations of the anti-CD38 x CD28 x CD3 trispecific binding protein or PBS control. **FIG. 23B** shows the change in tumor volume in mice treated with the indicated concentrations of the anti-CD38 x CD28 x CD3 trispecific binding protein or PBS control. **FIG. 23C** shows the tumor volumes in each group at Day 19. The tumor volumes in all treated groups showed marked reduction, which are statistically different form the PBS control group. **FIG. 23D** shows the serum concentration of inflammatory cytokines IFN-g, TNF, and IL-2 in mice four hours after the first dose of the indicated concentrations of the anti-CD38 x CD28 x CD3 trispecific binding protein or PBS control.

[0056] **FIGS. 24 & 25** show the *in vivo* activation of T cells in the CD34+ umbilical cord blood cells humanized NSG mouse model by administering an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5; triangles), an anti-CD28 x CD3 IgG4 bispecific antibody (squares), or an anti-CD28 IgG4 antibody (circles) by determining the increase in the percentage of $CD69^+$ T cells. **FIG. 24** shows the *in vivo* activation of $CD4^+$ T cells. **FIG. 25** shows the *in vivo* activation of $CD8^+$ T cells.

[0057] **FIGS. 26A-26C** show the *in vivo* activation of T cells in the CD34+ umbilical cord blood cells humanized NSG mouse model by administering an anti-CD38 x CD28 x CD3 IgG4 trispecific antibody (Binding protein 5; triangles), an anti-CD28 x CD3 IgG4 bispecific antibody (squares), or an anti-CD28 IgG4 antibody (circles) by determining the serum levels of inflammatory cytokines. **FIG. 26A** shows the serum levels of IL-2. **FIG. 26B** shows the serum levels of TNF. **FIG. 26C** shows the serum levels of IFN-γ.

[0058] **FIGS. 27A & 27B** show the purification of the indicated proteins by size exclusion chromatography. **FIG. 27A** shows the purification of Binding Proteins 9-15 by size exclusion chromatography. **FIG. 27B** shows the purification of Binding Proteins 16-19 by size exclusion chromatography.

[0059] **FIG. 28A** depicts the trispecific binding protein used in experiments for optimizing a purification scheme and configuration of optional binding protein features (*e.g.*, kappa/lambda light chains, knob/hole mutations, and H435R/Y436F mutations).

[0060] **FIG. 28B** shows each of the configurations tested.

[0061] **FIG. 29** shows representative chromatograms from analytical hydrophobic interaction chromatography (HIC), demonstrating that trispecific binding proteins were distinguishable from mispaired species.

[0062] **FIGS. 30A & 30B** show the successful purification of a binding protein with lambda light chain for CODV arm, kappa light chain for Fab arm, knob mutations on CODV arm, hole mutations on Fab arm, and RF mutations on Fab arm by Protein A followed by KappaSelect (GE Healthcare) purification steps. Successful purification of binding protein from mispaired species was demonstrated by hydrophobic interaction chromatography (HIC; **FIG. 30A**) and SDS-PAGE (**FIG. 30B**).

DETAILED DESCRIPTION

[0063] The disclosure provides trispecific and/or trivalent binding proteins comprising four polypeptide chains that form three antigen binding sites that specifically bind to one or more target proteins, wherein a first pair of polypeptides forming the binding protein possess dual variable domains having a cross-over orientation and wherein a second pair of polypeptides forming the binding protein possess a single variable domain.

General Definitions

[0064] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0065] The term "polynucleotide" as used herein refers to single-stranded or double-stranded nucleic acid polymers of at least 10 nucleotides in length. In certain embodiments, the nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Such modifications include base modifications such as bromuridine, ribose modifications such as arabinoside and 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate and phosphoroamidate. The term "polynucleotide" specifically includes single-stranded and double-stranded forms of DNA.

[0066] An "isolated polynucleotide" is a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which: (1) is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, (2) is linked to a polynucleotide to which it is not linked in nature, or (3) does not occur in nature as part of a larger sequence.

[0067] An "isolated polypeptide" is one that: (1) is free of at least some other polypeptides with which it would normally be found, (2) is essentially free of other

polypeptides from the same source, *e.g.*, from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is not associated (by covalent or noncovalent interaction) with portions of a polypeptide with which the "isolated polypeptide" is associated in nature, (6) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (7) does not occur in nature. Such an isolated polypeptide can be encoded by genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof. Preferably, the isolated polypeptide is substantially free from polypeptides or other contaminants that are found in its natural environment that would interfere with its use (therapeutic, diagnostic, prophylactic, research or otherwise).

[0068] Naturally occurring antibodies typically comprise a tetramer. Each such tetramer is typically composed of two identical pairs of polypeptide chains, each pair having one full-length "light" chain (typically having a molecular weight of about 25 kDa) and one full-length "heavy" chain (typically having a molecular weight of about 50-70 kDa). The terms "heavy chain" and "light chain" as used herein refer to any immunoglobulin polypeptide having sufficient variable domain sequence to confer specificity for a target antigen. The amino-terminal portion of each light and heavy chain typically includes a variable domain of about 100 to 110 or more amino acids that typically is responsible for antigen recognition. The carboxy-terminal portion of each chain typically defines a constant domain responsible for effector function. Thus, in a naturally occurring antibody, a full-length heavy chain immunoglobulin polypeptide includes a variable domain (V_H) and three constant domains (C_{H1}, C_{H2}, and C_{H3}), wherein the V_H domain is at the amino-terminus of the polypeptide and the C_{H3} domain is at the carboxyl-terminus, and a full-length light chain immunoglobulin polypeptide includes a variable domain (V_L) and a constant domain (C_L), wherein the V_L domain is at the amino-terminus of the polypeptide and the C_L domain is at the carboxyl-terminus.

[0069] Human light chains are typically classified as kappa and lambda light chains, and human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM has subclasses including, but not limited to, IgM1 and IgM2. IgA is similarly subdivided into subclasses including, but not limited to, IgA1 and IgA2. Within full-length light and heavy chains, the variable and constant domains typically are joined by a "J" region of about 12 or more

amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. *See, e.g.*, FUNDAMENTAL IMMUNOLOGY (Paul, W., ed., Raven Press, 2nd ed., 1989), which is incorporated by reference in its entirety for all purposes. The variable regions of each light/heavy chain pair typically form an antigen binding site. The variable domains of naturally occurring antibodies typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair typically are aligned by the framework regions, which may enable binding to a specific epitope. From the amino-terminus to the carboxyl-terminus, both light and heavy chain variable domains typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[0070] The term "CDR set" refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat *et al.*, SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST (National Institutes of Health, Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Chothia and coworkers (Chothia and Lesk, 1987, *J. Mol. Biol.* 196: 901-17; Chothia *et al.*, 1989, *Nature* 342: 877-83) found that certain sub-portions within Kabat CDRs adopt nearly identical peptide backbone conformations, despite having great diversity at the level of amino acid sequence. These sub-portions were designated as L1, L2, and L3 or H1, H2, and H3 where the "L" and the "H" designates the light chain and the heavy chain regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan, 1995, *FASEB J.* 9: 133-39; MacCallum, 1996, *J. Mol. Biol.* 262(5): 732-45; and Lefranc, 2003, *Dev. Comp. Immunol.* 27: 55-77. Still other CDR boundary definitions may not strictly follow one of the herein systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems, although certain embodiments use Kabat or Chothia defined CDRs. Identification of predicted CDRs using the amino acid sequence is well known in the field, such as in

Martin, A.C. "Protein sequence and structure analysis of antibody variable domains," *In Antibody Engineering*, Vol. 2. Kontermann R., Dübel S., eds. Springer-Verlag, Berlin, p. 33–51 (2010). The amino acid sequence of the heavy and/or light chain variable domain may be also inspected to identify the sequences of the CDRs by other conventional methods, *e.g.*, by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. The numbered sequences may be aligned by eye, or by employing an alignment program such as one of the CLUSTAL suite of programs, as described in Thompson, 1994, *Nucleic Acids Res.* 22: 4673-80. Molecular models are conventionally used to correctly delineate framework and CDR regions and thus correct the sequence-based assignments.

[0071] The term "Fc" as used herein refers to a molecule comprising the sequence of a non-antigen-binding fragment resulting from digestion of an antibody or produced by other means, whether in monomeric or multimeric form, and can contain the hinge region. The original immunoglobulin source of the native Fc is preferably of human origin and can be any of the immunoglobulins, although IgG1 and IgG2 are preferred. Fc molecules are made up of monomeric polypeptides that can be linked into dimeric or multimeric forms by covalent (*i.e.*, disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (*e.g.*, IgG, IgA, and IgE) or subclass (*e.g.*, IgG1, IgG2, IgG3, IgA1, and IgGA2). One example of a Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG. The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

[0072] A F(ab) fragment typically includes one light chain and the V_H and C_{H1} domains of one heavy chain, wherein the V_H-C_{H1} heavy chain portion of the F(ab) fragment cannot form a disulfide bond with another heavy chain polypeptide. As used herein, a F(ab) fragment can also include one light chain containing two variable domains separated by an amino acid linker and one heavy chain containing two variable domains separated by an amino acid linker and a C_{H1} domain.

[0073] A F(ab') fragment typically includes one light chain and a portion of one heavy chain that contains more of the constant region (between the C_{H1} and C_{H2} domains), such that an interchain disulfide bond can be formed between two heavy chains to form a $F(ab')_2$ molecule.

[0074] The term "binding protein" as used herein refers to a non-naturally occurring (or recombinant or engineered) molecule that specifically binds to at least one target antigen,

and which comprises four polypeptide chains that form at least three antigen binding sites, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain has a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain has a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0075] A "recombinant" molecule is one that has been prepared, expressed, created, or isolated by recombinant means.

[0076] One embodiment of the disclosure provides binding proteins having biological and immunological specificity to between one and three target antigens. Another embodiment of the disclosure provides nucleic acid molecules comprising nucleotide sequences encoding polypeptide chains that form such binding proteins. Another embodiment of the disclosure provides expression vectors comprising nucleic acid molecules comprising nucleotide sequences encoding polypeptide chains that form such binding proteins. Yet another embodiment of the disclosure provides host cells that express such binding proteins (*i.e.*, comprising nucleic acid molecules or vectors encoding polypeptide chains that form such binding proteins).

[0077] The term "swapability" as used herein refers to the interchangeability of variable domains within the binding protein format and with retention of folding and ultimate binding affinity. "Full swapability" refers to the ability to swap the order of both V_{H1} and V_{H2} domains, and therefore the order of V_{L1} and V_{L2} domains, in the polypeptide chain of formula I or the polypeptide chain of formula II (*i.e.*, to reverse the order) while maintaining full functionality of the binding protein as evidenced by the retention of binding affinity. Furthermore, it should be noted that the designations V_H and V_L refer only to the domain's location on a particular protein chain in the final format. For example, V_{H1} and V_{H2} could be derived from V_{L1} and V_{L2} domains in parent antibodies and placed into the V_{H1} and V_{H2} positions in the binding protein. Likewise, V_{L1} and V_{L2} could be derived from V_{H1} and V_{H2} domains in parent antibodies and placed in the V_{H1} and V_{H2} positions in the binding protein. Thus, the V_H and V_L designations refer to the present location and not the original location in a parent antibody. V_H and V_L domains are therefore "swappable."

[0078] The term "antigen" or "target antigen" or "antigen target" as used herein refers to a molecule or a portion of a molecule that is capable of being bound by a binding protein, and additionally is capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. A target antigen may have one or more epitopes. With respect to each target antigen recognized by a binding protein, the binding protein is capable of competing with an intact antibody that recognizes the target antigen.

[0079] The term "Her2" refers to human epidermal growth factor receptor 2 which is a member of the epidermal growth factor receptor family.

[0080] "CD3" is cluster of differentiation factor 3 polypeptide and is a T-cell surface protein that is typically part of the T cell receptor (TCR) complex.

[0081] "CD28" is cluster of differentiation 28 polypeptide and is a T-cell surface protein that provides co-stimulatory signals for T-cell activation and survival.

[0082] "CD19" is cluster of differentiation 19 polypeptide and is located on B-cells.

[0083] "CD20" is cluster of differentiation 20 polypeptide and is an activated-glycosylated phosphoprotein expressed on the surface of B-cells.

[0084] "CD38" is cluster of differentiation 38 polypeptide and is a glycoprotein found on the surface of many immune cells.

[0085] "LAMP1" is lysosomal-associated membrane protein 1.

[0086] "IL-4" is interleukin 4 and is a cytokine that induces differentiation of naïve helper T cells.

[0087] "IL-13" is interleukin 13 and is a cytokine secreted by many cell types such as T-cells.

[0088] "TNFa" is tumor necrosis factor alpha and is a cytokine involved in systematic inflammation.

[0089] The term "T-cell engager" refers to binding proteins directed to a host's immune system, more specifically the T cells' cytotoxic activity as well as directed to a tumor target protein.

[0090] The term "monospecific binding protein" refers to a binding protein that specifically binds to one antigen target.

[0091] The term "monovalent binding protein" refers to a binding protein that has one antigen binding site.

[0092] The term "bispecific binding protein" refers to a binding protein that specifically binds to two different antigen targets.

[0093] The term "bivalent binding protein" refers to a binding protein that has two binding sites.

[0094] The term "trispecific binding protein" refers to a binding protein that specifically binds to three different antigen targets.

[0095] The term "trivalent binding protein" refers to a binding protein that has three binding sites. In particular embodiments the trivalent binding protein can bind to one antigen target. In other embodiments, the trivalent binding protein can bind to two antigen targets. In other embodiments, the trivalent binding protein can bind to three antigen targets.

[0096] An "isolated" binding protein is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the binding protein, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In some embodiments, the binding protein will be purified: (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated binding proteins include the binding protein *in situ* within recombinant cells since at least one component of the binding protein's natural environment will not be present.

[0097] The terms "substantially pure" or "substantially purified" as used herein refer to a compound or species that is the predominant species present (*i.e.*, on a molar basis it is more abundant than any other individual species in the composition). In some embodiments, a substantially purified fraction is a composition wherein the species comprises at least about 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise more than about 80%, 85%, 90%, 95%, or 99% of all macromolar species present in the composition. In still other embodiments, the species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

[0098] A "neutralizing" binding protein as used herein refers to a molecule that is able to block or substantially reduce an effector function of a target antigen to which it binds. As used herein, "substantially reduce" means at least about 60%, preferably at least about 70%, more preferably at least about 75%, even more preferably at least about 80%, still more preferably at least about 85%, most preferably at least about 90% reduction of an effector function of the target antigen.

[0099] The term "epitope" includes any determinant, preferably a polypeptide determinant, capable of specifically binding to an immunoglobulin or T-cell receptor. In certain embodiments, epitope determinants include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics and/or specific charge characteristics. An epitope is a region of an antigen that is bound by an antibody or binding protein. In certain embodiments, a binding protein is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In some embodiments, a binding protein is said to specifically bind an antigen when the equilibrium dissociation constant is $\leq 10^{-8}$ M, more preferably when the equilibrium dissociation constant is $\leq 10^{-9}$ M, and most preferably when the dissociation constant is $\leq 10^{-10}$ M.

[0100] The dissociation constant (K_D) of a binding protein can be determined, for example, by surface plasmon resonance. Generally, surface plasmon resonance analysis measures real-time binding interactions between ligand (a target antigen on a biosensor matrix) and analyte (a binding protein in solution) by surface plasmon resonance (SPR) using the BIAcore system (Pharmacia Biosensor; Piscataway, NJ). Surface plasmon analysis can also be performed by immobilizing the analyte (binding protein on a biosensor matrix) and

presenting the ligand (target antigen). The term "K_D," as used herein refers to the dissociation constant of the interaction between a particular binding protein and a target antigen.

[0101] The term "specifically binds" as used herein refers to the ability of a binding protein or an antigen-binding fragment thereof to bind to an antigen containing an epitope with an Kd of at least about 1×10^{-6} M, 1×10^{-7} M, 1×10^{-8} M, 1×10^{-9} M, 1×10^{-10} M, 1×10^{-11} M, 1×10^{-12} M, or more, and/or to bind to an epitope with an affinity that is at least two-fold greater than its affinity for a nonspecific antigen.

[0102] The term "linker" as used herein refers to one or more amino acid residues inserted between immunoglobulin domains to provide sufficient mobility for the domains of the light and heavy chains to fold into cross over dual variable region immunoglobulins. A linker is inserted at the transition between variable domains or between variable and constant domains, respectively, at the sequence level. The transition between domains can be identified because the approximate size of the immunoglobulin domains are well understood. The precise location of a domain transition can be determined by locating peptide stretches that do not form secondary structural elements such as beta-sheets or alpha-helices as demonstrated by experimental data or as can be assumed by techniques of modeling or secondary structure prediction. The linkers described herein are referred to as L_1, which is located on the light chain between the C-terminus of the V_{L2} and the N-terminus of the V_{L1} domain; and L_2, which is located on the light chain between the C-terminus of the V_{L1} and the N-terminus of the C_L domain. The heavy chain linkers are known as L_3, which is located between the C-terminus of the V_{H1} and the N-terminus of the V_{H2} domain; and L_4, which is located between the C-terminus of the V_{H2} and the N-terminus of the C_{H1} domain.

[0103] The term "vector" as used herein refers to any molecule (*e.g.*, nucleic acid, plasmid, or virus) that is used to transfer coding information to a host cell. The term "vector" includes a nucleic acid molecule that is capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double-stranded DNA molecule into which additional DNA segments may be inserted. Another type of vector is a viral vector, wherein additional DNA segments may be inserted into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell and thereby are replicated along with the host genome. In addition, certain vectors are capable of directing

the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. The terms "plasmid" and "vector" may be used interchangeably herein, as a plasmid is the most commonly used form of vector. However, the disclosure is intended to include other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses, and adeno-associated viruses), which serve equivalent functions.

[0104] The phrase "recombinant host cell" (or "host cell") as used herein refers to a cell into which a recombinant expression vector has been introduced. A recombinant host cell or host cell is intended to refer not only to the particular subject cell, but also to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but such cells are still included within the scope of the term "host cell" as used herein. A wide variety of host cell expression systems can be used to express the binding proteins, including bacterial, yeast, baculoviral, and mammalian expression systems (as well as phage display expression systems). An example of a suitable bacterial expression vector is pUC19. To express a binding protein recombinantly, a host cell is transformed or transfected with one or more recombinant expression vectors carrying DNA fragments encoding the polypeptide chains of the binding protein such that the polypeptide chains are expressed in the host cell and, preferably, secreted into the medium in which the host cells are cultured, from which medium the binding protein can be recovered.

[0105] The term "transformation" as used herein refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain a new DNA. For example, a cell is transformed where it is genetically modified from its native state. Following transformation, the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, or may be maintained transiently as an episomal element without being replicated, or may replicate independently as a plasmid. A cell is considered to have been stably transformed when the DNA is replicated with the division of the cell. The term "transfection" as used herein refers to the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art. Such techniques can be used to introduce one or more exogenous DNA molecules into suitable host cells.

[0106] The term "naturally occurring" as used herein and applied to an object refers to the fact that the object can be found in nature and has not been manipulated by man. For example, a polynucleotide or polypeptide that is present in an organism (including viruses) that can be isolated from a source in nature and that has not been intentionally modified by man is naturally-occurring. Similarly, "non-naturally occurring" as used herein refers to an object that is not found in nature or that has been structurally modified or synthesized by man.

[0107] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids; unnatural amino acids and analogs such as α-, α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for the polypeptide chains of the binding proteins. Examples of unconventional amino acids include: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl-terminal direction, in accordance with standard usage and convention.

[0108] Naturally occurring residues may be divided into classes based on common side chain properties:

(1) hydrophobic: Met, Ala, Val, Leu, Ile, Phe, Trp, Tyr, Pro;

(2) polar hydrophilic: Arg, Asn, Asp, Gln, Glu, His, Lys, Ser, Thr ;

(3) aliphatic: Ala, Gly, Ile, Leu, Val, Pro;

(4) aliphatic hydrophobic: Ala, Ile, Leu, Val, Pro;

(5) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(6) acidic: Asp, Glu;

(7) basic: His, Lys, Arg;

(8) residues that influence chain orientation: Gly, Pro;

(9) aromatic: His, Trp, Tyr, Phe; and

(10) aromatic hydrophobic: Phe, Trp, Tyr.

[0109] Conservative amino acid substitutions may involve exchange of a member of one of these classes with another member of the same class. Non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class.

[0110] A skilled artisan will be able to determine suitable variants of the polypeptide chains of the binding proteins using well-known techniques. For example, one skilled in the art may identify suitable areas of a polypeptide chain that may be changed without destroying activity by targeting regions not believed to be important for activity. Alternatively, one skilled in the art can identify residues and portions of the molecules that are conserved among similar polypeptides. In addition, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[0111] The term "patient" as used herein includes human and animal subjects.

[0112] The terms "treatment" or "treat" as used herein refer to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those having a disorder as well as those prone to have the disorder or those in which the disorder is to be prevented. In particular embodiments, binding proteins can be used to treat humans with cancer, or humans susceptible to cancer, or ameliorate cancer in a human subject. The binding proteins can also be used to prevent cancer in a human patient. In particular embodiments, the cancer is multiple myeloma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, lymphoma, breast cancer such as Her2+ breast cancer, germinal center B-cell lympohoma or B-cell acute lymphoblastic leukemia, In other embodiments, the binding proteins can be used to treat humans with inflammatory disorders, or humans susceptible to inflammatory disorders, or ameliorate inflammatory disorders in a human subject.

[0113] The terms "pharmaceutical composition" or "therapeutic composition" as used herein refer to a compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

[0114] The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation materials suitable for accomplishing or enhancing the delivery of a binding protein.

[0115] The terms "effective amount" and "therapeutically effective amount" when used in reference to a pharmaceutical composition comprising one or more binding proteins refer to an amount or dosage sufficient to produce a desired therapeutic result. More specifically, a therapeutically effective amount is an amount of a binding protein sufficient to inhibit, for some period of time, one or more of the clinically defined pathological processes associated with the condition being treated. The effective amount may vary depending on the specific binding protein that is being used, and also depends on a variety of factors and conditions

related to the patient being treated and the severity of the disorder. For example, if the binding protein is to be administered *in vivo*, factors such as the age, weight, and health of the patient as well as dose response curves and toxicity data obtained in preclinical animal work would be among those factors considered. The determination of an effective amount or therapeutically effective amount of a given pharmaceutical composition is well within the ability of those skilled in the art.

[0116] One embodiment of the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a binding protein.

Trispecific and/or Trivalent Binding Proteins

[0117] In one embodiment, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) different antigen targets or target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0118] In one embodiment, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) antigen targets or target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0119] In one embodiment, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) different antigen targets or target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0120] In one embodiment, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) antigen targets or target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}\ C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}\ C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0121] In some embodiments, the first polypeptide chain and the second polypeptide chain have a cross-over orientation that forms two distinct antigen binding sites. In some embodiments, the VH1 and VL1 form a binding pair and form the first antigen binding site. In some embodiments, the VH2 and VL2 form a binding pair and form the second antigen binding site. In some embodiments, the third polypeptide and the fourth polypeptide form a third antigen binding site. In some embodiments, the VH3 and VL3 form a binding pair and form the third antigen binding site.

[0122] In one embodiment, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) antigen targets or target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{D1}\text{-}L_1\text{-}V_{D2}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{D3}\text{-}L_3\text{-}V_{D4}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}\ C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}\ C_L \qquad [IV]$$

wherein:

V_{D1} is a variable domain of heavy or light chain of a first immunoglobulin;

V_{D2} is a variable domain of heavy or light chain of a second immunoglobulin;

V_{D3} is a variable domain of heavy or light chain of a third immunoglobulin;

V_{D4} is a variable domain of heavy or light chain of a fourth immunoglobulin;

V_{H3} is an immunoglobulin heavy chain variable domain;

V_{L3} is an immunoglobulin light chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0123] In some embodiments, the binding protein of the disclosure comprises three antigen binding sites that specifically bind one, two, or three antigen targets or target proteins. In some embodiments, the binding protein binds three antigen targets. In some embodiments, the binding protein binds three different antigen targets. In some embodiments, two of the antigen binding sites bind the same antigen target. In those embodiments, the binding protein comprises the same binding domains twice, or different binding domains, and/or specifically binds different antigens or epitopes on the same antigen target. In some embodiments, three of the antigen binding sites bind the same antigen target. In those embodiments, the binding protein comprises the same binding domains three times, or different binding domains, and/or specifically binds different antigens or epitopes on the same antigen target.

[0124] In some embodiments, V_{L1}, V_{L2} and V_{L3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 2, 4, 10, 14, 18, 22 or 115; and V_{H1}, V_{H2} and V_{H3}, are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 1, 3, 9, 13, 17, 21 or 114. In other embodiments, V_{L1}, V_{L2} and V_{L3} are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 61, 63, 69, 71, 74, 76, 82, 86, 88 or 94; and V_{H1}, V_{H2} and V_{H3}, are each independently a variable domain derived from an amino acid sequence as set forth in any one of SEQ ID NOs: 60, 62, 68, 73, 75, 81, 85, 87 or 93. In other embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125; and V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122. In other embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 61, 63, 69, 71, 74, 76, 82, 86, 88 or 94; and V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining

regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 60, 62, 68, 73, 75, 81, 85, 87 or 93. In some embodiments, V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5.

[0125] In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173; and/or V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172. In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179; and/or V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137. In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167; and/or V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166. In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; and/or V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions of a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128. In some embodiments, V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions and/or a variable domain sequence shown in Tables 2-5.

[0126] In particular embodiments, the order of the V_{H1} and V_{H2} domains, and therefore the order of V_{L1} and V_{L2} domains, in the polypeptide chain of formula I or the polypeptide chain of formula II (*i.e.*, to reverse the order) are swapped.

[0127] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 3; the

third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 1; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 2.

[0128] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 1; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 2.

[0129] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 13 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 13; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is at least 95% identical to the amino acid

sequence of SEQ ID NO: 14 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 14.

[0130] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 13 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 13; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 14 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 14.

[0131] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 17 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 17; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 18 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 18.

[0132] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 10; the second polypeptide chain

comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 17 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 17; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 18 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 18.

[0133] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 21 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 21; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 22 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 22.

[0134] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 21 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of

SEQ ID NO: 21; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 22 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 22.

[0135] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 61 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 61.

[0136] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 61 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 61.

[0137] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the

amino acid sequence of SEQ ID NO: 69 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 71 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 71 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 71.

[0138] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 76 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 76 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 76; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 75 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 75 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 75; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 74.

[0139] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 82 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 82; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 81 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:81 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 81; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino

acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 74.

[0140] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 88 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 88; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 87 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 87; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 86.

[0141] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 94 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 94 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 94; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 93 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 93 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 93; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 86.

[0142] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 74.

[0143] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 86.

[0144] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62 optionally comprising

CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 74.

[0145] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 86.

[0146] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 114 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 115 or an amino acid sequence that is at least 95% identical to the amino acid

sequence of SEQ ID NO: 115 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 115.

[0147] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 114 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 115 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 115 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 115.

[0148] In other embodiments, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) different target proteins, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3}\text{ (hole)} \qquad [II]$$

and a third polypeptide chain has a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3}\text{ (knob)} \qquad [III]$$

and a fourth polypeptide chain has a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0149] In other embodiments, the binding protein of the disclosure is a trispecific and/or trivalent binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more (*e.g.*, three) target proteins, wherein a first polypeptide chain has a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain has a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3}\text{ (hole)} \qquad [II]$$

and a third polypeptide chain has a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3}\text{ (knob)} \qquad [III]$$

and a fourth polypeptide chain has a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0150] In some embodiments, the first polypeptide chain and the second polypeptide chain have a cross-over orientation that forms two distinct antigen binding sites. In some embodiments, the VH1 and VL1 form a binding pair and form the first antigen binding site. In some embodiments, the VH2 and VL2 form a binding pair and form the second antigen binding site. In some embodiments, the third polypeptide and the fourth polypeptide form a third antigen binding site. In some embodiments, the VH3 and VL3 form a binding pair and

form the third antigen binding site. In some embodiments, the second polypeptide chain and the third polypeptide chain comprise one or more modifications. In some embodiments, the second polypeptide chain and the third polypeptide chain of a binding protein are different, *e.g.*, having different C_{H1}, C_{H2}, and/or C_{H3} domain(s) (such as those including a modification described herein). In some embodiments, the first polypeptide chain and the fourth polypeptide chain comprise one or more modifications. In some embodiments, the first polypeptide chain and the fourth polypeptide chain of a binding protein are different, *e.g.*, having different C_L domains (such as those including a modification described herein, and/or lambda vs. kapp C_L domains).

[0151] In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:150, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 150, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:151, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 151. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:152, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 152, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:153, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 153. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:154, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 154, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:155, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 155. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an

amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:156, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 156, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:157, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 157. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:158, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 158, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:159, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 159. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:160, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 160, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:161, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 161. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:162, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 162, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:163, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 163. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:164, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 164, and/or a light chain variable domain comprising an amino acid

sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:165, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 165. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:166, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 166, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:167, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 167. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:168, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 168, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:169, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 169. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:170, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 170, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:171, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 171. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:172, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 172, and/or a light chain variable domain comprising an amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO:173, optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO: 173.

[0152] In some embodiments, a binding protein of the present disclosure binds to one, two, or three antigen targets with an equilibrium dissociation constant (K_D) that is less than or equal to 1μM, 500nM, 100nM, 50nM, 10nM, 5nM, or 1nM. Exemplary assays for determining K_D are known in the art. For example, in some embodiments, K_D is determined by measuring binding kinetics at between 0°C and 37°C *e.g.*, at 0°C, 4°C, 25°C, or 37°C) using the techniques described in Example 1 (*e.g.*, SPR or ELISA).

[0153] In some embodiments, a binding protein of the present disclosure activates CD4 and/or CD8 T cells *in vitro* and/or induces antibody-mediated *in vitro* cell killing of a cell expressing one or more antigen targets of one or more binding domains of the binding protein. Exemplary *in vitro* cell killing and T cell activation assays are known in the art. For example, in some embodiments, *in vitro* cell killing and/or T cell activation is assayed using the techniques described in Example 1.

[0154] In some embodiments, a binding protein of the present disclosure specifically binds to, and/or blocks signaling mediated by, one or more cytokines. Exemplary cytokine release assays are known in the art. For example, in some embodiments, cytokine release is assayed using the techniques described in Example 1.

[0155] In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds a target protein on T cells, a second antigen binding site that specifically binds a target protein on T cells, and a third antigen binding site that specifically binds an antigen target or target protein. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds a target protein on T cells, a second antigen binding site that specifically binds a target protein on T cells, and a third antigen binding site that specifically binds a tumor target protein. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds a target protein on T cells, a second antigen binding site that specifically binds a target protein on T cells, and a third antigen binding site that specifically binds a human tumor target protein. In some some embodiments, the first and second antigen binding sites specifically bind a tumor target protein for instance selected from CD3 and CD28, respectively. In some some embodiments, the first and second antigen binding sites specifically bind a tumor target protein for instance selected from CD28 and CD3, respectively. In some embodiments, the third antigen binding site specifically binds CD19, CD20, CD38, Her2, or LAMP1. Further examples of such targets and target proteins are provided *infra*.

[0156] In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds CD3, a second antigen binding site that specifically binds CD28, and a third antigen binding site that specifically binds an antigen target or target protein. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds CD28, a second antigen binding site that specifically binds CD3, and a third antigen binding site that specifically binds an antigen target or target protein. Further examples of such antigen targets or target proteins are provided *infra*. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds CD3, a second antigen binding site that specifically binds CD28, and a third antigen binding site that specifically binds a tumor target protein. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds human CD3, a second antigen binding site that specifically binds human CD28, and a third antigen binding site that specifically binds a human tumor target protein. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds CD28, a second antigen binding site that specifically binds CD3, and a third antigen binding site that specifically binds a tumor target protein. In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds human CD28, a second antigen binding site that specifically binds human CD3, and a third antigen binding site that specifically binds a human tumor target protein. In some embodiments, the third antigen binding site specifically binds CD19, CD20, CD38, Her2, or LAMP1. Further examples of such tumor antigen targets or tumor target proteins are provided *infra*.

[0157] In some embodiments, the antigen binding site that specifically binds CD3 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 152 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 153; or a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 154 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 155. Additional VH, VL, and/or CDR sequences of antibodies that specifically bind CD3 suitable for use in any of the binding proteins described herein may be found in International Publication No. WO2016/116626, which is incorporated by reference herein in its entirety. In some embodiments, the antigen binding site that specifically binds CD3 comprises six CDRs, or a heavy chain and a light chain variable domain, shown in Tables 2-5. In some embodiments, the antigen binding site that specifically binds CD3 comprises (i) three heavy chain CDRs of SEQ ID Nos. 34, 35 and 36, respectively, and three light chain

CDRs of SEQ ID Nos. 52, 53 and 54, respectively; or (ii) three heavy chain CDRs of SEQ ID Nos. 34, 35 and 36, respectively, and three light chain CDRs of SEQ ID Nos. 149, 53 and 54, respectively. In some embodiments, the antigen binding site that specifically binds CD3 is part of a polypeptide chain comprising the amino acid sequence of SEQ ID NO:3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO:3. In some embodiments, the antigen binding site that specifically binds CD3 is part of a polypeptide chain comprising the amino acid sequence of SEQ ID NO:4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO:4.

[0158] In some embodiments, the antigen binding site that specifically binds CD28 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 160 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 161; or a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 162 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 163. In some embodiments, the antigen binding site that specifically binds CD28 comprises six CDRs, or a heavy chain and a light chain variable domain, shown in Tables 2-5. In some embodiments, the antigen binding site that specifically binds CD28 comprises (i) three heavy chain CDRs of SEQ ID Nos. 28, 29 and 30, respectively, and three light chain CDRs of SEQ ID Nos. 46, 47 and 48, respectively; or (ii) three heavy chain CDRs of SEQ ID Nos. 31, 32 and 33, respectively, and three light chain CDRs of SEQ ID Nos. 49, 50 and 51, respectively. In some embodiments, the antigen binding site that specifically binds CD28 is part of a polypeptide chain comprising the amino acid sequence of SEQ ID NO:3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:3 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO:3. In some embodiments, the antigen binding site that specifically binds CD28 is part of a polypeptide chain comprising the amino acid sequence of SEQ ID NO:4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:4 optionally comprising CDRs that are 100% identical to the CDRs of the polypeptide chain of SEQ ID NO:4.

[0159] In some embodiments, a binding protein of the present disclosure comprises a first antigen binding site that specifically binds CD3, a second antigen binding site that specifically binds CD28, and a third antigen binding site that specifically binds CD38, or a

first antigen binding site that specifically binds CD28, a second antigen binding site that specifically binds CD3, and a third antigen binding site that specifically binds CD38, wherein:

- the antigen binding site specifically binding CD3 comprises (i) three heavy chain CDRs of SEQ ID Nos. 34, 35 and 36, respectively, and three light chain CDRs of SEQ ID Nos. 52, 53 and 54, respectively; or (ii) three heavy chain CDRs of SEQ ID Nos. 34, 35 and 36, respectively, and three light chain CDRs of SEQ ID Nos. 149, 53 and 54, respectively; and
- the antigen binding site specifically binding CD28 comprises (i) three heavy chain CDRs of SEQ ID Nos. 28, 29 and 30, respectively, and three light chain CDRs of SEQ ID Nos. 46, 47 and 48, respectively; or (ii) three heavy chain CDRs of SEQ ID Nos. 31, 32 and 33, respectively, and three light chain CDRs of SEQ ID Nos. 49, 50 and 51, respectively; and
- the antigen binding site specifically binding CD38 comprises (i) three heavy chain CDRs of SEQ ID Nos. 40, 41 and 42, respectively, and three light chain CDRs of SEQ ID Nos. 58, 44 and 59, respectively.

[0160] In some embodiments, the antigen binding site that specifically binds a tumor target protein comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 156 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 157; a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 158 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 159; a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 164 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 165; a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 150 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 151; or a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 166 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 167. In some embodiments, the antigen binding site that specifically binds a tumor target protein comprises six CDRs, or a heavy chain and a light chain variable domain, shown in Tables 2-5. In some embodiments, the antigen binding site that specifically binds a tumor target protein comprises six CDRs of an anti-Her2, anti-CD19, anti-CD20, anti-CD38, or anti-LAMP1 binding domain shown in Tables 2-5.

[0161] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173; and

wherein:

V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172.

[0162] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179; and

wherein:

V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137.

[0163] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \quad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167; and

wherein:

V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166.

[0164] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \quad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

V_{H3}-C_{H1}-hinge-C_{H2}-C_{H3} [III]

and a fourth polypeptide chain comprises a structure represented by the formula:

V_{L3}-C_L [IV]

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; and

wherein:

V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128.

[0165] In some embodiments, a binding protein of the present disclosure comprises an antigen binding site that specifically binds CD3, an antigen binding site that specifically binds CD28, and an antigen binding site that specifically binds an antigen target other than CD3 or CD28. In some embodiments, a binding protein of the present disclosure comprises an antigen binding site that specifically binds human CD3, an antigen binding site that specifically binds human CD28, and an antigen binding site that specifically binds a human antigen target other than CD3 or CD28. In some embodiments, a binding protein of the present disclosure comprises (a) an antigen binding site that specifically binds CD3, wherein

the antigen binding site that specifically binds CD3 comprises (i) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 152 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 153, (ii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 154 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 155, (iii) a heavy chain variable domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36, and a light chain variable domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54, or (iv) a heavy chain variable domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36, and a light chain variable domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:149, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; (b) an antigen binding site that specifically binds CD28, wherein the antigen binding site that specifically binds CD28 comprises (i) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 160 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 161, (ii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 162 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 163, (iii) a heavy chain variable domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30, and a light chain variable domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48, or (iv) a heavy chain variable domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33, and a light chain variable domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; and (c) an antigen binding site that specifically binds an antigen target other than CD3 or CD28. In some embodiments, a binding protein of the present disclosure comprises a

first polypeptide chain comprising the amino acid sequence of SEQ ID NO:4 or 10, a second polypeptide chain comprising the amino acid sequence of SEQ ID NO:3 or 9, and a third and a fourth polypeptide chain, wherein the third and fourth polypeptide chains form an antigen binding domain that specifically binds an antigen target other than CD3 or CD28. In some embodiments, the antigen binding site that specifically binds an antigen target other than CD3 or CD28 binds an antigen target selected from A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4 (also known as VTCN1), B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2 (also known as MCP-1), CCL3 (also known as MIP-1a), CCL4 (also known as MIP-1b), CCL5 (also known as RANTES), CCL7 (also known as MCP-3), CCL8 (also known as mcp-2), CCL11 (also known as eotaxin), CCL15 (also known as MIP-1d), CCL17 (also known as TARC), CCL19 (also known as MIP-3b), CCL20 (also known as MIP-3a), CCL21 (also known as MIP-2), CCL24 (also known as MPIF-2/eotaxin-2), CCL25 (also known as TECK), CCL26 (also known as eotaxin-3), CCR3, CCR4, CD19, CD20, CD23 (also known as FCER2, a receptor for IgE), CD24, CD27, CD38, CD39, CD40, CD70, CD80 (also known as B7-1), CD86 (also known as B7-2), CD122, CD137 (also known as 41BB), CD137L, CD152 (also known as CTLA4), CD154 (also known as CD40L), CD160, CD272, CD273 (also known as PDL2), CD274 (also known as PDL1), CD275 (also known as B7H2), CD276 (also known as B7H3), CD278 (also known as ICOS), CD279 (also known as PD-1), CDH1 (also known as E-cadherin), chitinase, CLEC9, CLEC91, CRTH2, CSF-1 (also known as M-CSF), CSF-2 (also known as GM-CSF), CSF-3 (also known as GCSF), CX3CL1 (also known as SCYD1), CXCL12 (also known as SDF1), CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb (also known as a receptor for IL25), IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4 (also known as b4 integrin), ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2 (also known as a receptor for IL33), STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP (also known as a co-receptor for IL7Ra), TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1 (also known as GPR5/CCXCR1).

[0166] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45.

[0167] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45.

[0168] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID

NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45.

[0169] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:37, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:38, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:39; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:55, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:56, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:57.

[0170] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2

comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:37, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:38, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:39; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:55, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:56, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:57.

[0171] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:42; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:58, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:59.

[0172] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid

sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:42; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:58, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:59.

[0173] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:126, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:127, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:128; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:140.

[0174] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2}

comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:126, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:127, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:128; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:140.

[0175] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142.

[0176] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the

amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142.

[0177] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142.

[0178] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ

ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147.

[0179] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147.

[0180] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2

comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144.

[0181] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144.

[0182] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147.

[0183] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144.

[0184] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147.

[0185] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID

NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144.

[0186] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:120, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:121, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:122; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:123, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:124, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:125.

[0187] In some embodiments, V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2

comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:120, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:121, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:122; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:123, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:124, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:125.

Antigen targets

[0188] In some embodiments, a binding protein of the present disclosure binds one or more (*e.g.*, one, two, or three) of the following antigen targets or target proteins: A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4 (also known as VTCN1), B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2 (also known as MCP-1), CCL3 (also known as MIP-1a), CCL4 (also known as MIP-1b), CCL5 (also known as RANTES), CCL7 (also known as MCP-3), CCL8 (also known as mcp-2), CCL11 (also known as eotaxin), CCL15 (also known as MIP-1d), CCL17 (also known as TARC), CCL19 (also known as MIP-3b), CCL20 (also known as MIP-3a), CCL21 (also known as MIP-2), CCL24 (also known as MPIF-2/eotaxin-2), CCL25 (also known as TECK), CCL26 (also known as eotaxin-3), CCR3, CCR4, CD3, CD19, CD20, CD23 (also known as FCER2, a receptor for IgE), CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80 (also known as B7-1), CD86 (also known as B7-2), CD122, CD137 (also known as 41BB), CD137L, CD152 (also known as CTLA4), CD154 (also known as CD40L), CD160, CD272, CD273 (also known as PDL2), CD274 (also known as PDL1), CD275 (also known as B7H2), CD276 (also known as B7H3), CD278 (also known as ICOS), CD279 (also known as PD-1), CDH1 (also known as E-cadherin), chitinase, CLEC9, CLEC91, CRTH2, CSF-1 (also known as M-CSF), CSF-2 (also known as GM-CSF), CSF-3 (also known as GCSF), CX3CL1 (also known as SCYD1), CXCL12 (also known as SDF1), CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra,

IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb (also known as a receptor for IL25), IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4 (also known as b4 integrin), ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2 (also known as a receptor for IL33), STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP (also known as a co-receptor for IL7Ra), TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1 (also known as GPR5/CCXCR1). In some embodiments, one or more of the above antigen targets are human antigen targets.

[0189] In one embodiment, the binding proteins specifically bind to one or more tumor antigen targets (*e.g.*, target proteins). In other embodiments, the binding proteins specifically bind to one or more tumor target protein and one or more target protein on a T-cell including a T cell receptor complex. These T-cell engager binding proteins are capable of recruiting T cells transiently to target cells and, at the same time, activating the cytolytic activity of the T cells. Examples of target proteins on T cells include but are not limited to CD3 and CD28, among others. Further examples of such antigen targets or target proteins are provided *supra*. In some embodiments, the trispecific binding proteins may be generated by combining the antigen binding domains of two or more monospecific antibodies (parent antibodies) into one antibody. In some embodiments, a binding protein of the present disclosure binds one or more (*e.g.*, one, two, or three) of the following antigen targets: CD3, CD19, CD20, CD28, CD38, Her2, LAMP1, IL-4, IL-13 and TNFa.

[0190] In some embodiments of the disclosure, the trivalent binding protein is capable of binding three antigen targets. In some embodiments of the disclosure, the trivalent binding protein is capable of binding three different antigen targets. In one embodiment, the binding protein is trispecific and one light chain-heavy chain pair is capable of binding two different antigen targets or epitopes and one light chain-heavy chain pair is capable of binding one antigen target or epitope. In another embodiment, the binding protein is capable of binding three tumor antigen targets. In another embodiment, the binding protein is capable of binding three different tumor antigen targets. In other embodiments, the binding protein is capable of inhibiting the function of one or more of the antigen targets.

[0191] In some embodiments, a binding protein of the present disclosure binds one or more tumor target proteins. In some embodiments, the binding protein is capable of specifically binding three epitopes on a single tumor target protein. In some embodiments, the binding protein is capable of specifically binding three different epitopes on a single

tumor target protein. In some embodiments, the binding protein is capable of binding two different epitopes on a first tumor target protein, and one epitope on a second tumor target protein. In some embodiments, the first and second tumor target proteins are different. In some embodiments, the binding protein is capable of specifically binding three different tumor target proteins.

[0192] In some embodiments, a binding protein of the present disclosure binds one or more cytokine target proteins. In some embodiments, the binding protein is capable of specifically binding three epitopes on a single cytokine target protein. In some embodiments, the binding protein is capable of specifically binding three different epitopes on a single cytokine target protein. In some embodiments, the binding protein is capable of binding two different epitopes on a first cytokine target protein, and one epitope on a second cytokine target protein. In some embodiments, the first and second cytokine target proteins are different. In some embodiments, the binding protein is capable of specifically binding three different cytokine target proteins. In some embodiments, the one or more cytokine target proteins are one or more of IL-4, IL-13 and/or TNFa. Further examples of cytokine target proteins are provided *infra*.

[0193] In some embodiments, a binding protein of the present disclosure binds one or more tumor target proteins and one or more T cell target proteins. In some embodiments, the binding protein is capable of specifically binding one tumor target protein and two different epitopes on a single T cell target protein. In some embodiments, the binding protein is capable of specifically binding one tumor target protein and two different T cell target proteins (e.g., CD28 and CD3). In some embodiments, the binding protein is capable of specifically binding one T cell target protein and two different epitopes on a single tumor target protein. In some embodiments, the binding protein is capable of specifically binding one T cell target protein and two different tumor target proteins. In some embodiments, the first and second polypeptide chains of the binding protein form two antigen binding sites that specifically target two T cell target proteins, and the third and fourth polypeptide chains of the binding protein form an antigen binding site that specifically binds a tumor target protein. In some embodiments, the first and second polypeptide chains of the binding protein form two antigen binding sites that specifically target two tumor target proteins, and the third and fourth polypeptide chains of the binding protein form an antigen binding site that specifically binds a T cell target protein. In some embodiments, the one or more tumor target proteins are one or more of CD3, CD19, CD20, CD28, CD38, Her2, LAMP1, IL-4, IL-13 and/or TNFa. In some embodiments, the one or more T cell target proteins are one or more of CD3 and

CD28. Further examples of tumor target proteins and T cell target proteins are provided *supra*.

[0194] In some embodiments, a binding protein of the present disclosure binds, independently of each other, same or different, one, two or three antigen targets or target proteins, selected from cytokine target proteins, tumor target antigens or tumor target proteins, T cell target proteins, immune checkpoint inhibitors, immune checkpoint modulators, immune checkpoint costimulatory molecules, and/or target molecules on the surface of an immune cell. In some embodiments, a binding protein of the present disclosure is trivalent but bispecific and capable of specifically binding twice to the same antigen targets or target proteins. In some embodiments, a binding protein of the present disclosure is capable of specifically binding two different epitopes on a single cytokine target proteins, tumor target antigens or tumor target proteins, T cell target proteins, immune checkpoint inhibitors, immune checkpoint modulators, immune checkpoint costimulatory molecules, and/or target molecules on the surface of an immune cell.. Further examples of such antigen targets or target proteins are provided *supra*.

[0195] The binding proteins of the disclosure may be prepared using domains or sequences obtained or derived from any human or non-human antibody, including, for example, human, murine, or humanized antibodies.

Linkers

[0196] In some embodiments, the linkers L_1, L_2, L_3 and L_4 range from no amino acids (length=0) to about 100 amino acids long, or less than 100, 50, 40, 30, 20, or 15 amino acids or less. The linkers can also be 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acids long. L_1, L_2, L_3 and L_4 in one binding protein may all have the same amino acid sequence or may all have different amino acid sequences.

[0197] Examples of suitable linkers include a single glycine (Gly) residue; a diglycine peptide (Gly-Gly); a tripeptide (Gly-Gly-Gly); a peptide with four glycine residues (Gly-Gly-Gly-Gly; SEQ ID NO: 98); a peptide with five glycine residues (Gly-Gly-Gly-Gly-Gly; SEQ ID NO: 99); a peptide with six glycine residues (Gly-Gly-Gly-Gly-Gly-Gly; SEQ ID NO: 100); a peptide with seven glycine residues (Gly-Gly-Gly-Gly-Gly-Gly-Gly; SEQ ID NO: 101); a peptide with eight glycine residues (Gly-Gly-Gly-Gly-Gly-Gly-Gly-Gly; SEQ ID NO: 102). Other combinations of amino acid residues may be used such as the peptide Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 103), the peptide Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 104), the peptide Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 105), and the peptide Gly-Gly-Ser-Gly-Ser-Ser-Gly-Ser-Gly-Gly

(SEQ ID NO:148). Other suitable linkers include a single Ser, and Val residue; the dipeptide Arg-Thr, Gln-Pro, Ser-Ser, Thr-Lys, and Ser-Leu; Thr-Lys-Gly-Pro-Ser (SEQ ID NO: 106), Thr-Val-Ala-Ala-Pro (SEQ ID NO: 107), Gln-Pro-Lys-Ala-Ala (SEQ ID NO: 108), Gln-Arg-Ile-Glu-Gly (SEQ ID NO: 109); Ala-Ser-Thr-Lys-Gly-Pro-Ser (SEQ ID NO: 110), Arg-Thr-Val-Ala-Ala-Pro-Ser (SEQ ID NO:111), Gly-Gln-Pro-Lys-Ala-Ala-Pro (SEQ ID NO:112), and His-Ile-Asp-Ser-Pro-Asn-Lys (SEQ ID NO:113). The examples listed above are not intended to limit the scope of the disclosure in any way, and linkers comprising randomly selected amino acids selected from the group consisting of valine, leucine, isoleucine, serine, threonine, lysine, arginine, histidine, aspartate, glutamate, asparagine, glutamine, glycine, and proline have been shown to be suitable in the binding proteins. For additional descriptions of linker sequences, *see, e.g.,* WO2012135345.

[0198] The identity and sequence of amino acid residues in the linker may vary depending on the type of secondary structural element necessary to achieve in the linker. For example, glycine, serine, and alanine are best for linkers having maximum flexibility. Some combination of glycine, proline, threonine, and serine are useful if a more rigid and extended linker is necessary. Any amino acid residue may be considered as a linker in combination with other amino acid residues to construct larger peptide linkers as necessary depending on the desired properties.

[0199] In some embodiments, the length of L_1 is at least twice the length of L_3. In some embodiments, the length of L_2 is at least twice the length of L_4. In some embodiments, the length of L_1 is at least twice the length of L_3, and the length of L_2 is at least twice the length of L_4. In some embodiments, L_1 is 3 to 12 amino acid residues in length, L_2 is 3 to 14 amino acid residues in length, L_3 is 1 to 8 amino acid residues in length, and L_4 is 1 to 3 amino acid residues in length. In some embodiments, L_1 is 5 to 10 amino acid residues in length, L_2 is 5 to 8 amino acid residues in length, L_3 is 1 to 5 amino acid residues in length, and L_4 is 1 to 2 amino acid residues in length. In some embodiments, L_1 is 7 amino acid residues in length, L_2 is 5 amino acid residues in length, L_3 is 1 amino acid residue in length, and L_4 is 2 amino acid residues in length. In some embodiments, L_1 is 10 amino acid residues in length, L_2 is 10 amino acid residues in length, L_3 is 0 amino acid residue in length, and L_4 is 0 amino acid residues in length. In some embodiments, L_1, L_2, L_3, and L_4 each have an independently selected length from 0 to 15 amino acids (*e.g.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids), wherein at least two of the linkers have a length of 1 to 15 amino acids (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids). In some embodiments, L_1, L_2, L_3, and L_4 are each 0 amino acids in length.

[0200] In some embodiments, L_1, L_2, L_3, and/or L_4 comprise the sequence Asp-Lys-Thr-His-Thr (SEQ ID NO: 525). In some embodiments, L_1 comprises the sequence Asp-Lys-Thr-His-Thr (SEQ ID NO: 525). In some embodiments, L_3 comprises the sequence Asp-Lys-Thr-His-Thr (SEQ ID NO: 525).

[0201] In some embodiments, L_1, L_2, L_3, and/or L_4 comprise a sequence derived from a naturally occurring sequence at the junction between an antibody variable domain and an antibody constant domain (*e.g.*, as described in WO2012/135345). For example, in some embodiments, the linker comprises a sequence found at the transition between an endogenous V_H and C_{H1} domain, or between an endogenous V_L and C_L domain (*e.g.*, kappa or lambda). In some embodiments, the linker comprises a sequence found at the transition between an endogenous human V_H and C_{H1} domain, or between an endogenous human V_L and C_L domain (*e.g.*, human kappa or lambda).

[0202] In some embodiments, L_1, L_2, L_3, and/or L_4 comprise the sequence Gly-Gln-Pro-Lys-Ala-Ala-Pro (SEQ ID NO: 175). In some embodiments, L_1 comprises the sequence Gly-Gln-Pro-Lys-Ala-Ala-Pro (SEQ ID NO: 175). In some embodiments, L_1 comprises the sequence Gly-Gln-Pro-Lys-Ala-Ala-Pro (SEQ ID NO: 175), L_2 comprises the sequence Thr-Lys-Gly-Pro-Ser-Arg (SEQ ID NO: 176), L_3 comprises the sequence Ser, and L_4 comprises the sequence Arg-Thr. In some embodiments, L_3 comprises the sequence Gly-Gln-Pro-Lys-Ala-Ala-Pro (SEQ ID NO: 175). In some embodiments, L_1 comprises the sequence Ser, L_2 comprises the sequence Arg-Thr, L_3 comprises the sequence Gly-Gln-Pro-Lys-Ala-Ala-Pro (SEQ ID NO: 175) and L_4 comprises the sequence Thr-Lys-Gly-Pro-Ser-Arg (SEQ ID NO: 176).

[0203] In some embodiments, L_1, L_2, L_3 and L_4 each independently comprise a sequence selected from $(GGGGS)_n$ (wherein n is an integer between 0 and 5; SEQ ID NO:174), GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148). In some embodiments, L_1 comprises the sequence GQPKAAP (SEQ ID NO: 175), L_2 comprises the sequence TKGPS (SEQ ID NO:106), L_3 comprises the sequence S, and L_4 comprises the sequence RT. In some embodiments, L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length. In some embodiments, L_1 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_2 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length. In some embodiments, L_1 comprises the sequence

GGGGSGGGGSGGGGS (SEQ ID NO:105), L_2 is 0 amino acids in length, L_3 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), and L_4 is 0 amino acids in length. In some embodiments, L_1 and L_2 are zero amino acids in length, and L_3 and L_4 each comprise an independently selected sequence selected from $(GGGGS)_n$ (wherein n is an integer between 0 and 5; SEQ ID NO:174), GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148). In some embodiments, L_3 and L_4 are zero amino acids in length, and L_1 and L_2 each comprise an independently selected sequence selected from $(GGGGS)_n$ (wherein n is an integer between 0 and 5; SEQ ID NO:174), GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148).

Fc regions and constant domains

[0204] In some embodiments, a binding protein of the present disclosure comprises a second polypeptide chain further comprising an Fc region linked to CH1, the Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains. In some embodiments, a binding protein of the present disclosure comprises a third polypeptide chain further comprising an Fc region linked to CH1, the Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains. In some embodiments, a binding protein of the present disclosure comprises a second polypeptide chain further comprising an Fc region linked to CH1, the Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, and a third polypeptide chain further comprising an Fc region linked to CH1, the Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains.

[0205] In some embodiments, a binding protein of the present disclosure includes one or two Fc variants. The term "Fc variant" as used herein refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage receptor, FcRn (neonatal Fc receptor). Exemplary Fc variants, and their interaction with the salvage receptor, are known in the art. Thus, the term "Fc variant" can comprise a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises regions that can be removed because they provide structural features or biological activity that are not required for the antibody-like binding proteins of the invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues, or in which one or more Fc sites or residues has be modified, that affect or are involved in: (1)

disulfide bond formation, (2) incompatibility with a selected host cell, (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC).

[0206] To improve the yields of the binding proteins, the C_{H3} domains can be altered by the "knob-into-holes" technology which is described in detail with several examples in, for example, International Publication No. WO 96/027011, Ridgway *et al.*, 1996, *Protein Eng.* 9: 617-21; and Merchant *et al.*, 1998, *Nat. Biotechnol.* 16: 677-81. Specifically, the interaction surfaces of the two C_{H3} domains are altered to increase the heterodimerisation of both heavy chains containing these two C_{H3} domains. Each of the two C_{H3} domains (of the two heavy chains) can be the "knob," while the other is the "hole." The introduction of a disulfide bridge further stabilizes the heterodimers (Merchant *et al.*, 1998; Atwell *et al.*, 1997, *J. Mol. Biol.* 270: 26-35) and increases the yield. In particular embodiments, the knob is on the second pair of polypeptides with a single variable domain. In other embodiments, the knob is on the first pair of polypeptides having the cross-over orientation. In yet other embodiments, the C_{H3} domains do not include a knob in hole.

[0207] In some embodiments, a binding protein of the present disclosure comprises a "knob" mutation on the second polypeptide chain and a "hole" mutation on the third polypeptide chain. In some embodiments, a binding protein of the present disclosure comprises a "knob" mutation on the third polypeptide chain and a "hole" mutation on the second polypeptide chain. In some embodiments, the "knob" mutation comprises substitution(s) at positions corresponding to positions 354 and/or 366 of human IgG1 or IgG4 according to EU Index. In some embodiments, the amino acid substitutions are S354C, T366W, T366Y, S354C and T366W, or S354C and T366Y. In some embodiments, the "knob" mutation comprises substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index. In some embodiments, the amino acid substitutions are S354C and T366W. In some embodiments, the "hole" mutation comprises substitution(s) at positions corresponding to positions 407 and, optionally, 349, 366, and/or 368 and of human IgG1 or IgG4 according to EU Index. In some embodiments, the amino acid substitutions are Y407V or Y407T and optionally Y349C, T366S, and/or L368A. In some embodiments, the "hole" mutation comprises substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index. In some embodiments, the amino acid substitutions are Y349C, T366S, L368A, and Y407V.

[0208] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitution(s) at positions corresponding to positions 366 and optionally 354 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are T366W or T366Y and optionally S354C; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitution(s) at positions corresponding to positions 407 and optionally 349, 366, and/or 368 and of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y407V or Y407T and optionally Y349C, T366S, and/or L368A.

[0209] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitution(s) at positions corresponding to positions 407 and optionally 349, 366, and/or 368 and of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y407V or Y407T and optionally Y349C, T366S, and/or L368A; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitution(s) at positions corresponding to positions 366 and optionally 354 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are T366W or T366Y and optionally S354C.

[0210] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitution at position corresponding to position 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitution is T366W; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitution(s) at positions corresponding to positions 366, 368, and/or 407 and of human

IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are T366S, L368A, and/or Y407V.

[0211] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitution(s) at positions corresponding to positions 366, 368, and/or 407 and of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are T366S, L368A, and/or Y407V; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitution at position corresponding to position 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitution is T366W.

[0212] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W.

In some embodiments, the first and/or second Fc regions are human IgG1 Fc regions. In some embodiments, the first and/or second Fc regions are human IgG4 Fc regions.

[0213] In some embodiments, a binding protein of the present disclosure comprises one or more mutations to improve serum half-life (See e.g., Hinton, P.R. et al. (2006) J. Immunol. 176(1):346-56). In some embodiments, the mutation comprises substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S. In some embodiments, the binding protein comprises a second polypeptide chain further comprising a first Fc region linked to CH1, the first Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, and a third polypeptide chain further comprising a second Fc region linked to CH1, the second Fc region comprising an immunoglobulin hinge region and CH2 and CH3 immunoglobulin heavy chain constant domains, wherein the first and/or second Fc regions comprise amino acid substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S. In some embodiments, a binding protein of the present disclosure comprises knob and hole mutations and one or more mutations to improve serum half-life. In some embodiments, the first and/or second Fc regions are human IgG1 Fc regions. In some embodiments, the first and/or second Fc regions are human IgG4 Fc regions.

[0214] In some embodiments, a binding protein of the present disclosure comprises one or more mutations to improve stability, *e.g.*, of the hinge region and/or dimer interface of IgG4 (*See e.g.*, Spiess, C. *et al.* (2013) *J. Biol. Chem.* 288:26583-26593). In some embodiments, the mutation comprises substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K. In some embodiments, the binding protein comprises a second polypeptide chain further comprising a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, and a third polypeptide chain further comprising a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are human IgG4 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K. In some embodiments, a binding protein of the present disclosure comprises knob and hole mutations

and one or more mutations to improve stability. In some embodiments, the first and/or second Fc regions are human IgG4 Fc regions.

[0215] In some embodiments, a binding protein of the present disclosure comprises one or more mutations to improve purification, *e.g.*, by modulating the affinity for a purification reagent. For example, it is known that heterodimeric binding proteins can be selectively purified away from their homodimeric forms if one of the two Fc regions of the heterodimeric form contains mutation(s) that reduce or eliminate binding to Protein A, because the heterodimeric form will have an intermediate affinity for Protein A-based purification than either homodimeric form and can be selectively eluted from Protein A, *e.g.*, by use of a different pH (*See e.g.*, Smith, E.J. *et al.* (2015) *Sci. Rep.* 5:17943). In some embodiments, the mutation comprises substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F. In some embodiments, the binding protein comprises a second polypeptide chain further comprising a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, and a third polypeptide chain further comprising a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; and wherein only one of the first and the second Fc regions comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F. In some embodiments, a binding protein of the present disclosure comprises knob and hole mutations and one or more mutations to improve purification. In some embodiments, the first and/or second Fc regions are human IgG1 Fc regions. In some embodiments, the first and/or second Fc regions are human IgG4 Fc regions.

[0216] In some embodiments, a binding protein of the present disclosure comprises one or more mutations to reduce effector function, *e.g.*, Fc receptor-mediated antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and/or antibody-dependent cellular cytotoxicity (ADCC). In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are

human IgG1 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A and L235A. In some embodiments, the Fc regions of the second and the third polypeptide chains are human IgG1 Fc regions, and wherein the Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A and L235A. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are human IgG1 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234, 235, 329 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A, L235A, and P329A. In some embodiments, the Fc regions of the second and the third polypeptide chains are human IgG1 Fc regions, and wherein the Fc regions each comprise amino acid substitutions at positions corresponding to positions 234, 235, and 329 of human IgG1 according to EU Index, wherein the amino acid substitutions are L234A, L235A, and P329A. In some embodiments, the mutation comprises substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A. In some embodiments, the binding protein comprises a second polypeptide chain further comprising a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, and a third polypeptide chain further comprising a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A. In some embodiments, a binding protein of the present disclosure comprises knob and hole mutations and one or more mutations to reduce effector function. In some embodiments, the first and/or second Fc regions are human IgG1 Fc regions. In some embodiments, the first and/or second Fc regions are human IgG4 Fc regions. For further

description of Fc mutations at position 329, *see, e.g.*, Shields, R.L. *et al.* (2001) *J. Biol. Chem.* 276:6591-6604 and WO1999051642.

[0217] In some embodiments, the types of mutations described *supra* can be combined in any order or combination. For example, a binding protein of the present disclosure can comprise two or more of the "knob" and "hole" mutations, the one or more mutations to improve serum half-life, the one or more mutations to improve IgG4 stability, the one or more mutations to improve purification, and/or the one or more mutations to reduce effector function described *supra*.

[0218] In certain embodiments, a binding protein of the present disclosure comprises: a first polypeptide chain that comprises a lambda C_L domain; a C_{H3} domain of a second polypeptide chain that comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; a C_{H3} domain of a third polypeptide chain that comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and a fourth polypeptide chain that comprises a kappa C_L domain. In some embodiments, the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain. In some embodiments, the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354, 366, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C, T366W, H435R, and Y436F; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the fourth polypeptide chain comprises a kappa C_L domain. In some embodiments, the first polypeptide chain comprises a kappa C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions

at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a lambda C_L domain.

[0219] In some embodiments, a binding protein of the present disclosure is purified by protein A affinity chromatography, kappa light chain affinity chromatography (*e.g.*, using a KappaSelect resin according to manufacturer's instructions; GE Healthcare), and optionally lambda light chain affinity chromatography (*e.g.*, using a LambdaFabSelect resin according to manufacturer's instructions; GE Healthcare). In some embodiments, a binding protein of the present disclosure is purified by Protein A affinity chromatography, lambda light chain affinity chromatography (*e.g.*, using a LambdaFabSelect resin according to manufacturer's instructions; GE Healthcare), and optionally kappa light chain affinity chromatography (*e.g.*, using a KappaSelect resin according to manufacturer's instructions; GE Healthcare). In some embodiments, the binding protein comprises two Fc regions, each comprising a C_{H3} domain, and only one of the C_{H3} domains comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F. In some embodiments, a binding protein of the present disclosure is purified by protein A affinity chromatography, then kappa light chain affinity chromatography (*e.g.*, using a KappaSelect resin according to manufacturer's instructions; GE Healthcare), then optionally lambda light chain affinity chromatography (*e.g.*, using a LambdaFabSelect resin according to manufacturer's instructions; GE Healthcare) in sequence. In some embodiments, a binding protein of the present disclosure is purified by Protein A affinity chromatography, then lambda light chain affinity chromatography (*e.g.*, using a LambdaFabSelect resin according to manufacturer's instructions; GE Healthcare), then optionally kappa light chain affinity chromatography (*e.g.*, using a KappaSelect resin according to manufacturer's instructions; GE Healthcare) in sequence. For example, in some embodiments, the binding protein is contacted with Protein A, eluted from Protein A under conditions suitable for isolating the binding protein away from binding proteins comprising either 0 or 2 C_{H3} domains comprising the amino acid substitutions are H435R and Y436F, contacted with a kappa light chain affinity medium (*e.g.*, as used in the KappaSelect resin; GE Healthcare), and eluted from the kappa light chain affinity medium under conditions suitable for isolating the binding protein away from binding

proteins comprising only lambda C_L domains (*e.g.*, according to manufacturer's instructions). Conditions suitable for the Protein A elution are known in the art, including without limitation a stepwise elution gradient from pH4.5-2.8. In some embodiments, Protein A or a Protein A variant useful for protein purification is employed. In some embodiments, the Protein A is attached to a substrate or resin, *e.g.*, as part of a chromatography medium. In some embodiments, after elution from the kappa light chain affinity medium, the binding protein is contacted with a lambda light chain affinity medium (*e.g.*, as used in the LambdaFabSelect resin; GE Healthcare), and eluted from the lambda light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only kappa C_L domains (*e.g.*, according to manufacturer's instructions). In some embodiments, a binding protein of the present disclosure is detected using HIC chromatography. In some embodiments, the binding protein comprises: a first polypeptide chain that comprises a lambda C_L domain; a C_{H3} domain of a second polypeptide chain that comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4according to EU Index, wherein the amino acid substitutions are S354C and T366W; a C_{H3} domain of a third polypeptide chain that comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 or IgG4according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and a fourth polypeptide chain that comprises a kappa C_L domain. In some embodiments, the binding protein is produced by a host cell. In some embodiments, the binding protein is purified from a cell culture medium or host cell extract. In some embodiments, the binding proteins are secreted by a host cell or produced and extracted from a host cell (*e.g.*, before being contacted with Protein A). In some embodiments, the binding protein is in a cell culture medium or host cell extract when contacted with Protein A. In some embodiments, the binding protein is purified away from other binding proteins, polypeptides, and/or other cellular components.

[0220] In some embodiments, CH1, CH2, CH3 and CL of the trispecific binding proteins described herein may comprise any of CH1, CH2, CH3 and CL sequences of binding proteins 1-53.

Nucleic acids

[0221] Standard recombinant DNA methodologies are used to construct the polynucleotides that encode the polypeptides which form the binding proteins, incorporate these polynucleotides into recombinant expression vectors, and introduce such vectors into host cells. *See e.g.*, Sambrook *et al.*, 2001, MOLECULAR CLONING: A LABORATORY MANUAL

(Cold Spring Harbor Laboratory Press, 3rd ed.). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications, as commonly accomplished in the art, or as described herein. Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Similarly, conventional techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of patients.

[0222] Other aspects of the present disclosure relate to isolated nucleic acid molecules comprising a nucleotide sequence encoding any of the binding proteins described herein. In some embodiments, the isolated nucleic acid is operably linked to a heterologous promoter to direct transcription of the binding protein-coding nucleic acid sequence. A promoter may refer to nucleic acid control sequences which direct transcription of a nucleic acid. A first nucleic acid sequence is operably linked to a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence of a binding protein if the promoter affects the transcription or expression of the coding sequence. Examples of promoters may include, but are not limited to, promoters obtained from the genomes of viruses (such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus, Simian Virus 40 (SV40), and the like), from heterologous eukaryotic promoters (such as the actin promoter, an immunoglobulin promoter, from heat-shock promoters, and the like), the CAG-promoter (Niwa et al., Gene 108(2):193-9, 1991), the phosphoglycerate kinase (PGK)-promoter, a tetracycline-inducible promoter (Masui et al., Nucleic Acids Res. 33:e43, 2005), the lac system, the trp system, the tac system, the trc system, major operator and promoter regions of phage lambda, the promoter for 3-phosphoglycerate kinase, the promoters of yeast acid phosphatase, and the promoter of the yeast alpha-mating factors. Polynucleotides encoding binding proteins of the present disclosure may be under the control of a constitutive promoter, an inducible promoter, or any other suitable promoter described herein or other suitable promoter that will be readily recognized by one skilled in the art.

[0223] In some embodiments, the isolated nucleic acid is incorporated into a vector. In some embodiments, the vector is an expression vector. Expression vectors may include one or more regulatory sequences operatively linked to the polynucleotide to be expressed. The term "regulatory sequence" includes promoters, enhancers and other expression control

elements (*e.g.*, polyadenylation signals). Examples of suitable enhancers may include, but are not limited to, enhancer sequences from mammalian genes (such as globin, elastase, albumin, α-fetoprotein, insulin and the like), and enhancer sequences from a eukaryotic cell virus (such as SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, adenovirus enhancers, and the like). Examples of suitable vectors may include, for example, plasmids, cosmids, episomes, transposons, and viral vectors (*e.g.*, adenoviral, vaccinia viral, Sindbis-viral, measles, herpes viral, lentiviral, retroviral, adeno-associated viral vectors, etc.). Expression vectors can be used to transfect host cells, such as, for example, bacterial cells, yeast cells, insect cells, and mammalian cells. Biologically functional viral and plasmid DNA vectors capable of expression and replication in a host are known in the art, and can be used to transfect any cell of interest.

[0224] Other aspects of the present disclosure relate to a vector system comprising one or more vectors encoding a first, second, third, and fourth polypeptide chain of any of the binding proteins described herein. In some embodiments, the vector system comprises a first vector encoding the first polypeptide chain of the binding protein, a second vector encoding the second polypeptide chain of the binding protein, a third vector encoding the third polypeptide chain of the binding protein, and a fourth vector encoding the fourth polypeptide chain of the binding protein. In some embodiments, the vector system comprises a first vector encoding the first and second polypeptide chains of the binding protein, and a second vector encoding the third and fourth polypeptide chains of the binding protein. In some embodiments, the vector system comprises a first vector encoding the first and third polypeptide chains of the binding protein, and a second vector encoding the second and fourth polypeptide chains of the binding protein. In some embodiments, the vector system comprises a first vector encoding the first and fourth polypeptide chains of the binding protein, and a second vector encoding the second and third polypeptide chains of the binding protein. In some embodiments, the vector system comprises a first vector encoding the first, second, third, and fourth polypeptide chains of the binding protein. The one or more vectors of the vector system may be any of the vectors described herein. In some embodiments, the one or more vectors are expression vectors.

Isolated host cells

[0225] Other aspects of the present disclosure relate to an isolated host cell comprising one or more isolated polynucleotides, vectors, and/or vector systems described herein. In some embodiments, the host cell is a bacterial cell (*e.g.*, an *E. coli* cell). In some

embodiments, the host cell is a yeast cell (*e.g.*, an *S. cerevisiae* cell). In some embodiments, the host cell is an insect cell. Examples of insect host cells may include, for example, Drosophila cells (*e.g.*, S2 cells), Trichoplusia ni cells (*e.g.*, High Five™ cells), and Spodoptera frugiperda cells (*e.g.*, Sf21 or Sf9 cells). In some embodiments, the host cell is a mammalian cell. Examples of mammalian host cells may include, for example, human embryonic kidney cells (*e.g.*, 293 or 293 cells subcloned for growth in suspension culture), Expi293TM cells, CHO cells, baby hamster kidney cells (*e.g.*, BHK, ATCC CCL 10), mouse sertoli cells (*e.g.*, TM4 cells), monkey kidney cells (*e.g.*, CV1 ATCC CCL 70), African green monkey kidney cells (*e.g.*, VERO-76, ATCC CRL-1587), human cervical carcinoma cells (*e.g.*, HELA, ATCC CCL 2), canine kidney cells (*e.g.*, MDCK, ATCC CCL 34), buffalo rat liver cells (*e.g.*, BRL 3A, ATCC CRL 1442), human lung cells (*e.g.*, W138, ATCC CCL 75), human liver cells (*e.g.*, Hep G2, HB 8065), mouse mammary tumor cells (*e.g.*, MMT 060562, ATCC CCL51), TRI cells, MRC 5 cells, FS4 cells, a human hepatoma line (*e.g.*, Hep G2), and myeloma cells (*e.g.*, NS0 and Sp2/0 cells).

[0226] Other aspects of the present disclosure relate to a method of producing any of the binding proteins described herein. In some embodiments, the method includes a) culturing a host cell (*e.g.*, any of the host cells described herein) comprising an isolated nucleic acid, vector, and/or vector system (*e.g.*, any of the isolated nucleic acids, vectors, and/or vector systems described herein) under conditions such that the host cell expresses the binding protein; and b) isolating the binding protein from the host cell. Methods of culturing host cells under conditions to express a protein are well known to one of ordinary skill in the art. Methods of isolating proteins from cultured host cells are well known to one of ordinary skill in the art, including, for example, by affinity chromatography (*e.g.*, two step affinity chromatography comprising protein A affinity chromatography followed by size exclusion chromatography).

Uses For Binding Proteins

[0227] The binding proteins can be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays for the detection and quantitation of one or more target antigens. The binding proteins will bind the one or more target antigens with an affinity that is appropriate for the assay method being employed.

[0228] For diagnostic applications, in certain embodiments, binding proteins can be labeled with a detectable moiety. The detectable moiety can be any one that is capable of producing, either directly or indirectly, a detectable signal. For example, the detectable

moiety can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{125}I, ^{99}Tc, ^{111}In, or ^{67}Ga; a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or an enzyme, such as alkaline phosphatase, β-galactosidase, or horseradish peroxidase.

[0229] The binding proteins are also useful for *in vivo* imaging. A binding protein labeled with a detectable moiety can be administered to an animal, preferably into the bloodstream, and the presence and location of the labeled antibody in the host assayed. The binding protein can be labeled with any moiety that is detectable in an animal, whether by nuclear magnetic resonance, radiology, or other detection means known in the art.

[0230] The binding proteins can also be used for cell activation, tumor targeting, neutralization of cytokine activities, neutralization of viral infection, combination of multiple signaling events, to treat cancer, arthritis, and/or inflammatory disorders. For example, in some embodiments, a binding protein specifically binds one, two, or three antigen targets selected from A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4 (also known as VTCN1), B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2 (also known as MCP-1), CCL3 (also known as MIP-1a), CCL4 (also known as MIP-1b), CCL5 (also known as RANTES), CCL7 (also known as MCP-3), CCL8 (also known as mcp-2), CCL11 (also known as eotaxin), CCL15 (also known as MIP-1d), CCL17 (also known as TARC), CCL19 (also known as MIP-3b), CCL20 (also known as MIP-3a), CCL21 (also known as MIP-2), CCL24 (also known as MPIF-2/eotaxin-2), CCL25 (also known as TECK), CCL26 (also known as eotaxin-3), CCR3, CCR4, CD3, CD19, CD20, CD23 (also known as FCER2, a receptor for IgE), CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80 (also known as B7-1), CD86 (also known as B7-2), CD122, CD137 (also known as 41BB), CD137L, CD152 (also known as CTLA4), CD154 (also known as CD40L), CD160, CD272, CD273 (also known as PDL2), CD274 (also known as PDL1), CD275 (also known as B7H2), CD276 (also known as B7H3), CD278 (also known as ICOS), CD279 (also known as PD-1), CDH1 (also known as E-cadherin), chitinase, CLEC9, CLEC91, CRTH2, CSF-1 (also known as M-CSF), CSF-2 (also known as GM-CSF), CSF-3 (also known as GCSF), CX3CL1 (also known as SCYD1), CXCL12 (also known as SDF1), CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb (also known as a receptor for IL25), IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4 (also known as b4 integrin), ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC

class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2 (also known as a receptor for IL33), STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP (also known as a co-receptor for IL7Ra), TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1 (also known as GPR5/CCXCR1). In some embodiments, one or more of the above antigen targets are human antigen targets.

[0231] In some embodiments, a binding protein of the present disclosure is adminstered to a patient in need thereof for the treatment or prevention of cancer. For example, in some embodiments, the binding protein comprises one antigen binding site that specifically binds a T-cell surface protein and another antigen binding site that specifically binds a tumor target protein (*e.g.*, two antigen binding sites that specifically bind T-cell surface proteins and one antigen binding site that specifically binds a tumor target protein, or two antigen binding sites that specifically bind tumor target proteins and one antigen binding site that specifically binds a T-cell surface protein). In certain embodiments, the binding protein comprises an antigen binding site that specifically binds CD3, an antigen binding site that specifically binds CD28, and an antigen binding site that specifically binds a tumor target protein selected from CD19, CD20, CD38, Her2, and LAMP1. In some embodiments, the binding protein is co-administered with a chemotherapeutic agent. In some embodiments, the patient is a human.

[0232] In some embodiments, a binding protein of the present disclosure is adminstered to a patient in need thereof for the treatment or prevention of an inflammatory disease or disorder. In some embodiments, the binding protein comprises three antigen binding sites that each specifically bind a cytokine target protein selected from IL-4, IL-13 and TNFa. In some embodiments, the binding protein is co-administered with an anti-inflammatory agent. In some embodiments, the patient is a human.

[0233] The disclosure also relates to a kit comprising a binding protein and other reagents useful for detecting target antigen levels in biological samples. Such reagents can include a detectable label, blocking serum, positive and negative control samples, and detection reagents. In some embodiments, the kit comprises a composition comprising any binding protein, polynucleotide, vector, vector system, and/or host cell described herein. In some embodiments, the kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing a condition and may have a

sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). In some embodiments, the label or package insert indicates that the composition is used for preventing, diagnosing, and/or treating the condition of choice. Alternatively, or additionally, the article of manufacture or kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Binding Protein Therapeutic Compositions and Administration Thereof

[0234] Therapeutic or pharmaceutical compositions comprising binding proteins are within the scope of the disclosure. Such therapeutic or pharmaceutical compositions can comprise a therapeutically effective amount of a binding protein, or binding protein-drug conjugate, in admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration.

[0235] Acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

[0236] The pharmaceutical composition can contain formulation materials for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption, or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, or lysine), antimicrobials, antioxidants (such as ascorbic acid, sodium sulfite, or sodium hydrogen-sulfite), buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, or other organic acids), bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)), complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin, or hydroxypropyl-beta-cyclodextrin), fillers, monosaccharides, disaccharides, and other carbohydrates (such as glucose, mannose, or dextrins), proteins (such as serum albumin, gelatin, or immunoglobulins), coloring, flavoring and diluting agents, emulsifying agents, hydrophilic polymers (such as polyvinylpyrrolidone), low molecular weight polypeptides, salt-forming counterions (such as sodium), preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid, or hydrogen peroxide), solvents (such as glycerin, propylene glycol, or polyethylene glycol), sugar alcohols (such as mannitol or sorbitol), suspending

agents, surfactants or wetting agents (such as pluronics; PEG; sorbitan esters; polysorbates such as polysorbate 20 or polysorbate 80; triton; tromethamine; lecithin; cholesterol or tyloxapal), stability enhancing agents (such as sucrose or sorbitol), tonicity enhancing agents (such as alkali metal halides – preferably sodium or potassium chloride – or mannitol sorbitol), delivery vehicles, diluents, excipients and/or pharmaceutical adjuvants (*see, e.g.,* REMINGTON'S PHARMACEUTICAL SCIENCES (18th Ed., A.R. Gennaro, ed., Mack Publishing Company 1990), and subsequent editions of the same, incorporated herein by reference for any purpose).

[0237] The optimal pharmaceutical composition will be determined by a skilled artisan depending upon, for example, the intended route of administration, delivery format, and desired dosage. Such compositions can influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the binding protein.

[0238] The primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier for injection can be water, physiological saline solution, or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Other exemplary pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which can further include sorbitol or a suitable substitute. In one embodiment of the disclosure, binding protein compositions can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents in the form of a lyophilized cake or an aqueous solution. Further, the binding protein can be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0239] The pharmaceutical compositions of the disclosure can be selected for parenteral delivery or subcutaneous. Alternatively, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the skill of the art.

[0240] The formulation components are present in concentrations that are acceptable to the site of administration. For example, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0241] When parenteral administration is contemplated, the therapeutic compositions for use can be in the form of a pyrogen-free, parenterally acceptable, aqueous solution

comprising the desired binding protein in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which a binding protein is formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which can then be delivered via a depot injection. Hyaluronic acid can also be used, and this can have the effect of promoting sustained duration in the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

[0242] In one embodiment, a pharmaceutical composition can be formulated for inhalation. For example, a binding protein can be formulated as a dry powder for inhalation. Binding protein inhalation solutions can also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions can be nebulized.

[0243] It is also contemplated that certain formulations can be administered orally. In one embodiment of the disclosure, binding proteins that are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the binding protein. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

[0244] Another pharmaceutical composition can involve an effective quantity of binding proteins in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0245] Additional pharmaceutical compositions of the disclosure will be evident to those skilled in the art, including formulations involving binding proteins in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous

beads and depot injections, are also known to those skilled in the art. Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, *e.g.* films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides, copolymers of L-glutamic acid and gamma ethyl-L-glutamate, poly(2-hydroxyethyl-methacrylate), ethylene vinyl acetate, or poly-D(-)-3-hydroxybutyric acid. Sustained-release compositions can also include liposomes, which can be prepared by any of several methods known in the art.

[0246] Pharmaceutical compositions to be used for *in vivo* administration typically must be sterile. This can be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method can be conducted either prior to, or following, lyophilization and reconstitution. The composition for parenteral administration can be stored in lyophilized form or in a solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0247] Once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. Such formulations can be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) requiring reconstitution prior to administration.

[0248] The disclosure also encompasses kits for producing a single-dose administration unit. The kits can each contain both a first container having a dried protein and a second container having an aqueous formulation. Also included within the scope of this disclosure are kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes).

[0249] The effective amount of a binding protein pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the binding protein is being used, the route of administration, and the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

[0250] Dosing frequency will depend upon the pharmacokinetic parameters of the binding protein in the formulation being used. Typically, a clinician will administer the

composition until a dosage is reached that achieves the desired effect. The composition can therefore be administered as a single dose, as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages can be ascertained through use of appropriate dose-response data.

[0251] The route of administration of the pharmaceutical composition is in accord with known methods, *e.g.*, orally; through injection by intravenous, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, intraportal, or intralesional routes; by sustained release systems; or by implantation devices. Where desired, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

[0252] The composition can also be administered locally via implantation of a membrane, sponge, or other appropriate material onto which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

[0253] In some embodiments, the present disclosure relates to a method of preventing and/or treating a proliferative disease or disorder (*e.g.*, cancer). In some embodiments, the method comprises administering to a patient a therapeutically effective amount of at least one of the binding proteins described herein. In some embodiments, the patient is a human. In some embodiments, the at least one binding protein is administered in combination with one or more anti-cancer therapies (*e.g.*, any anti-cancer therapy known in the art). In some embodiments, the at least one binding protein is administered before the one or more anti-cancer therapies. In some embodiments, the at least one binding protein is administered concurrently with the one or more anti-cancer therapies. In some embodiments, the at least one binding protein is administered after the one or more anti-retroviral therapies.

[0254] In some embodiments, the present disclosure relates to a method of preventing and/or treating an inflammatory disease or disorder (*e.g.*, cancer). In some embodiments, the method comprises administering to a patient a therapeutically effective amount of at least one of the binding proteins described herein. In some embodiments, the patient is a human. In some embodiments, the at least one binding protein is administered in combination with one or more anti-inflammatory therapies (*e.g.*, any anti-inflammatory therapy known in the art).

In some embodiments, the at least one binding protein is administered before the one or more anti-inflammatory therapies. In some embodiments, the at least one binding protein is administered concurrently with the one or more anti-inflammatory therapies. In some embodiments, the at least one binding protein is administered after the one or more anti-inflammatory therapies.

[0255] Without limiting the present disclosure, a number of embodiments of the present disclosure are described below for purpose of illustration.

[0256] Item 1: A binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0257] Item 2: A binding protein comprising four polypeptide chains that form three antigen binding sites that specifically bind one or more target proteins, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \quad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

and wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair.

[0258] Item 3: The binding protein of item 1, wherein the second and/or the third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains.

[0259] Item 4: The binding protein of any one of items 1-3, wherein at least one of L_1, L_2, L_3 or L_4 is independently 0 amino acids in length.

[0260] Item 5: The binding protein of any one of items 1-3, wherein L_1, L_2, L_3 or L_4 are each independently at least one amino acid in length.

[0261] Item 6: The binding protein of any one of items 1-3 and 5, wherein (a) L_1, L_2, L_3 and L_4 each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148); or (b) L_1, L_2, L_3 and L_4 each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104),

GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148).

[0262] Item 7: The binding protein of any one of items 1-5, wherein

(a) L_1 comprises the sequence GQPKAAP (SEQ ID NO: 175), L_2 comprises the sequence TKGPS (SEQ ID NO:106), L_3 comprises the sequence S, and L_4 comprises the sequence RT;

(b) L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length;

(c) L_1 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_2 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; or

(d) L_1 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), L_2 is 0 amino acids in length, L_3 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), and L_4 is 0 amino acids in length.

[0263] Item 8: The binding protein of any one of items 1-7, wherein the binding protein is trispecific and capable of specifically binding three different antigen targets.

[0264] Item 9: The binding protein of any one of items 1-8, wherein the binding protein specifically binds three target proteins that correspond to two target proteins on T cells and to one tumor target protein.

[0265] Item 10: The binding protein of item 9, wherein one of said target proteins on T cells is CD3.

[0266] Item 11: The binding protein of item 9 or item 10, wherein one of said target proteins on T cells is CD28.

[0267] Item 12: The binding protein of any one of items 9-11, wherein said tumor target protein is CD38.

[0268] Item 13: The binding protein of any one of items 1-8, wherein the binding protein specifically binds three target proteins that correspond to two target proteins on T cells and to one target protein selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276,

CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0269] Item 14: The binding protein of any one of items 1-13, wherein the binding protein is capable of inhibiting the function of one or more target proteins.

[0270] Item 15: The binding protein of item 14, wherein the one or more target proteins are selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0271] Item 16: A binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167; or

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; and

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166; or

(b) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128.

[0272] Item 17: A binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \quad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \quad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:151, 153, 155, 157, 159, 161, 163, 165, and 167; or

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 43-59, 123-125, 138-140, and 149; and

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:150, 152, 154, 156, 158, 160, 162, 164, and 166; or

(b) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence as set forth in any one of SEQ ID NOs: 25-42, 120-122, and 126-128.

[0273] Item 18: The binding protein of item 16, wherein the second and/or the third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains.

[0274] Item 19: The binding protein of any one of items 16-18, wherein at least one of L_1, L_2, L_3 or L_4, is independently 0 amino acids in length.

[0275] Item 20: The binding protein of any one of items 16-18, wherein L_1, L_2, L_3 or L_4 are each independently at least one amino acid in length.

[0276] Item 21: The binding protein of any one of items 16-18 and 20, wherein (a) L_1, L_2, L_3 and L_4 each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148); or (b) L_1, L_2, L_3 and L_4 each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148).

[0277] Item 22: The binding protein of any one of items 16-20, wherein:

(a) L_1 comprises the sequence GQPKAAP (SEQ ID NO: 175), L_2 comprises the sequence TKGPS (SEQ ID NO:106), L_3 comprises the sequence S, and L_4 comprises the sequence RT;

(b) L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length;

(c) L_1 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_2 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; or

(d) L_1 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), L_2 is 0 amino acids in length, L_3 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), and L_4 is 0 amino acids in length.

[0278] Item 23: The binding protein of any one of items 16-22, wherein:

(a) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino

acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45;

(b) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:25, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:26, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:27; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:43, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:45;

(c) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID

NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:37, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:38, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:39; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:55, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:56, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:57;

(d) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:37, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:38, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:39; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:55, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:56, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:57;

(e) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1

comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:42; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:58, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:59;

(f) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:42; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:58, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:44, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:59;

(g) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of

SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:126, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:127, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:128; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:140;

(h) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:126, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:127, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:128; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:140;

(i) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:28, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:29, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:120, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:121, and a CDR-

H3 comprising the amino acid sequence of SEQ ID NO:122; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:123, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:124, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:125; or

(j) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:33; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:49, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:50, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:51; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:34, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:35, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:36; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:52, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:53, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:54; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:120, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:121, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:122; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:123, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:124, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:125.

[0279] Item 24: A binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173; or

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179;

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172; or

(b) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137.

[0280] Item 25: A binding protein comprising four polypeptide chains that form three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair;

wherein:

(a) V_{L1}, V_{L2} and V_{L3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:169, 171, and 173; or

(b) V_{L1}, V_{L2} and V_{L3} each independently comprise light chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 141-147, 178, and 179;

wherein:

(a) V_{H1}, V_{H2}, and V_{H3} each independently comprise a variable domain sequence as set forth in any one of SEQ ID NOs:168, 170, and 172; or

(b) V_{H1}, V_{H2} and V_{H3} each independently comprise heavy chain complementarity determining regions comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129-137.

[0281] Item 26: The binding protein of item 24, wherein the second and/or the third polypeptide chain further comprises an Fc region linked to C_{H1}, the Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains.

[0282] Item 27: The binding protein of any one of items 24-26, wherein at least one of L_1, L_2, L_3 and L_4, is independently 0 amino acids in length.

[0283] Item 28: The binding protein of any one of items 24-26, wherein L_1, L_2, L_3 and L_4 are each independently at least one amino acid in length.

[0284] Item 29: The binding protein of any one of items 24-26 and 28, wherein (a) L_1, L_2, L_3 and L_4 each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP

(SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148); or (b) L_1, L_2, L_3 and L_4 each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148).

[0285] Item 30: The binding protein of any one of items 24-28, wherein:

(a) L_1 comprises the sequence GQPKAAP (SEQ ID NO: 175), L_2 comprises the sequence TKGPS (SEQ ID NO:106), L_3 comprises the sequence S, and L_4 comprises the sequence RT;

(b) L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length;

(c) L_1 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_2 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; or

(d) L_1 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), L_2 is 0 amino acids in length, L_3 comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:105), and L_4 is 0 amino acids in length.

[0286] Item 31: The binding protein of any one of items 24-30, wherein:

(a) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142;

(b) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:47, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142;

(c) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147;

(d) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-

H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147;

(e) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144;

(f) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:129, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:130, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:131; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:141, a CDR-L2 comprising the amino

acid sequence of SEQ ID NO:178, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:142; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144;

(g) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147;

(h) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ

ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144;

(i) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; or

(j) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:137; V_{L2} comprises a CDR-L1

comprising the amino acid sequence of SEQ ID NO:145, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:146, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:147; V_{H3} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO:132, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:133, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:134; and V_{L3} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO:143, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:179, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:144.

[0287] Item 32: The binding protein of any one of items 1, 3-16, 18-24, and 26-31, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V.

[0288] Item 33: The binding protein of any one of items 1, 3-16, 18-24, and 26-31, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the first Fc region comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains, wherein the second Fc region comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W.

[0289] Item 34: The binding protein of any one of items 1, 3-16, 18-24, and 26-33, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin

heavy chain constant domains, and wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions comprise amino acid substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S.

[0290] Item 35: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, and 27-31, wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V.

[0291] Item 36: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, and 27-31, wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W.

[0292] Item 37: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, 35, and 36, wherein the C_{H3} domains of the second and the third polypeptide chains both comprise amino acid substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S

[0293] Item 38: The binding protein of any one of items 1, 3-16, 18-24, and 26-34, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are human IgG1 or IgG4 Fc regions; and wherein only one of the first and the second Fc regions comprises amino acid substitutions at positions corresponding to

positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F.

[0294] Item 39: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, and 35-37, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG1 or IgG4 C_{H3} domains, and wherein only one of the C_{H3} domains comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F.

[0295] Item 40: The binding protein of any one of items 1, 3-16, 18-24, 26-34, and 38, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are human IgG4 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K.

[0296] Item 41: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, 35-37, and 39, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG4 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K.

[0297] Item 42: The binding protein of any one of items 1, 3-16, 18-24, 26-34, 38, and 40, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are human IgG4 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A.

[0298] Item 43: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, 35-37, 39, and 41, wherein the C_{H3} domains of the second and the third polypeptide chains

are human IgG4 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A.

[0299] Item 44: The binding protein of any one of items 1, 3-16, 18-24, 26-34, 38, and 40, wherein the second polypeptide chain further comprises a first Fc region linked to C_{H1}, the first Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the third polypeptide chain further comprises a second Fc region linked to C_{H1}, the second Fc region comprising an immunoglobulin hinge region and C_{H2} and C_{H3} immunoglobulin heavy chain constant domains; wherein the first and second Fc regions are human IgG1 Fc regions; and wherein the first and the second Fc regions each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are L234A and L235A.

[0300] Item 45: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, 35-37, 39, and 41, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG1 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are L234A and L235A.

[0301] Item 46: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, 35-37, 39, 41, 43, and 45, wherein VH1 and VL1 form a first antigen binding site that specifically binds human CD3, wherein VH2 and VL2 form a second antigen binding site that specifically binds human CD28, and wherein VH3 and VL3 form a third antigen binding site that specifically binds a human tumor target protein.

[0302] Item 47: The binding protein of any one of items 2, 4-15, 17, 19-23, 25, 27-31, 35-37, 39, 41, 43, and 45, wherein VH1 and VL1 form a first antigen binding site that specifically binds human CD28, wherein VH2 and VL2 form a second antigen binding site that specifically binds human CD3, and wherein VH3 and VL3 form a third antigen binding site that specifically binds a human tumor target protein.

[0303] Item 48: The binding protein of item 46 or item 47, wherein the third antigen binding site specifically binds a human tumor target protein selected from the group consisting of CD19, CD20, CD38, Her2, and LAMP1.

[0304] Item 49: The binding protein of any one of items 46-48, wherein the antigen binding site that specifically binds CD3 comprises:

(a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 152 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 153; or

(b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 154 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 155.

[0305] Item 50: The binding protein of any one of items 46-49, wherein the antigen binding site that specifically binds CD28 comprises:

(a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 160 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 161; or

(b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 162 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 163.

[0306] Item 51: The binding protein of any one of items 46-50, wherein the antigen binding site that specifically binds a tumor target protein comprises:

(a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 156 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 157;

(b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 158 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 159;

(c) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 164 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 165;

(d) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 150 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 151; or

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 166 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 167.

[0307] Item 52: The binding protein of any one of items 2, 17, 35-37, 39, 41, 43, and 45, wherein:

(a)VH1 and VL1 form a first antigen binding site that specifically binds human TNFa, VH2 and VL2 form a second antigen binding site that specifically binds human IL13, and VH3 and VL3 form a third antigen binding site that specifically binds human IL4;

(b) VH1 and VL1 form a first antigen binding site that specifically binds human TNFa, VH2 and VL2 form a second antigen binding site that specifically binds human IL4, and VH3 and VL3 form a third antigen binding site that specifically binds human IL13;

(c) VH1 and VL1 form a first antigen binding site that specifically binds human IL4, VH2 and VL2 form a second antigen binding site that specifically binds human TNFa, and VH3 and VL3 form a third antigen binding site that specifically binds human IL13;

(d) VH1 and VL1 form a first antigen binding site that specifically binds human IL4, VH2 and VL2 form a second antigen binding site that specifically binds human IL13, and VH3 and VL3 form a third antigen binding site that specifically binds human TNFa;

(e) VH1 and VL1 form a first antigen binding site that specifically binds human IL13, VH2 and VL2 form a second antigen binding site that specifically binds human IL4, and VH3 and VL3 form a third antigen binding site that specifically binds human TNFa; or

(f) VH1 and VL1 form a first antigen binding site that specifically binds human IL13, VH2 and VL2 form a second antigen binding site that specifically binds human TNFa, and VH3 and VL3 form a third antigen binding site that specifically binds human IL4.

[0308] Item 53: The binding protein of item 52, wherein the antigen binding site that specifically binds human TNFa comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:168 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:169.

[0309] Item 54: The binding protein of item 52 or item 53, wherein the antigen binding site that specifically binds human IL4 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:170 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:171.

[0310] Item 55: The binding protein of any one of items 52-54, wherein the antigen binding site that specifically binds human IL13 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:173.

[0311] Item 56: The binding protein of any one of items 1-55, wherein:

(a) the C_L domain of the first polypeptide chain is a human kappa C_L domain, and the C_L domain of the fourth polypeptide chain is a human lambda C_L domain; or

(b) the C_L domain of the first polypeptide chain is a human lambda C_L domain, and the C_L domain of the fourth polypeptide chain is a human kappa C_L domain.

[0312] Item 57: The binding protein of any one of items 2, 17, 25, 35-37, 39, 41, and 43-55, wherein the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain.

[0313] Item 58: A binding protein comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3

or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 13; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 14;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 13; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 14;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 17; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 18;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 17; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 18;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 21; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 22;

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 21; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 22;

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 61;

(j) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ

ID NO: 61 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 61;

(k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 71 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 71;

(l) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 76 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 76; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 75 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 75; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 82; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 81 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:81; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(n) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:88; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 87; the third polypeptide chain comprises the amino acid sequence of SEQ ID

NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(o) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 94 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 94; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 93 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 93; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(q) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 69; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 68; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(r) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID

NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 73; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 74;

(s) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 63; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 62; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 85; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 86;

(t) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 115 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 115; or

(u) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 10; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 9; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO: 115 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 115.

[0314] Item 59: An isolated nucleic acid molecule comprising a nucleotide sequence encoding the binding protein of any one of items 1-58.

[0315] Item 60: An expression vector comprising the nucleic acid molecule of item 59.

[0316] Item 61: An isolated host cell comprising the nucleic acid molecule of item 59.

[0317] Item 62: An isolated host cell comprising the expression vector of item 60.

[0318] Item 63: The isolated host cell of item 61 or item 62, wherein the host cell is a mammalian cell or an insect cell.

[0319] Item 64: A pharmaceutical composition comprising the binding protein of any one of items 1-58 and a pharmaceutically acceptable carrier.

[0320] Item 65: A method of preventing and/or treating cancer in a patient comprising administering to the patient a therapeutically effective amount of at least one binding protein of any one of items 1-23 and 32-58 or the pharmaceutical composition of item 64.

[0321] Item 66: The method of item 65, wherein the binding protein comprises one antigen binding site that specifically binds a T-cell surface protein and another antigen binding site that specifically binds a tumor target protein.

[0322] Item 67: The method of item 66, wherein the binding protein comprises a first antigen binding site that specifically binds CD3, a second antigen binding site that specifically binds CD28, and a third antigen binding site that specifically binds a tumor target protein selected from the group consisting of CD19, CD20, CD38, Her2, and LAMP1.

[0323] Item 68: The method of any one of items 65-67, wherein the at least one binding protein is co-administered with a chemotherapeutic agent.

[0324] Item 69: A method of preventing and/or treating an inflammatory disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of at least one binding protein of any one of items 1-15, 24-45, and 52-58 or the pharmaceutical composition of item 64.

[0325] Item 70: The method of item 69, wherein the binding protein comprises three antigen binding sites that each specifically bind a cytokine target protein selected from the group consisting of IL-4, IL-13 and TNFa.

[0326] Item 71: The method of item 69 or item 70, wherein the at least one binding protein is co-administered with an anti-inflammatory agent.

[0327] Item 72: The method of any one of items 65-71, wherein the patient is a human.

[0328] Item 73: The method of item 65 or item 69, wherein the binding protein is capable of inhibiting the function of one or more target proteins selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC,

B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, S152, SISP1, SLC, SPG64, ST2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0329] Item 74: The binding protein of any one of items 1-23 and 32-58 or the composition of item 64 for use in preventing and/or treating cancer in a patient.

[0330] Item 75: The binding protein for use or the composition for use of item 74, wherein the binding protein comprises one antigen binding site that specifically binds a T-cell surface protein and another antigen binding site that specifically binds a tumor target protein.

[0331] Item 76: The binding protein for use or the composition for use of item 75, wherein the binding protein comprises a first antigen binding site that specifically binds CD3, a second antigen binding site that specifically binds CD28, and a third antigen binding site that specifically binds a tumor target protein selected from the group consisting of CD19, CD20, CD38, Her2, and LAMP1.

[0332] Item 77: The binding protein for use or the composition for use of any one of items 74-76, wherein the binding protein is co-administered with a chemotherapeutic agent.

[0333] Item 78: The binding protein of any one of items 1-15, 24-45, and 52-58 or the pharmaceutical composition of item 64 for use in preventing and/or treating an inflammatory disease or disorder in a patient.

[0334] Item 79: The binding protein for use or the composition for use of item 78, wherein the binding protein comprises three antigen binding sites that each specifically bind a cytokine target protein selected from the group consisting of IL-4, IL-13 and TNFa.

[0335] Item 80: The binding protein for use or the composition for use of item 78 or item 79, wherein the binding protein is co-administered with an anti-inflammatory agent.

[0336] Item 81: The binding protein for use or the composition for use of any one of items 74-80, wherein the patient is a human.

[0337] Item 82: The binding protein for use or the composition for use of item 74 or item 78, wherein the binding protein is capable of inhibiting the function of one or more target proteins selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

[0338] Item 83: A method of purifying a binding protein produced by a host cell, comprising:

(a) producing the binding protein of any one of items 2, 17, 25, 35-37, 41, 43, 45, and 46-55 in a host cell, wherein only one of the C_{H3} domain of the second polypeptide chain and the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F;

(b) contacting the binding protein produced in (a) with Protein A; and

(c) eluting the binding protein from Protein A under conditions suitable for isolating the binding protein away from binding proteins comprising either 0 or 2 C_{H3} domains

comprising the amino acid substitutions are H435R and Y436F, thereby purifying the binding protein.

[0339] Item 84: The method of item 83, wherein the C_L domain of the first polypeptide chain is a human kappa C_L domain, and the C_L domain of the fourth polypeptide chain is a human lambda C_L domain; or the C_L domain of the first polypeptide chain is a human lambda C_L domain, and the C_L domain of the fourth polypeptide chain is a human kappa C_L domain, and the method further comprises:

(d) contacting the binding protein eluted in (c) with a kappa light chain affinity medium; and

(e) eluting the binding protein from the kappa light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only lambda C_L domains.

[0340] Item 85: The method of item 84, further comprising, after (e):

(f) contacting the binding protein eluted in (e) with a lambda light chain affinity medium; and

(g) eluting the binding protein from the lambda light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only kappa C_L domains.

[0341] Item 86: The method of item 83, wherein the C_L domain of the first polypeptide chain is a human kappa C_L domain, and the C_L domain of the fourth polypeptide chain is a human lambda C_L domain; or the C_L domain of the first polypeptide chain is a human lambda C_L domain, and the C_L domain of the fourth polypeptide chain is a human kappa C_L domain, and the method further comprises:

(d) contacting the binding protein eluted in (c) with a lambda light chain affinity medium; and

(e) eluting the binding protein from the lambda light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only kappa C_L domains.

[0342] Item 87: The method of item 86, further comprising, after (e):

(f) contacting the binding protein eluted in (e) with a kappa light chain affinity medium; and

(g) eluting the binding protein from the kappa light chain affinity medium under conditions suitable for isolating the binding protein away from binding proteins comprising only lambda C_L domains.

[0343] Item 88: The method of any one of items 83-87, wherein the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain.

[0344] Item 89: The method of any one of items 83-88, wherein the binding protein is detected in one or more of (c) and (e) using hydrophobic interaction chromatography (HIC).

[0345] Item 90: The method of any one of items 83-89, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG1 or IgG4 C_{H3} domains.

EXAMPLES

[0346] The Examples that follow are illustrative of specific embodiments of the disclosure, and various uses thereof. They are set forth for explanatory purposes only, and should not be construed as limiting the scope of the invention in any way.

Example 1: Materials and Methods

[0347] The following materials and methods were used for the experiments described in Examples 2-5.

Trispecific antibody design

[0348] A schematic illustration of the general trispecific antibody design is illustrated in **FIGS. 1A-1C**. Individual trispecific antibodies were designed based on 5 parameters: 1) Selection of antibody binding sites; 2) Consideration of the position of each binding site; 3) Choice of linkers for the bispecific binding arm (*i.e.*, heavy chain/light chain B in **FIG. 1C**); 4). "Knob" and "Hole" mutation integration into respective halves of the antibody; 5) Choice of Fc isotype (IgG1 or IgG4). After assembly of the amino acid sequences for each trispecific molecule, four genes for each trispecific Ab were synthesized using human preferred codons (CambrY Applied Biosciences, Cambridge, MA, USA), and cloned into a eukaryotic expression vector.

Production and purification of trispecific antibodies

[0349] Trispecific antibodies were produced by transient transfection of 4 expression plasmids into Expi293 cells using ExpiFectamine™ 293 Transfection Kit (Thermo Fisher Scientific) according to manufacturer's protocol. Briefly, 25% (w/w) of each plasmid was diluted into Opti-MEM, mixed with pre-diluted ExpiFectamine reagent for 20-30 minutes at room temperature (RT), and added into Expi293 cells ($2.5x10^6$ cells/ml). An optimization of transfection to determine the best ratio of plasmids was often used in order to produce the trispecific antibody with good yield and purity.

[0350] 4-5 days post transfection, the supernatant from transfected cells was collected and filtered through 0.45 μm filter unit (Nalgene). The trispecific antibody in the supernatant was purified using a 3-step procedure. First, protein A affinity purification was used, and the bound Ab was eluted using "IgG Elution Buffer"(Thermo Fisher Scientific). Second, product was dialyzed against PBS (pH7.4) overnight with 2 changes of PBS buffer. Any precipitate was cleared by filtration through 0.45 μm filter unit (Nalgene) before next step. Third, size-exclusion chromatography (SEC) purification (Hiload 16/600 Superdex 200pg, or Hiload 26/600 Superdex 200pg, GE Healthcare) was used to remove aggregates and different species in the prep. The fractions were analyzed on reduced and non-reduced SDS-PAGE to identify the fractions that contained the monomeric trispecific antibody before combining them. The purified antibody can be aliquoted and stored at -80°C long term.

ELISA assays

[0351] The binding properties of the purified antibodies were analyzed either using ELISA or SPR methods. For ELISA, corresponding antigens for each binding site in the trispecific antibody were used to coat a 96-well Immuno Plate (Nunc 439454, Thermo Fisher Scientific) overnight at 4°C using 2 μg/ml each antigen in PBS(pH7.4). The coated plate was blocked using 5% skim milk+2% BSA in PBS for one hour at RT, followed by washing with PBS+0.25% Tween 20 three times (Aqua Max 400, Molecular Devices). Serial dilution of antibodies (trispecific and control Abs) were prepared and added onto the ELISA plates (100 μl/well in duplicate), incubated at RT for one hour, followed by washing 5 times with PBS+0.25% Tween 20.

[0352] After washing, the HRP conjugated secondary anti-human Fab (1:5000, Cat. No. 109-035-097, Jackson ImmunoResearch Inc) was added to each well and incubated at RT for 30 minutes. After washing 5 times with PBS+0.25% Tween 20, 100 μl of TMB Microwell Peroxidase Substrate (KPL, Gaithersburg, MD, USA) was added to each well. The reaction

was terminated by adding 50 µl 1M H_2SO_4 , and OD_{450} was measured using SpectraMax M5 (Molecular Devices) and analyzed using SoftMax Pro6.3 software (Molecular Devices). The final data was transferred to GraphPad Prism software (GraphPad Software, CA, USA), and plotted as shown. EC50 was calculated using the same software.

SPR assays

[0353] Two pairs of heavy and light chains were selected for full kinetic analysis. Kinetic characterization of purified antibodies was performed using surface plasmon resonance (SPR) technology on a BIACORE 3000 (GE Healthcare). A capture assay using a tag specific antibody capture and orientation of the investigated antibodies was used. For capture of Fc containing protein constructs the human antibody capture kit (GE Healthcare) was used, for capture of His tag containing protein constructs the His capture kit (GE Healthcare) was used. The capture antibody was immobilized via primary amine groups (11000 RU) on a research grade CM5 chip (GE Life Sciences) using standard procedures. The analyzed antibody was captured at a flow rate of 10 µL/min with an adjusted RU value that would result in maximal analyte binding signal of typically 30 RU.

[0354] For an exemplary assay, recombinant human IL13 (catalog # IL012) and human IL4 (catalog # IL004) were purchased from Millipore, recombinant human TNFα (catalog # H8916) was purchased from Sigma Aldrich. Binding kinetics were measured against recombinant human IL4 and IL13 over a concentration range between 0.1 to 3 nM for IL4 and 0.8 to 25 nM for IL13. For human TNFα a concentration range from 3 to 100 nM was used. As assay buffer HBS EP (10 mM HEPES, pH 7.4, 150 mM NaCl, 3 mM EDTA, and 0.005 % Surfactant P20) was used at a flow rate of 30 µl/min. Chip surfaces were regenerated with the regeneration solution of the respective capture kit. Kinetic parameters were analyzed and calculated in the BIAevaluation program package v4.1 using a flow cell without captured antibody as reference and the 1:1 Langmuir binding model with mass transfer. To study simultaneous binding of antigens the trispecific antibodies were captured by an anti-human antibody capture surface. Antigens were used in single concentrations with IL4 at 3 nM, IL13 at 25nM and TNFα at 100nM. To show simultaneous binding of all three antigens, a mixture of IL4, IL13 and TNFα was injected. In separate analysis cycles, IL13 was injected alone, followed by either IL4 or TNFα, and followed by a co-inject of either IL4/TNFα or a co-inject of TNFα/IL4. The final response measured in each cycle was compared to show similarity of consecutive binding of either two or three antigens and simultaneous binding of a mixture of all three antigens.

In vitro *T cell activation and proliferation assays*

[0355] Human PBMCs were purified from buffy coat purchased from Blood Research Component (Brookline, MA, USA) using Ficoll-Paque Plus method. Briefly, fresh buffy coat was first diluted at 1:3 ratio in PBS (pH7.4), and mixed with Ficoll-Paque Plus solution (Ficoll) thoroughly before use by inverting the bottle several times. 15 mL density gradient medium was added to each Leucosep® tube and spin for 30s at 1000xg, RT. The medium is now located below the porous barrier. 30-40mL diluted buffy coat then was carefully poured into each Leucosep tube, and centrifuged at 800 x g for 15 minutes at room temperature, with the brake off and Max accel at 5. Plasma layer was removed, and the rest of the supernatant, which contains the enriched PBMCs, was transferred into a new tube (Leucosep tube was not held in the inverted position for longer than 2 seconds). Enriched PBMCs were washed with 45 ml PBS, and spun down at 250 x g for 10 minutes at room temperature. Wash was repeated, and multiple tubes were combined into one tube. Cells were resuspended in 20mL PBS and counted using a Bio-Rad TC20.

[0356] To set up the *in vitro* T cell activation assay, purified human PBMCs were resuspended in culture medium (RPMI1640 with 10% FBS and supplemented with glutamine/Streptomycin)(Thermo Fisher Scientific) (10^6 cells/ml). Indicated concentrations of different trispecific and control antibodies were added to each well, or used to coat the plate before use as described in Stebbings, R. *et al.* (2007) *J. Immunol.* 179:3325-3331, and incubated for 16-24 hours in a tissue culture incubator. The cells were spin down, and the supernatant was either collected for measuring cytokine release, or discarded. The cells were stained with florescent labeled antibodies for T cell markers (CD3, CD4, CD8, etc.) and activation markers (CD69, CD62L, etc.), and analyzed by running the samples on an Fortessa flow cytometer (Beckton Dickinson, San Jose, CA), followed by analysis using the Flowjo software (FlowJo v10) and plotted as shown.

[0357] To set up the *in vitro* T cell proliferation assay, purified human PBMCs were resuspended in culture medium (RPMI1640 with 10% FBS and supplemented with glutamine/Streptomycin)(Thermo Fisher Scientific) (10^6 cells/ml). Indicated concentrations of different trispecific and control antibodies were added to each well and incubated for 1-7 days in a tissue culture incubator. The cells were spun down, and the supernatant was either collected for measuring cytokine release, or discarded. The cells were stained with florescent labeled antibodies for T cell markers (CD3, CD4, CD8, etc.) and activation markers (CD69, CD62L, etc.), and analyzed by running the samples on an Fortessa flow cytometer (Beckton

Dickinson, San Jose, CA), followed by analysis using the Flowjo software (FlowJo v10) and plotted as shown.

In vitro *cell killing assay*

[0358] Purified human PBMCs were using for *in vitro* killing assays against various cancer cells using different trispecific antibodies. Briefly, the killing assay was set up in 96-well V-bottom plate. For each plate, 40 ml PBMCs from each donor were plated at 2x10^6 cells/ml, and 30 ml of PKH26 (Sigma #MINI26) labeled target cells at 2.5x10^5 cells/ml (4μL of dye to stain up to 1x10^7 cells) were prepared. First 20μL/well test proteins at various concentrations or PMA were added into each well, followed by adding 80μL/well labeled target cells into each well (2X10^4 cells/well). 100μL of PBMC were then added to each well, reaching E:T=10:1 well (2x10^5 cells/well), and incubated for 24 hours at 37°C 5% CO2 incubator. The cells were spin down, and the supernatant was either collected for measuring cytokine release, or discarded. The cells were stained with Vivid LIVE/DEAD™ Fixable Violet Dead Cell Staining buffer (Life Technology #L34955) (staining buffer was prepared by adding 60μL Vivid reagent into 60 ml PBS). Cells were resuspended into 100μL staining buffer by incubation for 15 min at RT in the dark. After washing the cells with 1xPBS, the cells were resuspended in 200μL PBS with 0.5% Paraformaldehyde, and PKH26+Vivid+ cancer cells were collected by Fortessa flow cytometer (Beckton Dickinson, San Jose, CA), followed by analysis using the Flowjo software. The percentage of killing is calculated as "specific killing-spontaneous killing/total cells and plotted as shown.

Cytokine release assay

[0359] For measuring inflammatory cytokine concentrations in the *in vitro* activation assays, *in vitro* killing assays, *in vivo* activation assays in CD34+ umbilical cord cell humanized NSG mice, and the toxicity study, cell culture supernatant was collected, and serum samples were diluted according to manufacturer's protocol using Milliplex Human High Sensitivity T cell 13-plex Kit (EMD Millipore). These were subsequently analyzed by EMD Millipore MAGPIX® System, and MILLIPLEX® Analyst 5.1 software.

In vivo *mouse models and efficacy studies*

[0360] Human CD34+ hematopoietic stem cell-engrafted NSG mice (hu-CD34) were used as an *in vivo* mouse model. These mice develop multi-lineage human immune cells, and are a validated platform for immuno-oncology efficacy studies (*see, e.g.,* Shultz, L.D. *et al.*

(2014) *Cold Spring Harb. Protoc.* 2014:694-708). Hu-CD34$^+$ NSG mice are produced by injecting CD34$^+$ hematopoietic stem cells, showing effective multi-lineage engraftment of human immune cell populations including T cells , B cells and some other populations (McDermott, S.P. *et al.* (2010) *Blood* 116:193-200). Multi-lineage hematopoiesis occurs within 12 weeks. Engraftment is stable for over one year without graft-versus-host disease.

[0361] For the efficacy study using hu-CD34 NSG mice, mice were purchased from The Jackson Laboratory (Maine, USA), and human cell populations were validated before use. In general, $5x10^6$ tumor cells mixed in Matrigel (BD Biosciences) (50% v/v) were used for inoculating tumor in each mouse. Once tumor size reached the range of 100-150 mm^3, mice were selected and randomized into each group for study. Antibodies were given intravenously at given doses 3 times weekly. Body weight was monitored 1-3 times weekly. Tumor size was measured by caliper tumor measurements 1-3 times/week. All mice were terminated when the tumor size reached 1,500 mm^3, or 24 hours after the last dose. Terminal blood samples (0.3mL) were collected into serum separator tubes, mixed by gently inverting five times, and placed into a tube rack. Terminal tumors were also collected and weighed before being put into fixative for immunohistochemistry analysis.

[0362] Human PBMC humanized (hu-PBMC) NSG mice were used as another *in vivo* mouse model. These mice are produced by injecting purified human PBMC from health donors, which have the fastest engraftment rate using adult peripheral blood mononuclear cells and enable short-term studies requiring a strong effector and memory T cell and NK cell function, and are suitable for short term efficacy study(3-4 weeks) due to graft-versus-host disease.

[0363] For the efficacy study using hu-PBMC NSG mice, 8-10 week old NSG mice (Cat. No: 005557, NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) were purchased from The Jackson Laboratory (Maine, USA). Each mouse was innoculated with $5x10^6$ tumor cells mixed in Matrigel (BD Biosciences) (50% v/v). Once tumor size reached the range of 50-100 mm^3, $10x10^6$ human PBMCs from a healthy donor were reconstituted to each mouse. Human cell reconstitution was validated the next day. Once tumor size reached the range of 100-150 mm^3, mice were selected and randomized into each group for study. Antibodies were given intravenously at given doses 3 times weekly. Body weight was monitored 1-3 times weekly. Tumor size was measured by caliper tumor measurements 1-3 times/week. All mice were terminated when the tumor size reached 1,500 mm^3 or 24 hours after the last dose. Terminal blood samples (0.3mL) were collected into serum separator tubes, mixed by gently inverting

five times, and placed into a tube rack. Terminal tumors were also collected and weighed before being put into fixative for immunohistochemistry analysis.

NHP tolerability and pharmacokinetic study

[0364] All NHP studies were carried out by Covance (Princeton, New Jersey, USA) according to Covance ICUCA protocol. Drug- and protein-naïve or protein-naïve male Cynomolgus Monkeys were used in all studies. Based on study design, monkeys were selected and grouped for each trispecific antibody. Antibody was given by intravenous infusion for 1 hour via saphenous vein. Increasing doses were given on consecutive days for low doses (<10 μg/kg), but with a 1-2 day interval for higher doses (>10 μg/kg) for observation purposes. Blood samples were collected at 0 hour (Day 1 only), 0.5 hour (mid-infusion), 1, and 6 hours from start of infusion for all animals after each dose, as specified. Additional unscheduled blood samples were collected at the discretion of the study director, pathologist, and/or clinical veterinarian. All animals were returned to colony on Day 60. PBMC and serum from the blood samples were prepared using standard methods, and preserved for future analysis.

Luciferase reporter assay

[0365] GloResponse™ IL2-luc2P Jurkat Cells, Thaw and Use (Promega part# CS187002) and GloResponse™ NFAT-Luc2 Jurkat Cells (Promega Cat# CS176401) were purchased from Promega (WI, USA), and prepared for use according to manufacturer's protocol.

[0366] Briefly, the cells were thawed for 2 min in a 37°C water bath and gently transferred to a 15mL conical centrifuge tube containing 10mL pre-warmed R10 media. Tube was centrifuged at 300g for 5 min at RT. Supernatant was removed, and the cells were resuspended in 20mL pre-warmed R10 media and transferred to a 75cm2 culture flask, followed by incubation in 37°C tissue culture incubator until cells were growing and stable (~3-4 days). The cells were split twice a week to 0.1e6 cells/mL. Cells were maintained in R10+Hygromycin B media for selection. Cells were used for assays ~7 days after thawing.

[0367] For antibody stimulation, trispecific or control antibodies were prepared at various concentrations and serially diluted in PBS. 25μL of antibodies were dispensed per well. For plate-bound Abs, Maxisorp plate was used and incubated at 4°C overnight. For soluble Abs, a U-bottom plate was used. Reporter cells were resuspended to 0.3-0.5 e6/mL, and 175uL cells

were added to each well, and incubated in 37°C CO_2 incubator for 6 hours. The plate was then taken out of the incubator and allowed to equilibrate to ambient temperature (10-15min). Then 50µl of Bio-Glo™ Reagent (Promega Cat# G7941) (ambient temperature) was added to the each well of the assay plate. After incubation for 5 minutes, luminescence activity was measured using MicroBeta2 LumiJET microplate counter (Perkin Elmer; 1s read time). Data were plotted using GraphPad Prism software.

Conformational stability

[0368] Thermostability measurements (*e.g.*, melting points, T_m) were determined using differential scanning fluorimetry (DSF). Samples were diluted in D-PBS buffer (Invitrogen) to a final concentration of 0.2µg/µl including a 4x concentrated solution of SYPRO-Orange dye (Invitrogen, 5000x stock in DMSO) in D-PBS in white semi-skirt 96-well plates (BIORAD). All measurements were done in duplicate using a MyiQ2 real time PCR instrument (BIORAD). Negative first derivative curves (-d(RFU)/dT) of the melting curves were generated in the iQ5 Software v2.1 (BIORAD). Data were then exported into Microsoft Excel for Tm determination and graphical display of the data.

IC50 measurements

Detection of antibody activity against IL-4 and IL-13 with a reporter cell line

[0369] Activities of bispecfic antibodies or derivatives against cytokines IL4 and IL13 were determined in commercially available HEK-Blue IL-4/IL-13 reporter cells (InvivoGen). HEK-Blue IL-4/IL-13 cells are designed to monitor the activation of the STAT6 pathway by IL-4 or IL13. Stimulation of the cells with either cytokine results in production of the reporter gene secreted embryonic alkaline phosphatase (SEAP) which can be measured in the culture supernatant with the QUANTI-Blue assay. To test antibody activities against IL4 or IL13, the cytokines were pre-incubated for 1 hour with different concentrations of the antibodies and added to 50.000 HEK-Blue IL-4/IL-13 cells. Cytokine-mediated induction of SEAP was measured after 24 hours incubation in the cell culture supernant with the QUANTI-Blue assay (InvivoGen). Each experiment was performed with n = 3 datapoints for each antibody concentration. The half-maximal inhibitory concentration (IC50) for each antibody was calculated via the internal application Biostat-Speed V2.0 (Sanofi).

Detection of antibody activity against TNFα with a reporter cell line

[0370] Activities of bispecific antibodies or derivatives against TNFa were determined by using commercially available HEK-Blue TNF-a reporter cells (InvivoGen). HEK-Blue TNF-a

cells are designed to detect bioactive TNFa by monitoring the activation of the NFkB pathway via the expression of the reporter gene secreted embryonic alkaline phosphatase (SEAP) which can be measured in the culture supernatant with an QUANTI Blue Assay (InvivoGen). To determine antibody activities against TNFa the cytokines were pre-incubated for 1 hour with different concentrations of the antibodies and added to 50,000 HEK Blue TNF-a cells. Cytokine mediated induction of SEAP was measured after 24 hours in the culture supernatant with the QUANTI-Blue assay (InvivoGen). Each experiment was performed with n = 3 datapoints for each antibody concentration. The half maximal inhibitory concentration for each antibody was calculated.

Example 2: Overview of the Trispecific Binding Proteins

[0371] A novel strategy was developed for the generation of trispecific binding proteins. The trispecific proteins comprised four polypeptides that formed three target binding sites (**FIGS. 1A-C**). Each target binding site comprised the V_H and V_L domain from an antibody that targeted a distinct human antigen target (*See e.g.*, **Table 1**). The trispecific binding proteins contained a first pair of polypeptides that possessed dual variable domains having a cross-over orientation forming two distinct antigen binding sites (called the CODV Ig format), and a second pair of polypeptides, each with a single variable domain that formed a third antigen binding site (**FIGS. 1A and 1B**).

Table 1: Heavy and light chain SEQ ID NOs for binding proteins 1-21, and the target antigens to which the binding proteins are directed.

Binding Protein #	SEQ ID NOS	Directed to:
1	1, 2, 3, 4	Her2 x (CD28 x CD3)
2	1, 2, 9, 10	Her2 x (CD28 x CD3)
3	13, 14, 3, 4	CD19 x (CD28 x CD3)
4	13, 14, 9, 10	CD19 x (CD28 x CD3)
5	17, 18, 3, 4	CD38 x (CD28 x CD3)
6	17, 18, 9, 10	CD38 x (CD28 x CD3)
7	21, 22, 3, 4	LAMP1 x (CD28 x CD3)
8	21, 22, 9, 10	LAMP1 x (CD28 x CD3)
9	60, 61, 62, 63	TNFa x (IL4 x IL13)
10	60, 61, 68, 69	TNFa x (IL13 x IL4)
11	60, 71, 68, 69	TNFa x (IL13 x IL4)
12	73, 74, 75, 76	IL13 x (IL4 x TNFa)
13	73, 74, 81, 82	IL13 x (TNFa x IL4)

14	85, 86, 87, 88	IL4 x (IL13 x TNFa)
15	85, 86, 93, 94	IL4 x (TNFa x IL13)
16	73, 74, 68, 69	IL13 x (IL13 x IL4)
17	85, 86, 68, 69	IL4 x (IL13 x IL4)
18	73, 74, 62, 63	IL13 x (IL4 x IL13)
19	85, 86, 62, 63	IL4 x (IL4 x IL13)
20	114, 115, 3, 4	CD20 x (CD28 x CD3)
21	114, 115, 9, 10	CD20 x (CD28 x CD3)

[0372] The first pair of polypeptides (that possessed the dual variable domains) comprised a first polypeptide having the structure V_{L2}-Linker-V_{L1}-Linker-Immunoglobulin light chain constant domain, and a second polypeptide having the structure V_{H1}-Linker-V_{H2}-Linker-Immunoglobulin C_{H1}heavy chain constant domain, resulting in a pair of polypeptides which had a cross over orienation that formed two distinct antigen binding sites: V_{H1}-V_{L1} and V_{H2}-V_{L2} (**FIG. 1C**, see light and heavy chains B). **Table A** provides a summary of the design of the bispecific arm (*i.e.*, the arm comprising heavy and light chains B) of IgG1 and IgG4 variants of representative trispecific binding proteins, including indicating the various combinations of the linkers used in the bispecific arm of the trispecific binding proteins. The second pair of polypeptides (that each posessed a single variable domain) comprised a first polypeptide having the structure V_{H3}-Immunoglobulin C_{H1} heavy chain constant domain, and a second polypeptide having the structure V_{L3}-Immunoglobulin light chain constant domain, resulting in a pair of polypetpides that formed a third antigen binding site: V_{H3}-V_{L3} (**FIG. 1C**, see light and heavy chains A). Furthermore, the trispecific binding proteins were constructed such that either of the C_{H3} domains could include a knob or a hole modification to facilitate antibody heterodimerization (**FIG. 1**).

Table A: summary of the design of the bispecific arm of the trispecific binding proteins as an IgG1 (Hole) or IgG4 (Hole)

		CD28 x CD3			CD3 x CD28			CD28 x CD3			CD3 x CD28		
		HC -1	HC -2	HC -3	HC -1	HC -2	HC -3	HC -1	HC -2	HC -3	HC -1	HC -2	HC -3
CD28 x CD3	LC-1	X											
	LC-2		X										
	LC-3			X									
CD3 x CD28	LC-1				X								
	LC-2					X							
	LC-3						X						
CD28 x	LC-1							X					
	LC-2								X				

CD3	LC-3									X			
CD3	LC-1										X		
x	LC-2											X	
CD28	LC-3												X

Linkers: [L3, L4]/[L1,L2] – [S, RT]/[GQPKAAP (SEQ ID NO:175), TKGPS (SEQ ID NO:106)];
[,] /[GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGS (SEQ ID NO:104)]; or
[GGGGSGGGGSGGGGS (SEQ ID NO:105),]/[GGGGSGGGGSGGGGS (SEQ ID NO:105),]

Example 3: *In Vitro* Binding Activity and Antibody-mediated Specific Killing of T Cell Engagers

[0373] This example describes *in vitro* assays for characterizing the activities of the T cell engagers.

[0374] Using the approach described in Example 2 above for trispecific binding protein design, four trispecific binding proteins (Binding Proteins 1, 3, 5, and 6) were generated. These trispecific binding proteins were created by grafting onto a trispecific binding protein framework the V_H and V_L domains isolated from antibodies targeting distinct human proteins: CD3, CD19, CD28, CD38, or Her2. Binding Protein 1 was constructed such that the first pair of polypeptides (which formed two antigen binding sites) targeted CD28 and CD3, and the second pair of polypeptides (which formed the single antigen binding site) targeted Her2 (Binding Protein 1 = Her2 x (CD28 x CD3)). Binding Protein 3 was constructed such that the first pair of polypeptides (which formed two antigen binding sites) targeted CD28 and CD3, and the second pair of polypeptides (which formed the single antigen binding site) targeted CD19 (Binding Protein 3 = CD19 x (CD28 x CD3)). Binding Protein 5 was constructed such that the first pair of polypeptides (which formed two antigen binding sites) targeted CD28 and CD3, and the second pair of polypeptides (which formed the single antigen binding site) targeted CD38 (Binding Protein 5 = CD38 x (CD28 x CD3)). Binding Protein 6 was constructed such that the first pair of polypeptides (which formed two antigen binding sites) targeted CD28 and CD3, and the second pair of polypeptides (which formed the single antigen binding site) targeted CD38 (Binding Protein 6 = CD38 x (CD28 x CD3)).

In Vitro Assays Using Trispecific Binding Proteins Comprising Anti-Her2

[0375] To test the ability of the trispecific binding proteins to target and bind three different human antigens, the specificity of Binding Protein 1 for its targets was first examined by ELISA assay. Binding Protein 1 was capable of binding all three of its target proteins—CD3, CD28, and Her2 (**FIG. 2**)—indicating that each binding domain in the trispecific format retained its function.

[0376] ZR-75-1, AU565 ($Her2^+$), ARH-77 ($CD19^+$), MOLP-8, RPMI-8226, KMS-12_BM, NCI-H929, MM.1.S, MM.1., R OPM-2, KMS-26, and U266 cells ($CD38^+$) were labeled with the membrane dye PKH-26 (Sigma) and used as target cells in a cytotoxicity assay. These labeled cell lines were co-cultured at an E:T ratio of 10:1 with enriched human Pan T cells in the presence of increasing concentrations of a trispecific antibody, bispecific

antibody, or control proteins for 24 hours. The extent of cell lysis in the target cells was determined by staining with a live/dead cell marker (Life Technologies) and measuring the number of dead cells in the labeled target cell population by running the samples on a Fortessa flow cytometer (Beckton Dickinson, San Jose, CA) followed by analysis using the Flowjo software (FlowJo v10).

[0377] Her2+, CD19+, CD38+ tumor cell lines were stained with fluorescently conjugated antibodies against human CD3, CD28, CD19, CD38, LAMP1, and/or Her2 (Biolegend). Staining with respective isotype-matched control antibodies was also included. The cells were then acquired on the Fortessa (Beckton Dickinson, San Jose, CA) instrument. Flow analysis was performed on FlowJo v10. The mediated killing results of various binding proteins are shown in **FIGS. 3A-5**, **9A**, **9B**, & **11A-16**.

[0378] The ability of Binding Protein 1 to induce antibody-mediated cell killing of tumor cells expressing HER2 proteins on their surface was tested. Not only was Binding Protein 1 capable of binding to all three of its target proteins, but it was also able to induce antibody-mediated cell killing of $Her2^+$ cell lines (**FIGS. 3A-4**). Binding Protein 1 exhibited potent antibody-mediated cell killing activities, while anti-CD3/CD28 bispecific Ab and anti-Her2 antibodies showed minimal killing activities.(**FIGS. 3A, 3B, 4, & 5**), demonstrating the effectiveness of using the trispecific Ab to engage tumor cells with T cells through a tumor antigen (HER2) and T cell markers (CD3 and CD28). Anti-CD3/CD28 is not only important for T cell recruitment, but it also provides more effective T cell activation and survival signaling, potentially improving the efficacy.

[0379] Additionally, studies were carried out on *in vitro* T cell activation and proliferation, as well as cytokine production, using the anti-Her2 x CD28 x CD3 trispecific antibody (Binding Protein 1). Binding protein 1 and control variants having one or two binding domains inactivated by site-directed mutagenesis (ΔCD28: anti-CD28 inactivated; ΔCD3: anti-CD3 inactivated; Δ(CD3xCD28): both anti-CD3 and anti-CD28 inactivated) were used in human PBMC *in vitro* activation assay as described in Example 1. The results showed that Binding protein 1 activated both human primary CD4 T cells and CD8 T cells effectively *in vitro*. Inactivation of anti-CD28 reduced the activation potency, indicating the importance of anti-CD28 co-signaling pathway. Inactivation of anti-CD3 binding site rendered Binding protein 1 to minimal activity, suggesting that the anti-CD3 provided the primary T cell activation signaling (**FIGS. 6A & 6B**). Similar results were obtained using IL2 and NFAT reporter human T cell lines (Jurkat-IL2 and Jurkat-NFAT) (**FIGS. 7A-7C**).

In Vitro Assays Using Trispecific Binding Proteins Comprising Anti-CD19

[0380] The anti-CD19 x CD28 x CD3 trispecific binding protein was capable of binding its target antigens (**FIG. 8**), indicating that each binding domain in the trispecific format retained its function.

[0381] The anti-CD19 x CD28 x CD3 trispecific binding protein was also capable of inducing antibody-mediated cell killing of CD19+ cells (**FIGS. 9A-9N**). Similarly, anti-CD19 x CD28 x CD3 trispecific binding protein exhibited potent killing activity against human lymphoma cells, while both the anti-CD3/CD28, anti-CD19, and isotype control antibodies showed minimal killing activities, demonstrating the effectiveness of using the trispecific Ab to engage tumor cells with T cells through a tumor antigen (CD19) and T cell markers (CD3 and CD28).

In Vitro Assays Using Trispecific Binding Proteins Comprising Anti-CD38

[0382] As observed with Binding Proteins 1 and 3, Binding Protein 5 was able to bind all three of its target proteins (CD3, CD28, and CD38), as assessed by ELISA assay (**FIG. 10**), indicating that each binding domain in the trispecific format retained its function.

[0383] Binding Protein 5 was also found to induce antibody-mediated cell killing of cells (**FIGS. 11A-15D**) against 9 human multiple myeloma cells with various levels of CD38 and CD28 expression (*see* **FIGS. 11D, 12D, & 13D**). Similarly, trispecific Binding protein 5 exhibited potent killing activity against human multiple myeloma cells, while both the anti-CD38 and isotype control antibodies showed minimal killing activities, demonstrating the effectiveness of using the trispecific Ab to engage tumor cells with T cells through tumor antigens (CD38 and CD28) and T cell markers (CD3 and CD28). Bispecific anti-CD3/CD28 control antibody also showed marginal killing activity against CD28+ MM cells *see* **FIGS. 11B, 12A-C, & 13A-C**).

[0384] These results demonstrate that the trispecific antibody platform described herein provides the possibility of integrating binding sites for two tumor markers, or two binding sites for T cell markers, allowing flexibility for scientific designs and various applications. Binding Protein 5 was also effective against 5 CD38+ human lymphoma cell lines (**FIGS. 14C & 15D**), showing potent killing activities (**FIGS. 14A-B & 15A-C**).

[0385] The antibody-mediated cell killing against multiple myeloma cell line RPMI8226 using Binding Proteins 5 and 6 were tested, and their EC_{50}s were calculated and compared to that of a CODV format bispecific antibody targeting CD28 and CD3 (**FIG. 16** and Table B). Binding proteins 5 and 6 differ only in anti-CD28 binding domain; Binding protein 5 contains

an anti-CD28 superagonist, while Binding protein 6 contains a conventional anti-CD28. Binding protein 5 showed more potent killing activity.

Table B: EC_{50} values calculated for bispecific and trispecific binding proteins

	EC_{50} (pM)
huCD28 x CD3 IgG4	56.16
Binding Protein 5 IgG4	0.3787
Binding Protein 6 IgG4	5.709

[0386] The activity of the anti-CD38 x CD28 x CD3 trispecific binding protein 5 and control variants having one or two binding domains inactivated by site-directed mutagenesis (ΔCD28: anti-CD28 inactivated; ΔCD3: anti-CD3 inactivated; Δ(CD3xCD28): both anti-CD3 and anti-CD28 inactivated) were tested using IL2 and NFAT reporter human T cell lines (Jurkat-IL2 and Jurkat-NFAT) in the *in vitro* activation assay as described in Example 1. The results showed that Binding protein 5 activated both human IL2 and NFAT promoters effectively *in vitro* (**FIGS. 17A & 17B**). Inactivation of anti-CD28 reduced the activation potency, which was more prominent for IL2 reporter, indicating the importance of anti-CD28 co-signaling pathway. Inactivation of anti-CD3 binding site rendered Binding protein 5 to minimal activity, suggesting that the anti-CD3 provided the primary T cell activation signaling.

Example 4: *In Vivo* Activity of the T Cell engagers

[0387] This example describes experiments characterizing the properties and activities of the anti-Her2 or anti-CD38 containing T cell engagers *in vivo*.

In Vivo Assays Using Trispecific Binding Proteins Comprising Anti-Her2

[0388] A dose escalation study using the Her2 x CD28 x CD3 trispecific antibody was carried out in non-human primates (**FIGS. 18A-18E**) as described in Example 1. All three binding domains in Binding protein 1 are cross-reactive with monkey CD3/CD28/HER2. A dose escalation toxicity study was devised to assess the potential toxicity profile of the molecular. Blood samples were collected for serum and PBMC isolations. Circulating T cell populations were investigated after each dosing (**FIGS.18A & 18B**), along with T cell

subpopulation activation (CD69+) (**FIGS. 18C & 18D**). Percentage of CD4 and CD8 T-cells in circulation were increased at low dose escalation, but eventually decreased at high dose escalation. Significant CD4 and CD8 T cell activation were only prominent at 100 µg/kg dose, suggesting rather a relative high tolerable dose. Serum level of several cytokines were also measured. Significant cytokine release was only observed at the highest dose (100 µg/kg; **FIG. 18E**).

[0389] Next, the effect of the trispecific anti-Her2 x CD28 x CD3 Binding protein 1 antibody on tumor growth in humanized mouse models was examined as described in Example 1 (**FIGS. 19A-20H**). **FIGS. 19A & 19B** summarize the results obtained using the human CD34+ hematopoietic stem cell-engrafted NSG mice (hu-CD34) model inoculated with human HER2+ breast cancer line BT474. Significant anti-tumor activities were evident within all dose groups. The anti-tumor activity was dose dependent, which is statistically different compared to the control group at 25 µg/kg. No significant body weight loss in any treated groups observed.

[0390] A 2nd in vivo study using human PBMC reconstituted NSG mice model inoculated with human HER2+ breast cancer line BT474 was also done (**FIGS. 20A-20H**). Significant anti-tumor activities were observed within high dose groups (100 and 500 µg/kg). Tumor shrinkage was seen in 40% of the mice in 500 µg/kg group. The anti-tumor activity was dose dependent. The anti-tumor activity in groups treated with 100 and 500 µg/kg doses were significantly better than anti-HER2-treated groups (0.1 to 10 mg/kg), indicating superior anti-tumor activity from Binding protein 1. No significant body weight loss in any treated groups observed.

In Vivo Assays Using Trispecific Binding Proteins Comprising Anti-CD38

[0391] A dose escalation study was conducted in non-human primates using the trispecific anti-CD38 x CD28 x CD3 antibody (Binding protein 5) as described in Example 1 (**FIGS. 21A-21F**). Two of the three binding domains in Binding protein 5 are cross-reactive with monkey CD3 and CD28. A dose escalation toxicity study was devised to assess the potential toxicity profile of the molecule. Blood samples were collected for serum and PBMC isolations. Circulating T cell populations were investigated after each dosing (**FIGS. 21A & 21B**, bar graphs), along with T cell subpopulation activation (CD69+) (**FIGS. 21A & 21B**, line graphs). Percentage of CD4 and CD8 T-cells in circulation increased at low dose escalation, but eventually decreased at high dose escalation. Significant CD4 and CD8 T cell activation were only prominent at 100 µg/kg dose, suggesting rather a relative high tolerable

dose. Serum level of several cytokines was also measured. Significant cytokine release was only observed at the highest dose (100 μg/kg; **FIGS. 21C-21F**).

[0392] The *in vivo* activity of the anti-CD38 x CD28 x CD3 trispecific antibody was next tested in humanized mice (**FIGS. 22A-23D**) as described in Example 1. **FIGS. 22A-22C** summarized the result from a dose determining pilot study using the human CD34+ hematopoietic stem cell-engrafted NSG mice (hu-CD34) model implanted with human MM cell line RPMI-8226 transduced with CD38 and PD-L1, treated with Binding protein 5 at doses 5, 50 and 100 μg/kg. Significant anti-tumor activity was only evident in group treated with 5 μg/kg (**FIG. 22A**). CD8 T cell infiltration was observed in Binding protein 5 treated mice (5 μg/kg) (**FIGS. 22B & 22C**).

[0393] A follow up study in the same model was performed using Binding protein 5 at dosing from 0.04-5 μg/kg (**FIGS. 23A-23D**). Significant anti-tumor activity was shown in all group treated with Binding protein 5 (**FIG. 23B**), which were statistically different from the control at the end of study (**FIG. 23C**). No significant body weight loss was observed in any treated groups (**FIG. 23A**). Dose dependent induction of serum inflammatory cytokines IFN-γ, TNF-α and IL-2 four hours after the first dose was observed in mice treated with indicated concentrations of the Binding protein 5 or PBS control (**FIG. 23D**), indicating effective T cell activation by trispecific Binding protein 5 in vivo.

[0394] Humanized CD34+ NSG mice (n=3) were injected i.v. with 100mcg/kg of Tri-specific Ab (triangel), Bi-specific Ab (square), or single-specific Ab (circle). Activation of CD4+ or CD8+ T cells was measured at 0 (pre-injection), 1, 24, and 72 hours after Ab injection by determining mean increase in % of CD69, decrease % of CD62L and/or concentration of inflammatory cytokines in plasma at each time points by Luminex's xMAP multiplexing technology. The T cell activation results of various trispecific antibodies are shown in **FIGS. 24-26C**.

[0395] Systemic in vivo T cell activation was studied in human CD34+ hematopoietic stem cell-engrafted NSG mice (hu-CD34) model after administration of Binding protein 5, anti-CD3/CD28_IgG4 bispecific antibody and anti-CD28 IgG4 antibody controls (**FIG. 24**). 100 μg/kg of the Binding protein 5 and control antibodies were administered into 3 mice/group. Blood samples were collected at pre, 1 hour, 24 hours and 72 hours post administration. Mouse sera and human T cells were isolated from blood, and preserved for T cell activation analysis and for measurement of serum cytokine level. **FIGS. 24 & 25** show that both human CD4 and CD8 T cell were activated 1 hour post antibody infusion, which returned to baseline at 72 hours. **FIGS. 26A-26C** shows the elevation of serum IFN-γ, TNF-α

and IL-2 release in the same mice, which was observed 1 hour post infusion, and returned to baseline 24 hours later. These results demonstrated both Binding protein 5 and anti-CD3/CD28 IgG4 bispecific antibody are effective in activating T cell in the given animal model, making it suitable for in vivo efficacy study.

Example 5: Characterization of Cytokine-directed Trispecific and Bispecific-Trivalent Binding Proteins

[0396] The follow example describes experiments characterizing the stability, binding properties, and activities of novel trispecific and bispecific-trivalent binding proteins that target human cytokines.

[0397] Trispecific binding proteins (*e.g.*, that bind three different target proteins; Binding Proteins 9-15), as well as bispecific-trivalent binding proteins (*e.g.*, that bind one antigen bivalently on one antigen monovalently; Binding Proteins 16-19), were designed (Table C). With the exception of Binding Protein 11 where a kappa constant domain was used on both the CODV-LC and the Fab-arm-LC, all other Binding Proteins (9-10 and 12-19) were produced with a kappa constant domain on the CODV-LC and a lambda constant domain on the Fab-arm-LC. As Fc-backbone the IgG1 sequence was used. Whereas the CODV-HC harbors the knob-RF mutations (S354C, T366W; H435R and Y436F) the Fab-arm-HC contains the hole mutations (Y349C, T366S, L368A, Y407V).

Table C: summary of the trispecific/trivalent binding proteins directed to anti-IL-4/IL-13/TNFα

Antibody	Specificity	Construct	Format
Binding Protein 9	(anti-IL4 x anti-IL13) x anti-TNFα	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 10	(anti-IL13 x anti-IL4) x anti-TNFα	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 11	(anti-IL13 x anti-IL4) x anti-TNFα	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 12	(anti-IL4 x anti-TNFα) x anti-IL13	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 13	(anti-TNFα x anti-IL4) x anti-IL13	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 14	(anti-IL13 x anti-TNFα) x anti-IL4	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 15	(anti-TNFα x anti-IL13) x anti-IL4	(CODV-Fab) x Fab-IgG1 Fc	Trispecific
Binding Protein 16	(anti-IL13 x anti-IL4) x anti-IL13	(CODV-Fab) x Fab-IgG1 Fc	Bispecific Trivalent
Binding Protein 17	(anti-IL13 x anti-IL4) x anti-IL4	(CODV-Fab) x Fab-IgG1 Fc	Bispecific Trivalent
Binding Protein 18	(anti-IL4 x anti-IL13) x anti-IL13	(CODV-Fab) x Fab-IgG1 Fc	Bispecific Trivalent

Binding Protein 19	(anti-IL4 x anti-IL13) x anti-IL4	(CODV-Fab) x Fab-IgG1 Fc	Bispecific Trivalent

[0398] The trispecific and bispecific-trivalent binding proteins were produced and purified as described above (**FIG. 27**).

Table D: SEC purification of Binding Proteins 16-19

Construct	Retention (mL)	Peak Height (mAU)	Area (mAU*mL)	Aggregation (%)	MW by SEC (kDa)	MW Calc. (kDa)
Binding Protein 16	3.02	64.8	8.1	1.5	211	11
Binding Protein 17	2.99	65.9	8.9	2.1	225	172
Binding Protein 18	3.01	72.9	8.8	0.0	214	171
Binding Protein 19	2.98	73.2	8.8	0.9	228	171

[0399] In order to assess the stability of the trispecific binding proteins, their melting point was assessed by DSF and compared with the thermostability of the parental antibodies (Table E).

Table E: summary of the thermostability by DSF and percent monomers from preparative size exclusion chromatography for various trispecific binding proteins

Construct	Tm (°C)		Prep SEC Monomer (%)
IL4	70	81	100
IL13	67	78	92.5
TNFα	70	-	nd
Binding Protein 9	63	-	92.2
Binding Protein 10	62	-	85.7
Binding Protein 11	63	70	65.7
Binding Protein 12	59	70	87.3
Binding Protein 13	59	70	94.5
Binding Protein 14	56	69	92.4
Binding Protein 15	58	66	92.2
IL13 x IL4	63	75	88.0
IL4 x IL13	64	-	nd

nd=not determined

[0400] To assess the binding affinity of every single antibody binding domain within the trispecific format, SPR analysis for each single antigen was performed as described

previously. The results were benchmarked against the afiinities of the parental antibodies (Tables F, G, and H).

Table F: summary of surface plasmon resonance results for IL-4 for various trispecific binding proteins

Construct	K_a [1/M*s]	K_d [1/s]	K_D [M]	Rmax	Chi^2
IL4	8.70E+07	1.57E-04	1.81E-12	24	0.24
IL13					
TNFα					
Binding Protein 9	7.86E+07	3.80E-04	4.83E-12	26	0.309
Binding Protein 10	1.88E+07	8.41E-05	4.47E-12	23	0.763
Binding Protein 11	5.92E+07	2.39E-04	4.04E-12	20	0.198
Binding Protein 12	6.02E+07	2.39E-04	3.97E-12	35	0.406
Binding Protein 13	3.57E+07	1.81E-04	5.07E-12	30	0.257
Binding Protein 14	8.96E+07	1.52E-04	1.69E-12	33	0.254
Binding Protein 15	7.35E+07	1.23E-04	1.67E-12	31	0.547

Table G: summary of surface plasmon resonance results for IL-13 for various trispecific binding proteins

Construct	K_a [1/M*s]	K_d [1/s]	K_D [M]	Rmax	Chi^2
IL4					
IL13	2.44E+05	2.50E-05	1.03E-10	33	0.938
TNFα					
Binding Protein 9	6.25E+05	9.27E-06	1.48E-11	22	0.176
Binding Protein 10	7.16E+05	3.76E-05	5.25E-11	25	0.145
Binding Protein 11	2.95E+05	4.28E-05	1.45E-10	16	0.372
Binding Protein 12	4.17E+05	5.06E-05	1.21E-10	28	0.338
Binding Protein 13	6.15E+05	7.58E-05	1.23E-10	23	0.186
Binding Protein 14	6.93E+05	1.19E-04	1.72E-10	22	0.232
Binding Protein 15	2.50E+05	5.61E-05	2.24E-10	30	0.631

Table H: summary of surface plasmon resonance results for TNFα for various trispecific binding proteins

Construct	K_a [1/M*s]	K_d [1/s]	K_D [M]	Rmax	Chi^2
IL4					
IL13					
TNFα	1.78E+05	1.64E-04	9.22E-10	33	0.745
Binding Protein 9	1.32E+05	3.20E-04	2.42E-9	23	0.213
Binding Protein 10	1.40E+05	2.90E-04	2.07E-9	27	0.241
Binding Protein 11	3.36E+05	1.82E-04	5.41E-10	28	0.539
Binding Protein 12	4.49E+05	1.80E-04	4.00E-10	28	0.647
Binding Protein 13	5.84E+05	1.96E-04	3.35E-10	27	0.529
Binding Protein 14	5.29E+05	1.86E-04	3.52E-10	25	0.485
Binding Protein 15	5.59E+05	1.84E-04	3.28E-10	27	0.409

[0401] In order to assess the neutralization activity of the trispecific binding proteins, a cellular assay was performed using different HEK Blue kits (Invivogen). Cytokines were preincubated with different concentrations of anti-cytokine antibodies for 30 minutes at room temperatues in a 96 well plate. Controls included use of only the cytokine or only the antibody. 50,000 HEK Blue Cells (HEK Blue TNFa/IL1ß cells (InvivoGen, Cat. # hkb-tnfil1; HEK Blue STAT-6 cells (InvivoGen, Cat. # Hkb.stat6) were added to the cytokine/antibody mixture and incubated for 23 hours at 37°C, 5% CO2 in an incubator. QuantiBlue Reagent was added to each culture well and incubated for 2 hours at 37°C. The OD was measured at 620 nm and the IC50 was calculated using BioStat Speed 2.0. The HEK Blue Reporter Cell Assay results of various trispecific antibodies are shown in Tables I and M.

[0402] Next, IC_{50} values were calculated for Binding Proteins 9-15 and benchmarked against the single parental antibodies (Table I).

Table I: summary of HEK Blue Reporter Assays (IC_{50} Data) for various trispecific binding proteins

Construct	IL4 IC_{50} (ng/mL)	IL13 IC_{50} (ng/mL)	TNFα IC_{50} (ng/mL)
IL4	2.14E+00 1.85E+00 1.82E+01	-	-

IL13	-	1.10E+02 8.83E+01 1.42E+01	-
TNFα	-	-	3.63E+00 5.78E+00 2.41E+00
Binding Protein 9	4.51E+00	1.77E+02	3.95E+01
Binding Protein 10	5.93E+00	4.68E+02	4.76E+01
Binding Protein 11	6.96E+00	4.89E+02	2.65E+01
Binding Protein 12	5.03E+00	1.83E+02	2.17E+01
Binding Protein 13	1.38E+01	7.54E+01	2.26E+01
Binding Protein 14	1.02E+01	1.20E+02	6.26E+00
Binding Protein 15	1.30E+01	1.07E+02	2.38E+01

[0403] The thermostability of the bispecific-trivalent binding proteins was measured by differential scanning fluorimetry (DSF; Table J).

Table J: summary of the thermostability by DSF for various trivalent binding proteins

Construct	Tm1 (°C)	Tm2 (°C)
IL4	70	81
IL13	67	78
Binding Protein 16	63	-
Binding Protein 17	63	-
Binding Protein 18	65	-
Binding Protein 19	55	-

[0404] The binding affinity and number of target proteins bound by each of the bispecific-trivalent binding proteins was measured for human IL-4 (Table K) and IL-13 (Tables K and L).

Table K: summary of surface plasmon resonance results for IL-4 for various trivalent binding proteins

Construct	RU Capture	Analyte	Ka (1/Ms)	Kd (1/s)	Rmax (RU)	KD (M)	Chi2	kDa Bound	No. of ILs Bound
IL4	116	IL4	8.70	1.57	24	1.81	0.240	15	1

			E+07	E-04		E-12			
Binding Protein 16	218	IL4	4.77 E+07	2.80 E-04	20	5.88 E-12	0.172	17	1
Binding Protein 17	218	IL4	3.16 E+08	7.60 E-04	43	2.40 E-12	0.278	35	2
Binding Protein 18	215	IL4	3.52 E+07	3.59 E-04	22	1.02 E-12	0.408	18	1
Binding Protein 19	226	IL4	8.27 E+07	3.85 E-04	43	4.65 E-12	0.486	34	2

Table L: summary of surface plasmon resonance results for IL-13 for various trivalent binding proteins

Construct	RU Capture	Analyte	Ka (1/Ms)	Kd (1/s)	Rmax (RU)	KD (M)	Chi2	kDa Bound	No. of ILs Bound
IL13	201	IL13	8.95 E+05	5.47 E-05	37	6.11 E-11	0.211	14	1
Binding Protein 16	226	IL13	7.17 E+05	4.54 E-05	35	6.34 E-11	0.132	26	2
Binding Protein 17	235	IL13	5.92 E+05	5.70 E-05	15	9.64 E-11	0.128	11	1
Binding Protein 18	231	IL13	1.00 E+06	3.54 E-05	35	3.53 E-11	0.166	28	2
Binding Protein 19	282	IL13	1.91 E+06	3.81 E-05	18	2.00 E-11	0.265	14	1

[0405] Finally, IC_{50} values were calculated for Binding Proteins 16-19 (Table M).

Table M: summary of HEK Blue Reporter Assays (IC_{50} Data) for various trivalent binding proteins

Construct	IL4 IC_{50} (ng/mL)	IL13 IC_{50} (ng/mL)
IL4	6.07E+00	-
IL13	-	1.12E+03
Binding Protein 16	1.30E+01	1.24E+03
Binding Protein 17	8.62E+00	9.30E+03
Binding Protein 18	1.46E+01	1.10E+03
Binding Protein 19	5.73E+00	6.93E+03

Example 6: Trispecific Binding Protein Format Optimization

[0406] A problem with many existing heterodimeric binding protein formats (*e.g.*, bispecific antibodies and variants thereof) is that it can be difficult to purify only the desired

heterodimeric species without also including either homodimeric species. Thus, a process for efficient purification of the desired, heterodimeric binding protein is of great interest, *e.g.*, for industrial-scale production.

[0407] As described herein, binding proteins of the present disclosoure can include several optional features, including without limitation knob and hole mutations (*e.g.*, to promote proper heterodimer formation) and mutations to improve purification. In addition, these binding proteins include two light chains, leading to four potential configurations: two kappa light chains, two lambda light chains, a kappa light chain on the arm with dual variable domains (the "CODV arm") and a lambda light chain on the traditional antibody arm (the "Fab arm"), and a lambda light chain on the CODV arm and a kappa light chain on the Fab arm.

[0408] Therefore, experiments were undertaken to identify a process that allows for efficient purification of the desired binding protein of interest. Binding protein variants were also tested for their efficiency of purification.

[0409] **FIG. 28A** shows a diagram of an exemplary binding protein of the present disclosure, indicating variations that lead to unique configurations. These experiments tested the effect of the placement of: kappa and lambda light chains (*e.g.*, two kappa, two lambda, kappa on CODV arm and lambda on Fab arm, and lambda on CODV arm and kappa on Fab arm), knob and hole mutations (*e.g.*, knob mutations on CODV arm and hole mutations on Fab arm, or hole mutations on CODV arm and knob mutations on Fab arm), and H435R/Y436F mutations ("RF mutations," *e.g.*, RF mutations on CODV or Fab arm, or no RF mutations). A total of 18 different variants were tested, as shown in **FIG. 28B**. For these experiments, the CODV arm had antigen binding sites specific for TNFa (*i.e.*, VH and VL sequences of SEQ ID NOs:168 and 169, respectively) and IL4 (*i.e.*, VH and VL sequences of SEQ ID NOs:170 and 171, respectively), whereas the Fab arm had an antigen binding site specific for IL13 (*i.e.*, VH and VL sequences of SEQ ID NOs:172 and 173, respectively). S354C and T366W were used for the knob mutations, and Y349C, T366S, L368A, and Y407V were used for the hole mutations.

[0410] Various processing steps were tested for the ability to monitor correct pairing of CODV and Fab arms (*e.g.*, as opposed to CODV or Fab homodimers), as well as correct heavy chain-light chain pairing (*e.g.*, as opposed to pairing between Fab arm light chain and CODV arm heavy chain, or between Fab arm heavy chain and CODV arm light chain). Analytical size exclusion chromatography (SEC) was found to be ineffective at distinguishing correct heavy chain and light chain pairing; binding proteins with Fab arm

light chain mispaired with CODV heavy chain and homodimeric binding proteins with two Fab arms were found to co-elute with the desired trispecific binding proteins. However, analytical hydrophobic interaction chromatography (HIC) was found to resolve the desired trispecific binding proteins from binding proteins with Fab arm light chain mispaired with CODV heavy chain and homodimeric binding proteins with two Fab arms (**FIG. 29**).

[0411] The 18 binding protein configurations shown in **FIG. 28B** were purified by Protein A affinity chromatography, then KappaSelect (GE Healthcare) purification. Species were monitored by HIC chromatography. One binding protein configuration was purified efficiently without inclusion of mispaired species: lambda light chain for CODV arm, kappa light chain for Fab arm, knob mutations on CODV arm, hole mutations on Fab arm, and RF mutations on Fab arm. HIC chromatography (**FIG. 30A**), SDS-PAGE (**FIG. 30B**), and intact mass analysis demonstrated that a single species corresponding to the desired trispecific binding protein was purified.

[0412] These results identify a binding protein configuration that allows for more efficient purification of binding proteins of interest away from mispaired species. Moreover, the purification process of Protein A followed by KappaSelect purification steps was shown to provide effective separation of binding proteins of interest away from mispaired species.

[0413] While the disclosure includes various embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the disclosure. In addition, the section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0414] Each embodiment herein described may be combined with any other embodiment or embodiments unless clearly indicated to the contrary. In particular, any feature or embodiment indicated as being preferred or advantageous may be combined with any other feature or features or embodiment or embodiments indicated as being preferred or advantageous, unless clearly indicated to the contrary.

[0415] All references cited in this application are expressly incorporated by reference herein.

SEQUENCES

Table 1: Heavy and light chain SEQ ID NOs for binding proteins 1-21 and the target antigens to which the binding proteins are directed.

Binding Protein #	SEQ ID NOs Included	Directed to:
1	1, 2, 3, 4	Her2 x (CD28 x CD3)
2	1, 2, 9, 10	Her2 x (CD28 x CD3)
3	13, 14, 3, 4	CD19 x (CD28 x CD3)
4	13, 14, 9, 10	CD19 x (CD28 x CD3)
5	17, 18, 3, 4	CD38 x (CD28 x CD3)
6	17, 18, 9, 10	CD38 x (CD28 x CD3)
7	21, 22, 3, 4	LAMP1 x (CD28 x CD3)
8	21, 22, 9, 10	LAMP1 x (CD28 x CD3)
9	60, 61, 62, 63	TNFa x (IL4 x IL13)
10	60, 61, 68, 69	TNFa x (IL13 x IL4)
11	60, 71, 68, 69	TNFa x (IL13 x IL4)
12	73, 74, 75, 76	IL13 x (IL4 x TNFa)
13	73, 74, 81, 82	IL13 x (TNFa x IL4)
14	85, 86, 87, 88	IL4 x (IL13 x TNFa)
15	85, 86, 93, 94	IL4 x (TNFa x IL13)
16	73, 74, 68, 69	IL13 x (IL13 x IL4)
17	85, 86, 68, 69	IL4 x (IL13 x IL4)
18	73, 74, 62, 63	IL13 x (IL4 x IL13)
19	85, 86, 62, 63	IL4 x (IL4 x IL13)
20	114, 115, 3, 4	CD20 x (CD28 x CD3)
21	114, 115, 9, 10	CD20 x (CD28 x CD3)

Table 2: Heavy and light chain sequences of binding proteins specifically directed to Her2, CD3, CD28, CD19 and/or CD20. CDR sequences are bolded and italicized.

Binding Protein 1 Amino Acid Sequences		
Heavy chain A (Anti-Her2-H_knob)	**Anti-Her2-H_Knob:** Evqlvesggglvqpggslrlscaas***gfnikdty***ihwvrqapgkglewva***riyptngy*** ***t***ryadsvkgrftisadtsknt**a**ylqmnslraedtavyyc***srwggdgfyamdy***wgqg tlvtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtf pavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcp apeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevh naktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgq prepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttppv ldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 1**
Light chain A	**Anti-Her2-L:** Diqmtqspsslsasvgdrvtitcras***qdvnta***vawyqqkpgkapklliy***sas***flysg vpsrfsgsrsgtdftltisslqpedfatyyc***qqhyttppt***fgqgtkveikrtvaapsvfifp	**SEQ ID NO: 2**

(Anti-Her2-L)	psdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlvqsgaevvkpgasvkvsckas***gytftsyy***ihwvrqapgqglewigs***iypgnvnt***nyaqkfqgratltvdtsistaymelsrlrsddtavyyc***trshygldw nfdv***wgkgttvtvsssqvqlvesgggvvqpgrslrlscaas***gftftkaw***mhwvrqapgkqlewvaq***ikdksns***yatyyadsvkgrftisrddskntlylqmnslraedtavyyc***rgvyyyalspfdy***wgqgtlvtvssrtastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctlppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsdgsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 3**
Light chain B (Anti-CD3 x Anti-CD28-L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckss***qslvhnnanty***lswylqkpgqspqsliy***kvs***nrfsgvpdrfsgsgsgtdftlkisrveaedvgvyyc***gqgtqyp***ftfgsgtkveikgqpkaapdiqmtqspsslsasvgdrvtitcqas***qniyvw***lnwyqqkpgkapklliy***kas***nlhtgvpsrfsgsgsgtdftltisslqpediatyyc***qqgqtypyt***fgqgtkleiktkgpsrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 4**
Binding Protein 1 Nucleotide Sequences		
Heavy chain A (Anti-Her2-H_Knob:)	**Anti-Her2-H_Knob:** gaagtgcagctggtggaatctggcggcggactggtgcagcctggcggatctctgagactgagctgtgccgccagcggcttcaacatcaaggacacctacatccactgggtgcgccaggccccctggcaagggactggaatgggtggccagaatctaccccaccaacggctacaccagatacgccgacagcgtgaagggccggttcaccatcagcgccgacaccagcaagaacaccgcctacctgcagatgaacagcctgcgggccgaggacaccgccgtgtactactgtagtagatggggaggcgacggcttctacgccatggactattggggccagggcaccctcgtgaccgtgtctagtgcgtcgaccaagggcccatcggtgttccctctggccccttgcagcagaagcaccagcgaatctacagcgccgccctgggctgcctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctgagcagcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctccctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtggatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagccccagagaggaacagttcaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaagtgtataccctgccccctgccaggaagagatgaccaagaaccaggtgtccctgtggtgtctcgtgaaaggcttctaccccagcgacattgccgtggaatgggagagcaacggccagcccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctgtactccaagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 5**
Light chain A (Anti-Her2-L:)	**Anti-Her2-L:** gacatccagatgacccagagccccagcagcctgtctgccagcgtgggcgacagagtgaccatcacctgtagagccagccaggacgtgaacaccgccgtggcctggtatcagcagaagcctggcaaggccccaagctgctgatctacagcgccagcttcctgtacagcggcgtgcccagcagattcagcggaagcagaagcggcaccgacttcaccctgaccatcagctcctgcagcccgaggacttcgccacctactactgccagcagcactacaccacccccccc	**SEQ ID NO: 6**

	acatttggccagggcaccaaggtggaaatcaagcgtacggtggccgctcccagcgtgt tcatcttcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgc tgaacaacttctaccccgcgaggccaaagtgcagtggaaggtggacaacgccctgca gagcggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctaca gcctgagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacg cctgcgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggg gcgagtgt	
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole:)	**Anti-CD28 x Anti-CD3-H_Hole:** caggtgcagctggtgcagtctggcgccgaggtcgtgaaacctggcgcctctgtgaagg tgtcctgcaaggccagcggctacaccttaccagctactacatccactgggtgcgccag gccccctggacagggactggaatggatcggcagcatctaccccggcaacgtgaacacc aactacgcccagaagttccagggcagagccaccctgaccgtggacaccagcatcagc accgcctacatggaactgagccggctgagaagcgacgacaccgccgtgtactactgca cccggtcccactacggcctggattggaacttcgacgtgtggggcaagggcaccaccgt gacagtgtctagcagccaggtgcagctggtggaatctggcggcggagtggtgcagcct ggcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctgga tgcactgggtgcgccaggcccctggaaagcagctggaatgggtggcccagatcaagg acaagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcacca tcagccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccg aggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattact ggggccagggaacctcgtgaccgtgtctagtcggaccgccagcacaaagggcccat cggtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctggg ctgcctcgtgaaggactactttccgagccccgtgaccgtgtcctggaactctggcgctct gacaagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctga gcagcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgt ggaccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggcc ctccctgcccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttccc cccaaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggt ggtggatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtg gaagtgcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccg ggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaag tgcaaggtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggcc aagggccagccccgcgagcctcaagtgtgtaccctgcccccctagccaggaagagatg accaagaaccaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgc cgtggaatgggagagcaacggccagcccgagaacaactacaagaccacccccctgt gctggacagcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggt ggcaggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccacta cacccagaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 7**
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagccccggccagagccccccagtccctgatctacaaggtgtccaa cagattcagcggcgtgccccgacagattctccggcagcggctctggcaccgacttcacc ctgaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggc acccagtacccccttcaccttttggcagcggcaccaaggtggaaatcaagggccagccca aggccgcccccgacatccagatgacccagagccccagcagcctgtctgccagcgtgg gcgacagagtgaccatcacctgtcaggccagccagaacatctacgtgtggctgaactg gtatcagcagaagccccggcaaggcccccaagctgctgatctacaaggccagcaacct gcacaccggcgtgccccagcagattttctggcagcggctccggcaccgacttcaccctg acaatcagctccctgcagccccgaggacattgccacctactactgccagcagggccaga cctaccccctacaccttttggccagggcaccaagctggaaatcaagaccaagggccccag ccgtacggtggccgctcccagcgtgttcatcttccccacctagcgacgagcagctgaagt ccggcacagcctctgtcgtgtgcctgctgaacaacttctaccccgcgaggccaaagtg	**SEQ ID NO: 8**

	cagtggaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtgaccga gcaggacagcaaggactccacctacagcctgagcagcaccctgacactgagcaaggc cgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctag ccccgtgaccaagagcttcaaccggggcgagtgt	
Binding Protein 2 Amino Acid Sequences		
Heavy chain A (Anti-Her2-H_knob)	**Anti-Her2-H_Knob:** Evqlvesggglvqpggslrlscaas***gfnikdty***ihwvrqapgkglewvar***iyptngy t***ryadsvkgrftisadtskntaylqmnslraedtavyyc***srwggdgfyamdy***wgqg tlvtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtf pavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcp apeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevh naktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgq prepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttppv ldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 1**
Light chain A (Anti-Her2-L)	**Anti-Her2-L:** Diqmtqspsslsasvgdrvtitcras***qdvnta***vawyqqkpgkapklliy***sas***flysg vpsrfsgsrsgtdftltisslqpedfatyyc***qqhyttppt***fgqgtkveikrtvaapsvfifp psdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslss stltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 2**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlqesgpglvkpsqtlsltctvsgfslsdygvhwvrqppgkglewlgvi wagggtnynpslksrktiskdtsknqvslklssvtaadtavyycardkgysyy ysmdywgqgttvtvsssqvqlvesgggvvqpgrslrlscaasgftftkawm hwvrqapgkqlewvaqikdksnsyatyyadsvkgrftisrddsknllylqm nslraedtavyycrgvyyalspfdywgqgtlvtvssrtastkgpsvfplapcsr stsestaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtv pssslgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflf ppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpre eqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprep qvctlppsqeemtknqvslscavkgfypsdiavewesngqpennykttppv ldsdgsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 9**
Light chain B (Anti-CD3 x Anti-CD28-L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckssqslvhnnantylswylqkpgqspqsliykvs nrfsgvpdrfsgsgsgtdftlkisrveaedvgvyycgqgtqypftfgsgtkveikgqp kaapdivltqspaslavspgqratitcrasesveyyvtslmqwyqqkpgqppkllifa asnvesgvparfsgsgsgtdftltinpveandvanyycqqsrkvpytfgqgtkleiktk gpsrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqe svteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 10**
Binding Protein 2 Nucleotide Sequences		
Heavy chain A (Anti-Her2-H_Knob:)	**Anti-Her2-H_Knob:** gaagtgcagctggtggaatctggcggcggactggtgcagcctggcggatctctgagac tgagctgtgccgccagcggcttcaacatcaaggacacctacatccactgggtgcgccag gccccctggcaagggactggaatgggtggccagaatctaccccaccaacggctacacc agatacgccgacagcgtgaagggccggttcaccatcagcgccgacaccagcaagaac accgcctacctgcagatgaacagcctgcgggccgaggacaccgccgtgtactactgta gtagatggggaggcgacggcttctacgccatggactattggggccagggcaccctcgt gaccgtgtctagtgcgtcgaccaagggcccatcggtgttccctctggccccttgcagca gaagcaccagcgaatctacagccgccctgggctgcctcgtgaaggactactttccgag cccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttccagc cgtgctccagagcagcggcctgtactctctgagcagcgtcgtgacagtgcccagcagc agcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaacaccaag gtggacaagcgggtggaatctaagtacggccctccctgccctccttgcccagccctga	**SEQ ID NO: 5**

	atttctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatgat cagccggaccccccgaagtgacctgcgtggtggtggatgtgtcccaggaagatcccgag gtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcccca gagaggaacagttcaacagcaccttaccgggtggtgtccgtgctgaccgtgctgcacca ggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgcccag ctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaagtgtat accctgccccctgccaggaagagatgaccaagaaccaggtgtccctgtggtgtctcgt gaaaggcttctaccccagcgacattgccgtggaatgggagagcaacggccagccccga gaacaactacaagaccaccccccctgtgctggacagcgacggctcattcttcctgtactc caagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctgctccgtg atgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccctgggcaa g	
Light chain A (Anti-Her2-L:)	**Anti-Her2-L:** gacatccagatgacccagagccccagcagcctgtctgccagcgtgggcgacagagtg accatcacctgtagagccagccaggacgtgaacaccgccgtggcctggtatcagcaga agcctggcaaggccccccaagctgctgatctacagcgccagcttcctgtacagcggcgt gccccagcagattcagcggaagcagaagcggcaccgacttcaccctgaccatcagctcc ctgcagccccgaggacttcgccacctactactgccagcagcactacaccaccccccccca catttggccagggcaccaaggtggaaatcaagcgtacggtggccgctcccagcgtgttc atcttcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctg aacaacttctaccccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcag agcggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctacag cctgagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacgc ctgcgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggggc gagtgt	**SEQ ID NO: 6**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole:)	**Anti-CD28 x Anti-CD3 _Hole:** caggtgcagctgcaggaatctggccctggcctcgtgaagcctagccagaccctgagcc tgacctgtaccgtgtccggcttcagcctgagcgactacggcgtgcactgggtgcgccag ccacctggaaaaggcctggaatggctgggcgtgatctgggctggcggaggcaccaac tacaaccccagcctgaagtccagaaagaccatcagcaaggacaccagcaagaaccag gtgtccctgaagctgagcagcgtgacagccgccgataccgccgtgtactactgcgcca gagacaagggctacagctactactacagcatggactactggggccagggcaccaccgt gaccgtgtcatcctctcaggtgcagctggtggaatctggcggcggagtggtgcagcctg gcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctggat gcactgggtgcgccaggccccctggaaagcagctggaatgggtggccccagatcaagga caagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccatc agccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccga ggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattactg gggccagggaaccctcgtgaccgtgtctagtcggaccgcttcgaccaagggcccatcg gtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctg cctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctgac aagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctgagca gcgtcgtgacagtgccccagcagcagcctgggcaccaagacctacacctgtaacgtgga ccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctcc ctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttcccccca aagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtg gatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagt gcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggt gtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaag gtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggc cagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgaccaaga accaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgtggaat gggagagcaacggccagcccgagaacaactacaagaccacccccccctgtgctggac	**SEQ ID NO: 11**

	agcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtggcagg aaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacaccca gaagtccctgtctctgtccctgggcaag	
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagcccggccagagcccccagtccctgatctacaaggtgtccaac agattcagcggcgtgcccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtacccccttcaccttttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatcgtgctgacacagagccctgctagcctggccgtgtctcctggaca gagggccaccatcacctgtagagccagcgagagcgtggaatattacgtgaccagcctg atgcagtggtatcagcagaagcccggccagcccccccaagctgctgattttcgccgccag caacgtggaaagcggcgtgccagccagattttccggcagcggctctggcaccgacttc accctgaccatcaacccccgtggaagccaacgacgtggccaactactactgccagcaga gccggaaggtgccctacacctttggccagggcaccaagctggaaatcaagaccaagg gccccagccgtacggtggccgctcccagcgtgttcatcttcccacctagcgacgagcag ctgaagtccggcacagcctctgtcgtgtgcctgctgaacaacttctaccccgcgaggc caaagtgcagtggaaggtggacaacgccctgcagagcggcaacagccaggaaagcg tgaccgagcaggacagcaaggactccacctacagcctgagcagcaccctgacactga gcaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggc ctgtctagccccgtgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 12**
Binding Protein 3 Amino Acid Sequences		
Heavy chain A (Anti-CD19(B34)-H_knob)	**Anti-CD19(B34)-H_Knob:** Qvqlvqsgaevkkpgssvkvsckasgyafssywmnwvrqapgqglewigqiw pgdgdtnynqkfkgratltadeststaymelsslrsedtavyycarretttvgryyyam dywgqgttvtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgal tsgvhtfpavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygpp cppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdg vevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiska kgqprepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennyktt ppvldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 13**
Light chain A (Anti-CD19(B34)-L)	**Anti-CD19(B34)-L:** Dlvltqspaslavspgqratitckasqsvdydgdsylnwyqqkpgqppklliydasn lvsgvparfsgsgsgtdftltinpveandtanyycqqstedpwtfgqgtkleikrtvaap svfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskd styslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 14**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlvqsgaevvkpgasvkvsckas***gytftsyy***ihwvrqapgqglewigs***i ypgnvnt***nyaqkfqgratltvdtsistaymelsrlrsddtavyyc***trshygldw nfdv***wgkgttvtvsssqvqlvesgggvvqpgrslrlscaas***gftftkaw***mhw vrqapgkqlewvaq***ikdksns***yatyyadsvkgrftisrddskntlylqmnslr aedtavyyc***rgvyyalspfdy***wgqgtlvtvssrtastkgpsvfplapcsrstses taalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpsssl gtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkpk dtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnst yrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctlp psqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsdgs fflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 3**
Light chain B (Anti-CD3 x Anti-	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckss***qslvhnnanty***lswylqkpgqspqsliy***kvs*** nrfsgvpdrfsgsgsgtdftlkisrveaedvgvyyc***gqgtqyp***ftfgsgtkveikgqpk aapdiqmtqspsslsasvgdrvtitcqas***qniyvw***lnwyqqkpgkapklliy***kas***nl	**SEQ ID NO: 4**

CD28-L)	htgvpsrfsgsgsgtdftltisslqpediatyyc***qqgqtypyt***fgqgtkleiktkgpsrtva apsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqds kdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	
Binding Protein 3 Nucleotide Sequences		
Heavy chain A (Anti-CD19(B34)-H_Knob)	**Anti-CD19(B34)-H_Knob:** caggtgcagctggtgcagagcggcgccgaagtgaagaagcctggcagcagcgtgaa ggtgagctgcaaggccagcggctatgccttcagcagctactggatgaactgggtgagg caggcacctggccagggcctggagtggataggccaaatatggcctggcgatggcgac accaactacaaccagaagttcaagggcagagcgaccttgaccgccgacgagagcacc agcaccgcgtacatggagctgagcagcctgaggagcgaggacaccgccgtgtactatt gcgccagaagggagaccaccaccgtgggcaggtactactacgccatggactactggg gccagggaaccaccgtgaccgtgagcagcgcctcgaccaagggcccatcggtgttcc ctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctgcctcgtg aaggactactttccgagccccgtgaccgtgtcctggaactctggcgctctgacaagcgg cgtgcacaccttccagccgtgctccagagcagcggcctgtactctctgagcagcgtcgt gacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgtggaccacaa gcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctccctgccct ccttgcccagcccctgaatttctgggcggaccctccgtgttcctgttcccccccaaagccca aggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtggatgtgtc ccaggaagatcccgaggtgcagttcaattggtacgtggacggcgtggaagtgcacaac gccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggtgtccgtg ctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtcca acaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggccagcccc gcgagcctcaagtgtataccctgcccccttgccaggaagagatgaccaagaaccaggt gtccctgtggtgtctcgtgaaaggcttctaccccagcgacattgccgtggaatgggagag caacggccagcccgagaacaactacaagaccacccccccctgtgctggacagcgacgg ctcattcttcctgtactccaagctgaccgtggacaagagccggtggcaggaaggcaacg tgttcagctgctccgtgatgcacgaggccctgcacaaccactacacccagaagtccctgt ctctgtccctgggcaag	**SEQ ID NO: 15**
Light chain A (Anti-CD19(B34)-L)	**Anti-CD19(B34)-L:** gacctcgtgctgacccagagccctgcgagcctggctgtgagccctggccagagagcc accatcacctgcaaagccagccagagcgtggactacgacggcgacagctacctcaact ggtaccagcagaagcctggccagccccccaagctgctgatttacgatgccagcaacct ggtgagcggcgtgcctgctagattcagcggctccggcagcggcaccgacttcaccctg accatcaacccccgtggaggccaacgacaccgccaactactactgccagcagagcacg gaggaccccctggaccttcggccagggcacaaagctggagatcaagcgtacggtggcc gctcccagcgtgttcatcttcccacctagcgacgagcagctgaagtccggcacagcctct gtcgtgtgcctgctgaacaacttctacccccgcgaggccaaagtgcagtggaaggtgga caacgccctgcagagcggcaacagccaggaaagcgtgaccgagcaggacagcaag gactccacctacagcctgagcagcaccctgacactgagcaaggccgactacgagaag cacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagccccgtgaccaaga gcttcaaccggggcgagtgt	**SEQ ID NO: 16**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** caggtgcagctggtgcagtctggcgccgaggtcgtgaaacctggcgcctctgtgaagg tgtcctgcaaggccagcggctacaccttaccagctactacatccactgggtgcgccag gccccctggacagggactggaatggatcggcagcatctaccccggcaacgtgaacacc aactacgcccagaagttccagggcagagccaccctgaccgtggacaccagcatcagc accgcctacatggaactgagccggctgagaagcgacgacaccgccgtgtactactgca cccggtcccactacggcctggattggaacttcgacgtgtggggcaagggcaccaccgt gacagtgtctagcagccaggtgcagctggtggaatctggcggcggagtggtgcagcct ggcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctgga tgcactgggtgcgccaggcccctggaaagcagctggaatgggtggcccagatcaagg acaagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccat	**SEQ ID NO: 7**

	cagccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccga ggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattactg gggccagggaaccctcgtgaccgtgtctagtcggaccgccagcacaaagggcccatc ggtgttccctctggcccctttgcagcagaagcaccagcgaatctacagccgccctgggct gcctcgtgaaggactactttccgagccctgaccgtgtcctggaactctggcgctctga caagcggcgtgcacacctttccagccgtgctccagagcagcggcctgtactctctgagc agcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgtgg accacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctc cctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttccccc aaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtg gatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagt gcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggt gtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaag gtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggc cagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgaccaaga accaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgtggaat gggagagcaacggccagccgagaacaactacaagaccacccccccctgtgctggac agcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtggcagg aaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacaccca gaagtccctgtctctgtccctgggcaag	
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagaccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagcccggccagagcccccagtccctgatctacaaggtgtccaac agattcagcggcgtgcccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtaccccttcacctttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatccagatgacccagagccccagcagcctgtctgccagcgtgggc gacagagtgaccatcacctgtcaggccagccagaacatctacgtgtggctgaactggta tcagcagaagccccggcaaggcccccaagctgctgatctacaaggccagcaacctgca caccggcgtgcccagcagattttctggcagcggctccggcaccgacttcaccctgacaa tcagctccctgcagccccgaggacattgccacctactactgccagcagggccagacctac ccctacacctttggccagggcaccaagctggaaatcaagaccaagggccccagccgta cggtggccgctcccagcgtgttcatcttccccacctagcgacgagcagctgaagtccggc acagcctctgtcgtgtgcctgctgaacaacttctaccccccgcgaggccaaagtgcagtg gaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtgaccgagcag gacagcaaggactccacctacagcctgagcagcaccctgacactgagcaaggccgac tacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagccccg tgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 8**
Binding Protein 4 Amino Acid Sequences		
Heavy chain A (Anti-CD19(B34)-H_knob)	**Anti-CD19(B34)-H_Knob:** Qvqlvqsgaevkkpgssvkvsckasgyafssywmnwvrqapgqglewigqiw pgdgdtnynqkfkgratltadeststaymelsslrsedtavyycarretttvgryyyam dywgqgttvtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgal tsgvhtfpavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygpp cppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdg vevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiska kgqprepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennyktt ppvldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 13**
Light chain A (Anti-CD19(B34	**Anti-CD19(B34)-L:** Dlvltqspaslavspgqratitckasqsvdydgdsylnwyqqkpgqppklliydasn lvsgvparfsgsgsgtdftltinpveandtanyycqqstedpwtfgqgtkleikrtvaap svfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskd	**SEQ ID NO: 14**

)-L)	styslsstltlskadyekhkvyacevthqglsspvtksfnrgec	
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlqesgpglvkpsqtlsltctvsgfslsdygvhwvrqppgkglewlgviw agggtnynpslksrktiskdtsknqvslklssvtaadtavyycardkgysyyys mdywgqgttvtvsssqvqlvesgggvvqpgrslrlscaasgftftkawmhw vrqapgkqlewvaqikdksnsyatyyadsvkgrftisrddskntlylqmnslr aedtavyycrgvyyalspfdywgqgtlvtvssrtastkgpsvfplapcsrstse staalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpsss lgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkp kdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfns tyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctl ppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsd gsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 9**
Light chain B (Anti-CD3 x Anti-CD28-L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckssqslvhnnantylswylqkpgqspqsliykvsn rfsgvpdrfsgsgsgtdftlkisrveaedvgvyycgqgtqypftfgsgtkveikgqpka apdivltqspaslavspgqratitcrasesveyyvtslmqwyqqkpgqppkllifaas nvesgvparfsgsgsgtdftltinpveandvanyycqqsrkvpytfgqgtkleiktkg psrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesv teqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 10**
Binding Protein 4 Nucleotide Sequences		
Heavy chain A (Anti-CD19(B34)-H_Knob)	**Anti-CD19(B34)-H_Knob:** caggtgcagctggtgcagagcggcgccgaagtgaagaagcctggcagcagcgtgaa ggtgagctgcaaggccagcggctatgccttcagcagctactggatgaactgggtgagg caggcacctggccagggcctggagtggataggccaaatatggcctggcgatggcgac accaactacaaccagaagttcaagggcagagcgaccttgaccgccgacgagagcacc agcaccgcgtacatggagctgagcagcctgaggagcgaggacaccgccgtgtactatt gcgccagaagggagaccaccaccgtgggcaggtactactacgccatggactactggg gccagggaaccaccgtgaccgtgagcagcgcctcgaccaagggcccatcggtgttcc ctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctgcctcgtg aaggactactttccgagccccgtgaccgtgtcctggaactctggcgctctgacaagcgg cgtgcacaccttccagccgtgctccagagcagcggcctgtactctctgagcagcgtcgt gacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgtggaccacaa gcccagcaacaccaaggtggacaagcgggtggaatctaagtacggcccctccctgccct ccttgcccagcccctgaatttctgggcggaccctccgtgttcctgttcccccccaaagccca aggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtggatgtgtc ccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagtgcacaac gccaagaccaagccccagagaggaacagttcaacagcacctaccgggtggtgtccgtg ctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtcca acaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggccagccccc gcgagcctcaagtgtataccctgccccctgccaggaagagatgaccaagaaccaggt gtccctgtggtgtctcgtgaaaggcttctaccccagcgacattgccgtggaatgggagag caacggccagccccgagaacaactacaagaccacccccccctgtgctggacagcgacgg ctcattcttcctgtactccaagctgaccgtggacaagagccggtggcaggaaggcaacg tgttcagctgctccgtgatgcacgaggccctgcacaaccactacacccagaagtccctgt ctctgtccctgggcaag	**SEQ ID NO: 15**
Light chain A (Anti-CD19(B34)-L)	**Anti-CD19(B34)-L:** gacctcgtgctgacccagagccctgcgagcctggctgtgagccctggccagagagcc accatcacctgcaaagccagccagagcgtggactacgacggcgacagctacctcaact ggtaccagcagaagcctggccagccccccaagctgctgatttacgatgccagcaacct ggtgagcggcgtgcctgctagattcagcggctccggcagcggcaccgacttcaccctg accatcaaccccgtggaggccaacgacaccgccaactactactgccagcagagcacg gaggacccctggaccttcggccagggcacaaagctggagatcaagcgtacggtggcc	**SEQ ID NO: 16**

	gctcccagcgtgttcatcttcccacctagcgacgagcagctgaagtccggcacagcctct gtcgtgtgcctgctgaacaacttctacccccgcgaggccaaagtgcagtggaaggtgga caacgccctgcagagcggcaacagccaggaaagcgtgaccgagcaggacagcaag gactccacctacagcctgagcagcaccctgacactgagcaaggccgactacgagaag cacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagccccgtgaccaaga gcttcaaccggggcgagtgt	
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole:)	**Anti-CD28 x Anti-CD3-H_Hole:** caggtgcagctgcaggaatctggccctggcctcgtgaagcctagccagaccctgagcc tgacctgtaccgtgtccggcttcagcctgagcgactacggcgtgcactgggtgcgccag ccacctggaaaaggcctggaatggctgggcgtgatctgggctggcggaggcaccaac tacaaccccagcctgaagtccagaaagaccatcagcaaggacaccagcaagaaccag gtgtccctgaagctgagcagcgtgacagccgccgataccgccgtgtactactgcgcca gagacaagggctacagctactactacagcatggactactggggccagggcaccaccgt gaccgtgtcatcctctcaggtgcagctggtggaatctggcggcggagtggtgcagcctg gcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctggat gcactgggtgcgccaggccccctggaaagcagctggaatgggtggccccagatcaagga caagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccatc agccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccga ggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattactg gggccagggaaccctcgtgaccgtgtctagtcggaccgcttcgaccaagggcccatcg gtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctg cctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctgac aagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctgagca gcgtcgtgacagtgccccagcagcagcctgggcaccaagacctacacctgtaacgtgga ccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctcc ctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttccccca aagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtg gatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagt gcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggt gtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaag gtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggc cagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgaccaaga accaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgtggaat gggagagcaacggccagccccgagaacaactacaagaccacccccccctgtgctggac agcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtggcagg aaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacacccca gaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 11**
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagaccccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagccccggccagagccccccagtccctgatctacaaggtgtccaac agattcagcggcgtgccccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtacccccttcaccttttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatcgtgctgacacagagccctgctagcctggccgtgtctcctggaca gagggccaccatcacctgtagagccagcgagagcgtggaatattacgtgaccagcctg atgcagtggtatcagcagaagccccggccagccccccaagctgctgatttttcgccgccag caacgtggaaagcggcgtgccagccagatttttccggcagcggctctggcaccgacttc accctgaccatcaacccccgtggaagccaacgacgtggccaactactactgccagcaga gccggaaggtgccctacacctttggccagggcaccaagctggaaatcaagaccaagg gccccagccgtacggtggccgctcccagcgtgttcatcttcccacctagcgacgagcag ctgaagtccggcacagcctctgtcgtgtgcctgctgaacaacttctacccccgcgaggc caaagtgcagtggaaggtggacaacgccctgcagagcggcaacagccaggaaagcg	**SEQ ID NO: 12**

	tgaccgagcaggacagcaaggactccacctacagcctgagcagcaccctgacactga gcaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggc ctgtctagccccgtgaccaagagcttcaaccggggcgagtgt	
Binding Protein 5 Amino Acid Sequences		
Heavy chain A (Anti-CD38-H_knob)	**Anti-CD38-H_Knob:** Qvqlvqsgaevakpgtsvklsckasgytftdywmqwvkqrpgqglewigtiypg dgdtgyaqkfqgkatltadkssktvymhlsslasedsavyycargdyygsnsldyw gqgtsvtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsg vhtfpavlqssglylssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcp pcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgve vhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskak gqprepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttp pvldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 17**
Light chain A (Anti-CD38-L)	**Anti-CD38-L:** Divmtqshlsmstslgdpvsitckasqdvstvvawyqqkpgqsprrliysasyryig vpdrftgsgagtdftftissvqaedlavyycqqhysppytfgggtkleikrtvaapsvfi fppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstys lsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 18**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlvqsgaevvkpgasvkvsckas***gytftsyy***ihwvrqapgqglewigs***i ypgnvnt***nyaqkfqgratltvdtsistaymelsrlrsddtavyyc***trshygldw nfdv***wgkgttvtvsssqvqlvesgggvvqpgrslrlscaas***gftftkaw***mhw vrqapgkqlewvaq***ikdksns***yatyyadsvkgrftisrddsknt lylqmnslr aedtavyyc***rgvyyalspfdy***wgqgtlvtvssrtastkgpsvfplapcsrstses taalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglylssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkp kdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfns tyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctl ppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsd gsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 3**
Light chain B (Anti-CD3 x Anti-CD28-L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckss***qslvhnnanty***lswylqkpgqspqsliy***kvs*** nrfsgvpdrfsgsgsgtdftlkisrveaedvgvyyc***gqgtqyp***fttgsgtkveikgqpk aapdiqmtqspsslsasvgdrvtitcqas***qniyvw***lnwyqqkpgkapklliy***kas***nl htgvpsrfsgsgsgtdftltisslqpediatyyc***qqgqtypyt***fgqgtkleiktkgpsrtv aapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqd skdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 4**
Binding Protein 5 Nucleotide Sequences		
Heavy chain A (Anti-CD38-H_Knob)	**Anti-CD38-H_Knob:** caggtgcagctggtgcagtctggcgccgaagtggccaagcctggcacaagcgtgaag ctgagctgcaaggccagcggctacaccttcaccgactactggatgcagtgggtcaagc agaggccaggccagggcctggaatggatcggcacaatctatccggcgacggcgata ccggctacgcccagaagtttcagggcaaggccaccctgaccgccgacaagagcagca agaccgtgtacatgcacctgagcagcctggccagcgaggacagcgccgtgtactattg cgccagaggcgactactacggcagcaacagcctggactattggggccagggcaccag cgtgacagtgtctagtgcgtcgaccaagggcccatcggtgttcccctctggccccttgcag cagaagcaccagcgaatctacagccgccctgggctgcctcgtgaaggactactttccg agccccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttcca gccgtgctccagagcagcggcctgtactctctgagcagcgtcgtgacagtgcccagca gcagcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaacacca aggtggacaagcgggtggaatctaagtacggccctcccctgcccctccttgcccagcccct gaatttctgggcggaccctccgtgttcctgttcccccaaagcccaaggacaccctgatg atcagccggacccccgaagtgacctgcgtggtggtggatgtgtcccaggaagatcccg	**SEQ ID NO: 19**

	aggtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcc cagagaggaacagttcaacagcacctaccgggtggtgtccgtgctgaccgtgctgcac caggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgccc agctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaagtg tataccctgccccctgccaggaagagatgaccaagaaccaggtgtccctgtggtgtctc gtgaaaggcttctaccccagcgacattgccgtggaatgggagagcaacggccagccc gagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctgta ctccaagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctgctcc gtgatgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccctggg caag	
Light chain A (Anti-CD38-L)	**Anti-CD38-L:** gacatcgtgatgacccagagccacctgagcatgagcaccagcctgggcgaccccgtgt ccatcacctgtaaagccagccaggacgtgtccaccgtggtggcctggtatcagcagaa gcctggccagagccccagacggctgatctacagcgccagctatcggtacatcggcgtg cccgacagattcaccggaagcggagccggcaccgacttcaccttcaccatcagctctgt gcaggccgaggacctggccgtgtactactgccagcagcactacagccccccctacacc tttggcggaggcaccaagctggaaatcaagcgtacggtggccgctcccagcgtgttcat cttcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctga acaacttctaccccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcaga gcggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctacagc ctgagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacgcc tgcgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggggc gagtgt	**SEQ ID NO: 20**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** caggtgcagctggtgcagtctggcgccgaggtcgtgaaacctggcgcctctgtgaagg tgtcctgcaaggccagcggctacacctttaccagctactacatccactgggtgcgccag gccccctggacagggactggaatggatcggcagcatctaccccggcaacgtgaacacc aactacgcccagaagttccagggcagagccaccctgaccgtggacaccagcatcagc accgcctacatggaactgagccggctgagaagcgacgacaccgccgtgtactactgca cccggtcccactacggcctggattggaacttcgacgtgtggggcaagggcaccaccgt gacagtgtctagcagccaggtgcagctggtggaatctggcggcggagtggtgcagcct ggcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctgga tgcactgggtgcgccaggccccctggaaagcagctggaatgggtggcccagatcaagg acaagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccat cagccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccg aggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattact ggggccagggaaccctcgtgaccgtgtctagtcggaccgccagcacaaagggcccat cggtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctggg ctgcctcgtgaaggactactttccgagccccgtgaccgtgtcctggaactctggcgctct gacaagcggcgtgcacaccttccagccgtgctccagagcagcggcctgtactctctga gcagcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgt ggaccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggcc ctccctgcctccttgcccagcccctgaatttctgggcggacccteegtgttcctgttcccc ccaaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtg gtggatgtgtcccaggaagatccegaggtgcagttcaattggtacgtggacggcgtgga agtgcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggt ggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgc aaggtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaag ggccagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgacc aagaaccaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgt ggaatgggagagcaacggccagcccgagaacaactacaagaccacccccccctgtgct ggacagcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtgg caggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactaca	**SEQ ID NO: 7**

	cccagaagtccctgtctctgtccctgggcaag	
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagccccggccagagccccccagtccctgatctacaaggtgtccaac agattcagcggcgtgcccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtacccccttcacctttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatccagatgacccagagccccagcagcctgtctgccagcgtgggc gacagagtgaccatcacctgtcaggccagccagaacatctacgtgtggctgaactggta tcagcagaagccccggcaaggccccccaagctgctgatctacaaggccagcaacctgca caccggcgtgccccagcagattttctggcagcggctccggcaccgacttcaccctgacaa tcagctccctgcagccccgaggacattgccacctactactgccagcagggccagacccta ccccctacacctttggccagggcaccaagctggaaatcaagaccaagggccccagccgt acggtggccgctcccagcgtgttcatcttcccacctagcgacgagcagctgaagtccgg cacagcctctgtcgtgtgcctgctgaacaacttctaccccccgcgaggccaaagtgcagt ggaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtgaccgagca ggacagcaaggactccacctacagcctgagcagcaccctgacactgagcaaggccga ctacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagcccc gtgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 8**
Binding Protein 6 Amino Acid Sequences		
Heavy chain A (Anti-CD38-H_knob)	**Anti-CD38-H_Knob:** qvqlvqsgaevakpgtsvklsckasgytftdywmqwvkqrpgqglewigtiypgd gdtgyaqkfqgkatltadkssktvymhlsslasedsavyycargdyygsnsldywg qgtsvtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgv htfpavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcpp cpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvev hnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakg qprepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttpp vldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 17**
Light chain A (Anti-CD38-L)	**Anti-CD38-L:** Divmtqshlsmstslgdpvsitckasqdvstvvawyqqkpgqsprrliysasyryig vpdrftgsgagtdftftissvqaedlavyycqqhysppytfgggtkleikrtvaapsvfi fppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstys lsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 18**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlqesgpglvkpsqtlsltctvsgfslsdygvhwvrqppgkglewlgviw agggtnynpslksrktiskdtsknqvslklssvtaadtavyycardkgysyyy smdywgqgttvtvsssqvqlvesgggvvqpgrslrlscaasgftftkawmh wvrqapgkqlewvaqikdksnsyatyyadsvkgrftisrddskntlylqmn slraedtavyycrgvyyalspfdywgqgtlvtvssrtastkgpsvfplapcsrst sestaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvp ssslgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfpp kpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeq fnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqv ctlppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvld sdgsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 9**
Light chain B (Anti-CD3 x Anti-CD28-L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckssqslvhnnantylswylqkpgqspqsliykvs nrfsgvpdrfsgsgsgtdftlkisrveacdvgvyycgqgtqypftfgsgtkveikgqp kaapdivltqspaslavspgqratitcrasesveyyvtslmqwyqqkpgqppkllifa asnvesgvparfsgsgsgtdftltinpveandvanyycqqsrkvpytfgqgtkleiktk	**SEQ ID NO: 10**

	gpsrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqe svteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	
Binding Protein 6 Nucleotide Sequences		
Heavy chain A (Anti-CD38-H_Knob)	**Anti-CD38-H_Knob:** caggtgcagctggtgcagtctggcgccgaagtggccaagcctggcacaagcgtgaag ctgagctgcaaggccagcggctacaccttcaccgactactggatgcagtgggtcaagc agaggccaggccagggcctggaatggatcggcacaatctatccggcgacggcgata ccggctacgcccagaagtttcagggcaaggccaccctgaccgccgacaagagcagca agaccgtgtacatgcacctgagcagcctggccagcgaggacagcgccgtgtactattg cgccagaggcgactactacggcagcaacagcctggactattggggccagggcaccag cgtgacagtgtctagtgcgtcgaccaagggcccatcggtgttccctctggccccttgcag cagaagcaccagcgaatctacagccgccctgggctgcctcgtgaaggactactttccg agccccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttcca gccgtgctccagagcagcggcctgtactctctgagcagcgtcgtgacagtgcccagca gcagcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaacacca aggtggacaagcgggtggaatctaagtacggccctccctgccctccttgcccagccct gaatttctgggcggaccctccgtgttcctgttcccccaaagcccaaggacaccctgatg atcagccggacccccgaagtgacctgcgtggtggtggatgtgtcccaggaagatcccg aggtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcc cagagaggaacagttcaacagcacctaccgggtggtgtccgtgctgaccgtgctgcac caggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgccc agctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaagtg tataccctgccccctgccaggaagagatgaccaagaaccaggtgtccctgtggtgtctc gtgaaaggcttctaccccagcgacattgccgtggaatgggagagcaacggccagccc gagaacaactacaagaccacccccctgtgctggacagcgacggctcattcttcctgta ctccaagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctgctcc gtgatgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccctggg caag	**SEQ ID NO: 19**
Light chain A (Anti-CD38-L)	**Anti-CD38-L:** gacatcgtgatgacccagagccacctgagcatgagcaccagcctgggcgaccccgtgt ccatcacctgtaaagccagccaggacgtgtccaccgtggtggcctggtatcagcagaa gcctggccagagccccagacggctgatctacagcgccagctatcggtacatcggcgtg cccgacagattcaccggaagcggagccggcaccgacttcaccttcaccatcagctctgt gcaggccgaggacctggccgtgtactactgccagcagcactacagccccccctacacc tttggcggaggcaccaagctggaaatcaagcgtacggtggccgctcccagcgtgttcat cttcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctga acaacttctaccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcaga gcggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctacagc ctgagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacgcc tgcgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggggc gagtgt	**SEQ ID NO: 20**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole:)	**Anti-CD28 x Anti-CD3_Hole:** caggtgcagctgcaggaatctggccctggcctcgtgaagcctagccagaccctgagcc tgacctgtaccgtgtccggcttcagcctgagcgactacggcgtgcactgggtgcgccag ccacctggaaaaggcctggaatggctgggcgtgatctgggctggcggaggcaccaac tacaaccccagcctgaagtccagaaagaccatcagcaaggacaccagcaagaaccag gtgtccctgaagctgagcagcgtgacagccgccgataccgccgtgtactactgcgcca gagacaagggctacagctactactacagcatggactactggggccagggcaccaccgt gaccgtgtcatcctctcaggtgcagctggtggaatctggcggcggagtggtgcagcctg gcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctggat gcactgggtgcgccaggccccctggaaagcagctggaatgggtggcccagatcaagga caagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccatc agccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccga	

	ggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattactg gggccagggaaccctcgtgaccgtgtctagtcggaccgcttcgaccaagggcccatcg gtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctg cctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctgac aagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctgagca gcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgtgga ccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctcc ctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttcccccca aagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtg gatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagt gcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggt gtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaag gtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggc cagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgaccaag aaccaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgtgga atgggagagcaacggccagccgagaacaactacaagaccacccccccctgtgctgga cagcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtggcag gaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacaccc agaagtccctgtctctgtccctgggcaag	
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagcccggccagagccccagtccctgatctacaaggtgtccaac agattcagcggcgtgcccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtacccccttcaccttttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatcgtgctgacacagagccctgctagcctggccgtgtctcctggac agagggccaccatcacctgtagagccagcgagagcgtggaatattacgtgaccagcct gatgcagtggtatcagcagaagcccggccagccccccaagctgctgattttcgccgcc agcaacgtggaaagcggcgtgccagccagattttccggcagcggctctggcaccgact tcaccctgaccatcaacccccgtggaagccaacgacgtggccaactactactgccagca gagccggaaggtgccctacacctttggccagggcaccaagctggaaatcaagaccaa gggccccagccgtacggtggccgctcccagcgtgttcatcttcccacctagcgacgag cagctgaagtccggcacagcctctgtcgtgtgcctgctgaacaacttctacccccgcga ggccaaagtgcagtggaaggtggacaacgccctgcagagcggcaacagccaggaaa gcgtgaccgagcaggacagcaaggactccacctacagcctgagcagcaccctgacac tgagcaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagg gcctgtctagccccgtgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 12**
Binding Protein 7 Amino Acid Sequences:		
Heavy chain A (Anti-LAMP1-H_knob)	**Anti-LAMP1-H_Knob:** qvqlvqsgaevkkpgssvkvsckas***gyiftnynih***wvkkspgqglewig***aiypgn gdap***ysqkfqgkatltadtststtymelsslrsedtavyycvr***anwdvafay***wgqgtl vtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtfpa vlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcpape flggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnakt kpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprep qvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttppvldsd gsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 21**
Light chain A (Anti-LAMP1-L)	**Anti-LAMP1-L:** Diqmtqspsslsasvgdrvtitc***kasqdidryma***wyqdkpgkaprllih***dtstlqs***g vpsrfsgsgsgrdytltisnlepedfatyyc***lqydnlwt***fgggtkveikrtvaapsvfifp psdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslss tltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 22**
Heavy	**Anti-CD28 x Anti-CD3-H_Hole:**	**SEQ ID NO: 3**

chain B (Anti-CD28 x Anti-CD3-H_Hole)	Qvqlvqsgaevvkpgasvkvsckas***gytftsyy***ihwvrqapgqglewigs***i ypgnvnt***nyaqkfqgratltvdtsistaymelsrlrsddtavyyc***trshygldw nfdv***wgkgttvtvsssqvqlvesgggvvqpgrslrlscaas***gftftkaw***mhw vrqapgkqlewvaq***ikdksns***yatyyadsvkgrftisrddsknt lylqmnslr aedtavyyc***rgvyyyalspfdy***wgqgtlvtvssrtastkgpsvfplapcsrstses taalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctlppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsdgsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	
Light chain B (Anti-CD3 x Anti-CD28L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckss***qslvhnnanty***lswylqkpgqspqsliy***kvs***nrfsgvpdrfsgsgsgtdftlkisrveaedvgvyyc***gqgtqyp***ftfgsgtkveikgqpkaapdiqmtqspsslsasvgdrvtitcqas***qniyvw***lnwyqqkpgkapklliy***kas***nlhtgvpsrfsgsgsgtdftltisslqpediatyyc***qqgqtypyt***fgqgtkleiktkgpsrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 4**
Binding Protein 7 Nucleotide Sequences		
Heavy chain A (Anti-LAMP1-H_Knob)	**Anti-LAMP1-H_Knob:** caggtgcagctggtgcagtctggcgccgaagtgaagaaaccccggcagcagcgtgaaggtgtcctgcaaggccagcggctacatcttcaccaactacaacatccactgggtcaagaagtccccaggccagggcctggaatggatcggcgccatctatccccggaaacggcgacgccccttacagccagaagttccagggcaaggccacactgaccgccgataccagcacctccaccacctacatggaactgagcagcctgcggagcgaggacaccgccgtgtactattgcgtgcgggccaactgggatgtggccttcgcctattggggccagggcacactcgtgaccgtgtcctctgcgtcgaccaagggcccatcggtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctgcctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctgagcagcgtcgtgacagtgccccagcagcagcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaacaccaaggtggacaagcgcgggtggaatctaagtacggccctccctgccctccttgcccagcccctgaatttctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtggatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaagtgtataccctgccccccttgccaggaagagatgaccaagaaccaggtgtccctgtggtgtctcgtgaaaggctctacccccagcgacattgccgtggaatgggagagcaacggccagccccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctgtactccaagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 23**
Light chain A (Anti-LAMP1-L)	**Anti-LAMP1-L:** gacatccagatgacccagagccccagcagcctgtctgccagcgtgggcgacagagtgaccatcacatgcaaggccagccaggacatcgatcggtacatggcctggtatcaggacaagccccggcaaggcccccagactgctgatccacgataccagcacactgcagagcggcgtgcccagcagatttttcggctctggcagcggcagagactacaccctgaccatcagcaacctggaacccgaggacttcgccacctactactgcctgcagtacgacaacctgtggaccttcggcggaggcaccaaggtggaaatcaagcgtacggtggccgctcccagcgtgttcatctcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctgaacaacttctaccccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctacagcct	**SEQ ID NO: 24**

	gagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacgcctg cgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggggcga gtgt	
Heavy chain B(Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** caggtgcagctggtgcagtctggcgccgaggtcgtgaaacctggcgcctctgtgaagg tgtcctgcaaggccagcggctacaccttaccagctactacatccactgggtgcgccag gccccctggacagggactggaatggatcggcagcatctaccccggcaacgtgaacacc aactacgcccagaagttccagggcagagccaccctgaccgtggacaccagcatcagc accgcctacatggaactgagccggctgagaagcgacgacaccgccgtgtactactgca cccggtcccactacggcctggattggaacttcgacgtgtggggcaagggcaccaccgt gacagtgtctagcagccaggtgcagctggtggaatctggcggcggagtggtgcagcct ggcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctgga tgcactgggtgcgccaggccccctggaaagcagctggaatgggtggcccagatcaagg acaagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccat cagccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccga ggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattactg gggccagggaaccctcgtgaccgtgtctagtcggaccgccagcacaaagggcccatc ggtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggct gcctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctga caagcggcgtgcacaccttccagccgtgctccagagcagcggcctgtactctctgagc agcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgtgg accacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctc cctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttccccc caaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtg gatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagt gcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggt gtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaag gtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggc cagccccgcgagcctcaagtgtgtaccctgcccctagccaggaagagatgaccaaga accaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgtggaat gggagagcaacggccagcccgagaacaactacaagaccacccccctgtgctggac agcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtggcagg aaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacaccca gaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 7**
Light chain B (Anti-CD3 x Anti-CD28-L:)	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagcccggccagagccccccagtccctgatctacaaggtgtccaac agattcagcggcgtgccccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtaccccttcacctttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatccagatgacccagagccccagcagcctgtctgccagcgtgggc gacagagtgaccatcacctgtcaggccagccagaacatctacgtgtggctgaactggta tcagcagaagcccggcaaggccccccaagctgctgatctacaaggccagcaacctgca caccggcgtgccccagcagattttctggcagcggctccggcaccgacttcaccctgacaa tcagctccctgcagcccgaggacattgccacctactactgccagcagggccagacctac ccctacaccttttggccagggcaccaagctggaaatcaagaccaagggccccagccgta cggtggccgctcccagcgtgttcatcttccccacctagcgacgagcagctgaagtccggc acagcctctgtcgtgtgcctgctgaacaacttctaccccccgcgaggccaaagtgcagtg gaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtgaccgagcag gacagcaaggactccacctacagcctgagcagcaccctgacactgagcaaggccgac tacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagcccg tgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 8**

Binding Protein 8 Amino Acid Sequences		
Heavy chain A (Anti-LAMP1-H_knob)	**Anti-LAMP1-H_Knob:** qvqlvqsgaevkkpgssvkvsckas***gyiftnynih***wvkkspgqglewig***aiypgn gdap***ysqkfqgkatltadtststtymelsslrsedtavyycvr***anwdvafay***wgqgtl vtvssastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtfpa vlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcpape flggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnakt kpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprep qvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttppvldsd gsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 21**
Light chain A (Anti-LAMP1-L)	**Anti-LAMP1-L:** Diqmtqspsslsasvgdrvtitc***kasqdidryma***wyqdkpgkaprllih***dtstlqs***g vpsrfsgsgsgrdytltisnlepedfatyyc***lqydnlwt***fgggtkveikrtvaapsvfifp psdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstyslss tltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 22**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole)	**Anti-CD28 x Anti-CD3-H_Hole:** Qvqlqesgpglvkpsqtlsltctvsgfslsdygvhwvrqppgkglewlgviw agggtnynpslksrktiskdtsknqvslklssvtaadtavyycardkgysyyys mdywgqgttvtvsssqvqlvesgggvvqpgrslrlscaasgftftkawmhw vrqapgkqlewvaqikdksnsyatyyadsvkgrftisrddsknt lylqmnslr aedtavyycrgvyyalspfdywgqgtlvtvssrtastkgpsvfplapcsrstse staalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpsss lgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkp kdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfns tyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctl ppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsd gsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 9**
Light chain B (Anti-CD3 x Anti-CD28-L)	**Anti-CD3 x Anti-CD28-L:** Divmtqtplslsvtpgqpasisckssqslvhnnantylswylqkpgqspqsliykvsn rfsgvpdrfsgsgsgtdftlkisrveaedvgvyycgqgtqypftfgsgtkveikgqpka apdivltqspaslavspgqratitcrasesveyyvtslmqwyqqkpgqppkllifaas nvesgvparfsgsgsgtdftltinpveandvanyycqqsrkvpytfgqgtkleiktkg psrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesv teqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 10**
Binding Protein 8 Nucleotide Sequences		
Heavy chain A (Anti-LAMP1-H_Knob)	**Anti-LAMP1-H_Knob:** caggtgcagctggtgcagtctggcgccgaagtgaagaaacccggcagcagcgtgaag gtgtcctgcaaggccagcggctacatcttcaccaactacaacatccactgggtcaagaa gtccccaggccagggcctggaatggatcggcgccatctatcccggaaacggcgacgc ccttacagccagaagttccagggcaaggccaccctgaccgccgataccagcacctcc accacctacatggaactgagcagcctgcggagcgaggacaccgccgtgtactattgcg tgcgggccaactgggatgtggccttcgcctattggggccagggcacactcgtgaccgtg tcctctgcgtcgaccaagggcccatcggtgttccctctggccccttgcagcagaagcac cagcgaatctacagccgccctgggctgcctcgtgaaggactactttccgagccccgtga ccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttccagccgtgctcc agagcagcggcctgtactctctgagcagcgtcgtgacagtgcccagcagcagcctggg caccaagacctacacctgtaacgtggaccacaagcccagcaacaccaaggtggacaa gcgggtggaatctaagtacggccctccctgccctccttgcccagccccctgaatttctggg cggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatgatcagccgga cccccgaagtgacctgcgtggtggtggatgtgtcccaggaagatccccgaggtgcagttc aattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcccagagaggaa cagttcaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggct	**SEQ ID NO: 23**

	gaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgcccagctccatcga gaaaaccatcagcaaggccaagggccagccccgcgagcctcaagtgtataccctgcc ccctgccaggaagagatgaccaagaaccaggtgtccctgtggtgtctcgtgaaaggct tctaccccagcgacattgccgtggaatgggagagcaacggccagcccgagaacaact acaagaccaccccccctgtgctggacagcgacggctcattcttcctgtactccaagctga ccgtggacaagagccggtggcaggaaggcaacgtgttcagctgctccgtgatgcacga ggccctgcacaaccactacacccagaagtccctgtctctgtccctgggcaag	
Light chain A (Anti-LAMP1-L)	**Anti-LAMP1-L:** gacatccagatgacccagagccccagcagcctgtctgccagcgtgggcgacagagtg accatcacatgcaaggccagccaggacatcgatcggtacatggcctggtatcaggaca agccccggcaaggcccccagactgctgatccacgataccagcacactgcagagcggcg tgcccagcagattttccggctctggcagcggcagagactacaccctgaccatcagcaac ctggaacccgaggacttcgccacctactactgcctgcagtacgacaacctgtggaccttc ggcggaggcaccaaggtggaaatcaagcgtacggtggccgctcccagcgtgttcatct tcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctgaac aacttctaccccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcagagc ggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctacagcct gagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacgcctg cgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggggcga gtgt	**SEQ ID NO: 24**
Heavy chain B (Anti-CD28 x Anti-CD3-H_Hole:)	**Anti-CD28 x Anti-CD3-H_Hole:** caggtgcagctgcaggaatctggccctggcctcgtgaagcctagccagaccctgagcc tgacctgtaccgtgtccggcttcagcctgagcgactacggcgtgcactgggtgcgccag ccacctggaaaaggcctggaatggctgggcgtgatctgggctggcggaggcaccaac tacaaccccagcctgaagtccagaaagaccatcagcaaggacaccagcaagaaccag gtgtccctgaagctgagcagcgtgacagccgccgataccgccgtgtactactgcgcca gagacaagggctacagctactactacagcatggactactggggccagggcaccaccgt gaccgtgtcatcctctcaggtgcagctggtggaatctggcggcggagtggtgcagcctg gcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctggat gcactgggtgcgccaggccccctggaaagcagctggaatgggtggccccagatcaagga caagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccatc agccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccga ggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattactg gggccagggaaccctcgtgaccgtgtctagtcggaccgcttcgaccaagggcccatcg gtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctgggctg cctcgtgaaggactactttccccgagccccgtgaccgtgtcctggaactctggcgctctgac aagcggcgtgcacaccttttccagccgtgctccagagcagcggcctgtactctctgagca gcgtcgtgacagtgccccagcagcagcctgggcaccaagacctacacctgtaacgtgga ccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggccctcc ctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttccccccca aagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtg gatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtggaagt gcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggtggt gtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaag gtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggc cagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgaccaaga accaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgtggaat gggagagcaacggccagccccgagaacaactacaagaccacccccccctgtgctggac agcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtggcagg aaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactacaccca gaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 11**
Light chain B	**Anti-CD3 x Anti-CD28-L:** gacatcgtgatgacccagaccccctgagcctgagcgtgacacctggacagcctgcca	**SEQ ID NO: 12**

(Anti-CD3 x Anti-CD28-L:)	gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagcccggccagagcccccagtccctgatctacaaggtgtccaac agattcagcggcgtgcccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtaccccttcaccttttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatcgtgctgacacagagccctgctagcctggccgtgtctcctggaca gagggccaccatcacctgtagagccagcgagagcgtggaatattacgtgaccagcctg atgcagtggtatcagcagaagcccggccagccccccaagctgctgatttttcgccgccag caacgtggaaagcggcgtgccagccagattttccggcagcggctctggcaccgacttc accctgaccatcaacccccgtggaagccaacgacgtggccaactactactgccagcaga gccggaaggtgccctacacctttggccagggcaccaagctggaaatcaagaccaagg gccccagccgtacggtggccgctcccagcgtgttcatcttcccacctagcgacgagcag ctgaagtccggcacagcctctgtcgtgtgcctgctgaacaacttctaccccgcgaggc caaagtgcagtggaaggtggacaacgccctgcagagcggcaacagccaggaaagcg tgaccgagcaggacagcaaggactccacctacagcctgagcagcaccctgacactga gcaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggc ctgtctagccccgtgaccaagagcttcaaccggggcgagtgt	
Binding Protein 20 Amino Acid Sequences		
Heavy chain A (Anti-CD20-H_knob)	**Anti-CD20-H_Knob:** Qvqlqqpgaelvkpgasvkmsckas***gytftsyn***mhwvkqtpgrglewiga***iypg ngdt***synqkfkgkatltadkssstaymqlssltsedsavyyc***arstyyggdwyfnv***w gagttvtvsaastkgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgv htfpavlqssglyslssvvtvpssslgtktytcnvdhkpsntkvdkrveskygppcpp cpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvev hnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakg qprepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttpp vldsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 114**
Light chain A (Anti-CD20-L)	**Anti-CD20-L:** Qivlsqspailsaspgekvtmtcras***ssvsy***ihwfqqkpgsspkpwiy***ats***nlasgv pvrfsgsgsgtsysltisrveaedaatyyc***qqwtsnp***ptfgggtkleikrtvaapsvfif ppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstysl sstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 115**
Heavy chain B (CD28 x CD3-H_Hole)	**CD28 x CD3-H_Hole:** Qvqlvqsgaevvkpgasvkvsckas***gytftsyy***ihwvrqapgqglewigs***i ypgnvnt***nyaqkfqgratltvdtsistaymelsrlrsddtavyyc***trshygldw nfdv***wgkgttvtvsssqvqlvesgggvvqpgrslrlscaas***gftftkaw***mhw vrqapgkqlewvaq***ikdksns***yatyyadsvkgrftisrddsknt lylqmnslr aedtavyyc***rgvyyyalspfdy***wgqgtlvtvssrtastkgpsvfplapcsrstses taalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpsssl gtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkp kdtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfns tyrvvsvltvlhqdwlngkeykckvsnkglpssiektiskakgqprepqvctl ppsqeemtknqvslscavkgfypsdiavewesngqpennykttppvldsd gsfflvskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 3**
Light chain B (CD3 x CD28-L)	**CD3 x CD28-L:** Divmtqtplslsvtpgqpasisckss***qslvhnnanty***lswylqkpgqspqsliy***kvs*** nrfsgvpdrfsgsgsgtdftlkisrveaedvgvyyc***gqgtqyp***ftfgsgtkveikgqpk aapdiqmtqspsslsasvgdrvtitcqas***qniyvw***lnwyqqkpgkapklliy***kas***nl htgvpsrfsgsgsgtdftltisslqpediatyyc***qqgqtypyt***fgqgtkleiktkgpsrtv aapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqd skdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 4**
Binding Protein 20 Nucleotide Sequences		
Heavy	**Anti-CD20-H_Knob:**	**SEQ ID NO: 116**

chain A (Anti-CD20-H_Knob:)	caggtgcagctgcagcagcctggcgccgaactcgtgaaacctggcgcctccgtgaag atgagctgcaaggccagcggctacaccttcaccagctacaacatgcactgggtcaagc agacccccggcagaggcctggaatggatcggcgccatctaccccggcaacggcgac acctcctacaaccagaagttcaagggcaaggccaccctgaccgccgacaagagcagc agcacagcctacatgcagctgtccagcctgaccagcgaggacagcgccgtgtactact gcgccagaagcacctactacggcggcgactggtacttcaacgtgtggggagccggca ccaccgtgacagtgtctgctgcttcgaccaagggcccatcggtgttccctctggccccctt gcagcagaagcaccagcgaatctacagccgccctgggctgcctcgtgaaggactactt tccccgagccccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacacct ttccagccgtgctccagagcagcggcctgtactctctgagcagcgtcgtgacagtgccc agcagcagcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaac accaaggtggacaagcgggtggaatctaagtacggccctccctgccctccttgcccag ccctgaatttctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccc tgatgatcagccggacccccgaagtgacctgcgtggtggtggatgtgtcccaggaagat cccgaggtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagacca agcccagagaggaacagttcaacagcacctaccgggtggtgtccgtgctgaccgtgct gcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcct gcccagctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctc aagtgtataccctgccccctgccaggaagagatgaccaagaaccaggtgtccctgtgg tgtctcgtgaaaggcttctaccccagcgacattgccgtggaatgggagagcaacggcca gccccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcc tgtactccaagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctg ctccgtgatgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccct gggcaag	
Light chain A (Anti-CD20-L)	**Anti-CD20-L:** cagatcgtgctgagccagagccctgccatcctgagcgcttccccaggcgagaaagtga ccatgacctgcagagccagcagcagcgtgtcctacatccactggttccagcagaagcc cggcagcagccccaagccttggatctacgccaccagcaatctggccagcggagtgcct gtgcggtttagcggctctggcagcggcacaagctacagcctgaccatcagccgggtgg aagccgaagatgccgccacctactactgccagcagtggaccagcaacccccccacatt tggcggaggcaccaagctggaaatcaagcgtacggtggccgctcccagcgtgttcatc ttcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctgaa caacttctaccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcagag cggcaacagccaggaaagcgtgaccgagcaggacagcaaggactccacctacagcc tgagcagcaccctgacactgagcaaggccgactacgagaagcacaaggtgtacgcct gcgaagtgacccaccagggcctgtctagccccgtgaccaagagcttcaaccggggcg agtgt	**SEQ ID NO: 117**
Heavy chain B (CD28xCD3-H_Hole:)	CD28xCD3-H_Hole: caggtgcagctggtgcagtctggcgccgaggtcgtgaaacctggcgcctctgtgaagg tgtcctgcaaggccagcggctacaccttttaccagctactacatccactgggtgcgccag gccccctggacagggactggaatggatcggcagcatctaccccggcaacgtgaacacc aactacgcccagaagttccagggcagagccaccctgaccgtggacaccagcatcagc accgcctacatggaactgagccggctgagaagcgacgacacgccgtgtactactgca cccggtcccactacggcctggattggaacttcgacgtgtggggcaagggcaccaccgt gacagtgtctagcgccaggtgcagctggtggaatctggcggcggagtggtgcagcct ggcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctgga tgcactgggtgcgccaggccccctggaaagcagctggaatgggtggcccagatcaagg acaagagcaacagctacgccacctactacgccgacagcgtgaagggccggttcaccat cagccgggacgacagcaagaacaccctgtacctgcagatgaacagcctgcgggccg aggacaccgccgtgtactactgtcggggcgtgtactatgccctgagccccttcgattact ggggccagggaaccctcgtgaccgtgtctagtcggaccgccagcacaaagggcccat cggtgttccctctggccccttgcagcagaagcaccagcgaatctacagccgccctggg	**SEQ ID NO: 7**

	ctgcctcgtgaaggactactttccgagccgtgaccgtgtcctggaactctggcgctct gacaagcggcgtgcacaccttccagccgtgctccagagcagcggcctgtactctctga gcagcgtcgtgacagtgcccagcagcagcctgggcaccaagacctacacctgtaacgt ggaccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacggcc ctccctgcccctccttgcccagcccctgaatttctgggcggaccctccgtgttcctgttcccc ccaaagcccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtg gtggatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtggacggcgtgga agtgcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggt ggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgc aaggtgtccaacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaag ggccagccccgcgagcctcaagtgtgtaccctgccccctagccaggaagagatgacc aagaaccaggtgtccctgagctgtgccgtgaaaggcttctaccccagcgacattgccgt ggaatgggagagcaacggccagccccgagaacaactacaagaccacccccccctgtgct ggacagcgacggctcattcttcctggtgtccaagctgaccgtggacaagagccggtgg caggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccactaca cccagaagtccctgtctctgtccctgggcaag	
Light chain B (CD3xCD28-L_Hole:)	**CD3 x CD28-L_Hole:** gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgcca gcatcagctgcaagagcagccagagcctggtgcacaacaacgccaacacctacctga gctggtatctgcagaagcccggccagagccccccagtccctgatctacaaggtgtccaac agattcagcggcgtgccccgacagattctccggcagcggctctggcaccgacttcaccct gaagatcagccgggtggaagccgaggacgtgggcgtgtactattgtggccagggcac ccagtaccccttcacctttggcagcggcaccaaggtggaaatcaagggccagcccaag gccgccccccgacatccagatgacccagagccccagcagcctgtctgccagcgtgggc gacagagtgaccatcacctgtcaggccagccagaacatctacgtgtggctgaactggta tcagcagaagcccggcaaggccccccaagctgctgatctacaaggccagcaacctgca caccggcgtgcccagcagattttctggcagcggctccggcaccgacttcaccctgacaa tcagctccctgcagcccgaggacattgccacctactactgccagcagggccagaccta ccccctacacctttggccagggcaccaagctggaaatcaagaccaagggccccagccgt acggtggccgctcccagcgtgttcatcttccccacctagcgacgagcagctgaagtccgg cacagcctctgtcgtgtgcctgctgaacaacttctaccccccgcgaggccaaagtgcagt ggaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtgaccgagca ggacagcaaggactccacctacagcctgagcagcaccctgacactgagcaaggccga ctacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagcccc gtgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 8**
Binding Protein 21 Amino Acid Sequences		
Heavy chain A (Anti-CD20-H_knob)	**Anti-CD20-H_Knob:** qvqlqqpgaelvkpgasvkmsckas***gytftsyn***mhwvkqtpgrglewiga***iypgngdt***synqkf kgkatltadkssstaymqlssltsedsavyyc***arstyyggdwyfnv***wgagttvtvsaastkgpsvfpl apcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvvtvpssslgtktyt cnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkpkdtlmisrtpevtcvvvdvsq edpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkeykckvsnkglpssie ktiskakgqprepqvytlppcqeemtknqvslwclvkgfypsdiavewesngqpennykttppvl dsdgsfflyskltvdksrwqegnvfscsvmhealhnhytqkslslslgk	**SEQ ID NO: 114**
Light chain A (Anti-CD20-L)	**Anti-CD20-L:** qivlsqspailsaspgekvtmtcras***ssvsy***ihwfqqkpgsspkpwiy***ats***nlasgvpvrfsgsgsgt sysltisrveaedaatyyc***qqwtsnp***ptfgggtkleikrtvaapsvfifppsdeqlksgtasvvcllnnf ypreakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspvt ksfnrgec	**SEQ ID NO: 115**
Heavy chain B	**CD28 x CD3-H_Hole:** qvqlqesgpglvkpsqtlsltctvsgfslsdygvhwvrqppgkglewlgviwagggtnynp slksrktiskdtsknqvslklssvtaadtavyycardkgysyyysmdywgqgttvtvsssqv	**SEQ ID NO: 9**

(CD28 x CD3-H_Hole)	qlvesgggvvqpgrslrlscaasgftftkawmhwvrqapgkqlewvaqikdksnsyatyy adsvkgrftisrddsknt lylqmnslraedtavyycrgvyyalspfdywgqgtlvtvssrtast kgpsvfplapcsrstsestaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslss vvtvpssslgtktytcnvdhkpsntkvdkrveskygppcppcpapeflggpsvflfppkpk dtlmisrtpevtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvl hqdwlngkeykckvsnkglpssiektiskakgqprepqvctlppsqeemtknqvslscav kgfypsdiavewesngqpennyk ttppvldsdgsfflvskltvdksrwqegnvfscsvmh ealhnhytqkslslslgk	
Light chain B (CD3 x CD28-L)	CD3 x CD28-L divmtqtplslsvtpgqpasisckssqslvhnnantylswylqkpgqspqsliykvsnrfsgvpdrfs gsgsgtdftlkisrveaedvgvyycgqgtqypftfgsgtkveikgqpkaapdivltqspaslavspgqr atitcrasesveyyvtslmqwyqqkpgqppkllifaasnvesgvparfsgsgsgtdftltinpveandv anyycqqsrkvpytfgqgtkleiktkgpsrtvaapsvfifppsdeqlksgtasvvcllnnfypreakvq wkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspvtksfnrgec	**SEQ ID NO: 10**
Binding Protein 21 Nucleotide Sequences		
Heavy chain A (Anti-CD20-H_Knob:)	**Anti-CD20-H_Knob:** caggtgcagctgcagcagcctggcgccgaactcgtgaaacctggcgcctccgtgaagatgagctgca aggccagcggctacaccttcaccagctacaacatgcactgggtcaagcagacccccggcagaggcct ggaatggatcggcgccatctaccccggcaacggcgacacctcctacaaccagaagttcaagggcaa ggccacactgaccgccgacaagagcagcagcacagcctacatgcagctgtccagcctgaccagcga ggacagcgccgtgtactactgcgccagaagcacctactacggcggcgactggtacttcaacgtgtgg ggagccggcaccaccgtgacagtgtctgctgcttcgaccaagggcccatcggtgttcccctctggcccc ttgcagcagaagcaccagcgaatctacagccgccctgggctgcctcgtgaaggactactttccgagc ccgtgaccgtgtcctggaactctggcgctctgacaagcggcgtgcacaccttccagccgtgctccaga gcagcggcctgtactctctgagcagcgtcgtgacagtgcccagcagcagcctgggcaccaagaccta cacctgtaacgtggaccacaagcccagcaacaccaaggtggacaagcgggtggaatctaagtacgg ccctccctgccctccttgcccagccccctgaatttctgggcggaccctccgtgttcctgttcccccaaag cccaaggacaccctgatgatcagccggacccccgaagtgacctgcgtggtggtggatgtgtcccagg aagatcccgaggtgcagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcc cagagaggaacagttcaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactgg ctgaacggcaaagagtacaagtgcaaggtgtccaacaagggcctgcccagctccatcgagaaaacca tcagcaaggccaagggccagccccgcgagcctcaagtgtataccctgccccccttgccaggaagagat gaccaagaaccaggtgtccctgtggtgtctcgtgaaaggcttctaccccagcgacattgccgtggaatg ggagagcaacggccagccccgagaacaactacaagaccacccccccctgtgctggacagcgacggct cattcttcctgtactccaagctgaccgtggacaagagccggtggcaggaaggcaacgtgttcagctgct ccgtgatgcacgaggccctgcacaaccactacacccagaagtccctgtctctgtccctgggcaag	**SEQ ID NO: 116**
Light chain A (Anti-CD20-L:)	**Anti-CD20-L:** cagatcgtgctgagccagagccctgccatcctgagcgcttccccaggcgagaaagtgaccatgacct gcagagccagcagcagcgtgtcctacatccactggttccagcagaagcccggcagcagccccaagc cttggatctacgccaccagcaatctggccagcggagtgcctgtgcggtttagcggctctggcagcggc acaagctacagcctgaccatcagccgggtggaagccgaagatgccgccacctactactgccagcagt ggaccagcaacccccccacatttggcggaggcaccaagctggaaatcaagcgtacggtggccgctc ccagcgtgttcatcttcccacctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgc tgaacaacttctaccccgcgaggccaaagtgcagtggaaggtggacaacgccctgcagagcggca acagccaggaaagcgtgaccgagcaggacagcaaggactccacctacagcctgagcagcaccctg acactgagcaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctg tctagccccgtgaccaagagcttcaaccggggcgagtgt	**SEQ ID NO: 117**
Heavy chain B (**CD28 x CD3-H_Hole:**	**CD28 x CD3-H_Hole:** caggtgcagctgcaggaatctggccctggcctcgtgaagcctagccagaccctgagcctgacctgtac cgtgtccggcttcagcctgagcgactacggcgtgcactgggtgcgccagccacctggaaaaggcctg gaatggctgggcgtgatctgggctggcggaggcaccaactacaaccccagcctgaagtccagaaag accatcagcaaggacaccagcaagaaccaggtgtccctgaagctgagcagcgtgacagccgccgat accgccgtgtactactgcgccagagacaagggctacagctactactacagcatggactactggggcca	**SEQ ID NO: 118**

	gggcaccaccgtgaccgtgtcatcctctcaggtgcagctggtggaatctggcggcggagtggtgcag cctggcagaagcctgagactgagctgtgccgccagcggcttcaccttcaccaaggcctggatgcactg ggtgcgccaggccccctggaaagcagctggaatgggtggcccagatcaaggacaagagcaacagct acgccacctactacgccgacagcgtgaagggccggttcaccatcagccgggacgacagcaagaaca ccctgtacctgcagatgaacagcctgcgggccgaggacaccgccgtgtactactgtcggggcgtgta ctatgccctgagccccttcgattactggggccagggaaccctcgtgaccgtgtctagtcggaccgcttc gaccaagggcccatcggtgttcctctggccccttgcagcagaagcaccagcgaatctacagccgcc ctgggctgcctcgtgaaggactactttccgagccccgtgaccgtgtcctggaactctggcgctctgaca agcggcgtgcacaccttccagccgtgctccagagcagcggcctgtactctctgagcagcgtcgtgac agtgcccagcagcagcctgggcaccaagacctacacctgtaacgtggaccacaagcccagcaacac caaggtggacaagcgggtggaatctaagtacggccctccctgccctccttgcccagccccctgaatttct gggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatgatcagccggacccccc gaagtgacctgcgtggtggtggatgtgtcccaggaagatccccgaggtgcagttcaattggtacgtgga cggcgtggaagtgcacaacgccaagaccaagcccagagaggaacagttcaacagcacctaccgggt ggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtcc aacaagggcctgcccagctccatcgagaaaaccatcagcaaggccaagggccagccccgcgagcc tcaagtgtgtaccctgcccccctagccaggaagagatgaccaagaaccaggtgtccctgagctgtgccg tgaaaggcttctaccccagcgacattgccgtggaatgggagagcaacggccagccccgagaacaacta caagaccacccccccctgtgctggacagcgacggctcattcttcctggtgtccaagctgaccgtggaca agagccggtggcaggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaaccacta cacccagaagtccctgtctctgtccctgggcaag	
Light chain B (CD3_CD28-L:)	(CD3_CD28-L:: gacatcgtgatgacccagacccccctgagcctgagcgtgacacctggacagcctgccagcatcagct gcaagagcagccagagcctggtgcacaacaacgccaacacctacctgagctggtatctgcagaagcc cggccagagccccagtccctgatctacaaggtgtccaacagattcagcggcgtgccccgacagattct ccggcagcggctctggcaccgacttcaccctgaagatcagccgggtggaagccgaggacgtgggcg tgtactattgtggccagggcacccagtacccctttcacctttggcagcggcaccaaggtggaaatcaagg gccagcccaaggccgccccccgacatcgtgctgacacagagccctgctagcctggccgtgtctcctgg acagagggccaccatcacctgtagagccagcgagagcgtggaatattacgtgaccagcctgatgcag tggtatcagcagaagcccggccagccccccaagctgctgatttttcgccgccagcaacgtggaaagcg gcgtgccagccagattttccggcagcggctctggcaccgacttcaccctgaccatcaaccccgtggaa gccaacgacgtggccaactactactgccagcagagccggaaggtgccctacaccttggccagggca ccaagctggaaatcaagaccaagggccccagccgtacggtggccgctcccagcgtgttcatcttccca cctagcgacgagcagctgaagtccggcacagcctctgtcgtgtgcctgctgaacaacttctaccccg cgaggccaaagtgcagtggaaggtggacaacgccctgcagagcggcaacagccaggaaagcgtga ccgagcaggacagcaaggactccacctacagcctgagcagcaccctgacactgagcaaggccgact acgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagccccgtgaccaaga gcttcaaccggggcgagtgt	**SEQ ID NO: 119**

Table 3: Heavy and light chain sequences of binding proteins specifically directed to IL-4, IL-13 and/or TNFa.

Binding Protein 9 Amino Acid Sequences		
Heavy chain A	HC : EVQLVESGGGLVQPGRSLRLSCAAS*GFTFDDYAMH*WVRQAP GKGLEWVS*AITWNSGHID*YADSVEGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAK*VSYLSTASSLDY*WGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI	**SEQ ID NO: 60**

	SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	
Light chain A	**LC:** DIQMTQSPSSLSASVGDRVTITC***RASQGIRNYLA***WYQQKPGKA PKLLIY***AASTLQS***GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC ***QRYNRAPYT***FGQGTKVEIKGQPKAAPSVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	**SEQ ID NO: 61**
Heavy chain B	**HC:** QVQLQQSGPELVKPGASVKISCKAS***GYSFTSYWIH***WIKQRPGQ GLEWIG***MIDPSDGET***RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR***LKEYGNYDSFYFDV***WGAGTLVTVSSEVQLK ESGPGLVAPGGSLSITCTVS***GFSLTDSSIN***WVRQPPGKGLEWLG ***MIWGDGRID***YADALKSRLSISKDSSKSQVFLEMTSLRTDDTAT YYCAR***DGYFPYAMDF***WGQGTSVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 62**
Light chain B	**LC:** DIVLTQSPASLAVSLGQRATISC***RASESVDSYGQSYMH***WYQQK AGQPPKLLIY***LASNLES***GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC***QQNAEDSRT***FGGGTKLEIKGGSGSSGSGGDIQMTQSPA SLSVSVGDTITLTC***HASQNIDVWLS***WFQQKPGNIPKLLIY***KASN LHT***GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC***QQAHSYPFT***F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 63**
Binding Protein 9 Nucleotide Sequences		
Heavy chain A	**HC:** gaggtgcagctggtggaaagcggcggaggactggtgcagcccggcagaagcctgagactgagc tgcgccgccagcggcttcaccttcgacgactacgccatgcactgggtccgccaggccccctggcaa gggcctggaatgggtgtccgccatcacctggaacagcggccacatcgactacgccgacagcgtg gaaggccggttcaccatcagccgggacaacgccaagaacagcctgtacctgcagatgaacagcc tgcgggccgaggacaccgccgtgtactactgcgccaaggtgtcctacctgagcaccgccagcag cctggactactggggccagggcaccctggtgacagtgtccagcgcttccaccaagggccccagc gtgttccccctggccccctagcagcaagagcacatctggcggcacagccgccctgggctgcctggt caaggactacttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcggagtgc atacctteectgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacagtgccca gcagcagcctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacaccaaggt ggacaagaaggtggaacccaagagctgcgacaagacccacacctgtccccctgccctgccct gaactgctgggcggacccteegtgttcctgttcccccaaagcccaaggacaccctgatgatcagc cggacccccgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaagttcaa ttggtacgtggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagtacaac agcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagta caagtgcaaggtgtccaacaaggccctgcctgccccatcgagaaaaccatcagcaaggccaag ggccagcctagagagccccaagtctgcaccctgccccccagcagagatgagctgaccaagaacc	**SEQ ID NO: 64**

	aggtgtccctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgggagagc aacggccagcccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattctt cctggtgtccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctgcagc gtgatgcacgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	
Light chain A	LC: gacatccagatgacccagagccccagcagcctgagcgccagcgtgggcgacagagtgaccatc acctgtcgggccagccagggcatccggaactacctggcctggtatcagcagaagccccggcaagg ccccccaagctgctgatctacgccgccagcacactgcagagcggcgtgcccagcagattcagcgg cagcggctccggcaccgacttcaccctgaccatcagcagcctgcagccccgaggacgtggccacc tactactgccagcggtacaacagagccccctacaccttcggccagggcaccaaggtggaaatcaa gggacagcccaaggctgccccctcggtcaccctgttcccccccaagcagcgaggaactgcaggcc aacaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaag gccgatagctctccccgtgaaggccggcgtggaaaccaccacccccagcaagcagagcaacaac aaatacgccgcctccagctacctgagcctgacccccgagcagtggaagtcccaccggtcctacag ctgccaggtcacacacgagggcagcaccgtggaaaagaccgtggcccccaccgagtgcagc	SEQ ID NO: 65
Heavy chain B	HC : caggtgcagctgcagcagagcggccctgagctggtcaagcctggcgccagcgtgaagatcagct gcaaggccagcggctacagcttcaccagctactggatccactggatcaagcagcggcctggcca gggcctggaatggatcggcatgatcgaccccagcgacggcgagacacggctgaaccagagattc cagggcagagccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcggagc cccaccagcgaggacagcgccgtgtactactgcacccggctgaaagagtacggcaactacgaca gcttctacttcgacgtgtggggagccggcaccctggtcaccgtgtccagcgaagtgcagctgaaag aaagcggccctggcctggtggccccctggcggcagcctgagcatcacctgtaccgtgtccggcttc agcctgaccgacagcagcatcaactgggtccgacagccccctggcaagggcctcgagtggctgg gaatgatctggggcgacggccggatcgactacgccgacgccctgaagtccccggctgagcatcag caaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcggaccgacgacaccgc cacctactactgcgccagggacggctacttccctacgccatggatttctggggccagggcaccag cgtgaccgtgtcctctgcttccaccaagggccccagcgtgttccctctggccccctagcagcaagag cacatctggcggaacagccgccctgggctgcctggtcaaggactactttccccgagccccgtgaccgt gtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcgg cctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctg caacgtgaaccacaagcccctccaacaccaaggtggacaagaaggtggaacccaagagctgcga caagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttcc ctccaaagcccaaggataccctgatgatcagccggaccccctgaagtgacctgcgtggtggtggac gtgtcccacgaggatccccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgcc aagaccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgc tgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagc ccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactg cctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctac ccctccgatatcgccgtggaatgggagagcaacggccagccccgagaacaactacaagaccaccc ctccccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtccccggt ggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccag aagtccctgagcctgagccctggc	SEQ ID NO: 66
Light chain B	LC: Gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatca gctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaa ggccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgcccgcc agattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagg acgccgccacctactactgccagcagaacgccgaggacagccggacctttcggcggaggcacca agctggaaatcaagggcggctccggcagcagcggctctggcggcgatatccagatgacccagtc ccccgcctccctgagcgtgtccgtgggcgacaccatcaccctgacatgccacgccagccagaaca tcgacgtgtggctgagctggttccagcagaagcctggcaacatccctaagctgctcatctataaggc ctccaacctgcacaccggcgtgcccagcaggttttccggctctggcagcggcaccggctttaccct gacaatcagcagcctgcagccccgaggatatcgccacatattactgtcagcaggcccacagctacc	SEQ ID NO: 67

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Binding Protein 10 _Amino Acid Sequences		
Heavy chain A	**HC :** EVQLVESGGGLVQPGRSLRLSCAAS*GFTFDDYAMH*WVRQAP GKGLEWVS*AITWNSGHID*YADSVEGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAK*VSYLSTASSLDY*WGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	**SEQ ID NO: 60**
Light chain A	**LC:** DIQMTQSPSSLSASVGDRVTITC*RASQGIRNYLA*WYQQKPGKA PKLLIY*AASTLQS*GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC *QRYNRAPYT*FGQGTKVEIKGQPKAAPSVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	**SEQ ID NO: 61**
Heavy chain B	**HC:** EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSQVQLQQSGPE LVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQGLEWIG*MIDP SDGET*RLNQRFQGRATLTVDESTSTAYMQLRSPTSEDSAVYYC TR*LKEYGNYDSFYFDV*WGAGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 68**
Light chain B	**LC:** DIQMTQSPASLSVSVGDTITLTC*HASQNIDVWLS*WFQQKPGNIP KLLIY*KASNLHT*GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC*Q QAHSYPFT*FGGGTKLEIKGGSGSSGSGGDIVLTQSPASLAVSLG QRATISC*RASESVDSYGQSYMH*WYQQKAGQPPKLLIY*LASNLE S*GVPARFSGSGSRTDFTLTIDPVQAEDAATYYC*QQNAEDSRT*F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 69**
Binding Protein 10 Nucleotide Sequences		
Heavy chain A	**HC:** gaggtgcagctggtggaaagcggcggaggactggtgcagcccggcagaagcctgagactgagc tgcgccgccagcggcttcaccttcgacgactacgccatgcactgggtccgccaggccccctggcaa gggcctggaatgggtgtccgccatcacctggaacagcggccacatcgactacgccgacagcgtg	**SEQ ID NO: 64**

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Light chain A	**LC:** gacatccagatgacccagagccccagcagcctgagcgccagcgtgggcgacagagtgaccatc acctgtcgggccagccagggcatccggaactacctggcctggtatcagcagaagcccggcaagg ccccaagctgctgatctacgccgccagcacactgcagagcggcgtgccccagcagattcagcgg cagcggctccggcaccgacttcaccctgaccatcagcagcctgcagcccgaggacgtggccacc tactactgccagcggtacaacagagccccctacaccttcggccagggcaccaaggtggaaatcaa gggacagccccaaggctgccccctcggtcaccctgttcccccccaagcagcgaggaactgcaggcc aacaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaag gccgatagctctccgtgaaggccggcgtggaaaccaccacccccagcaagcagagcaacaac aaatacgccgcctccagctacctgagcctgacccccgagcagtggaagtcccaccggtcctacag ctgccaggtcacacacgagggcagcaccgtggaaaagaccgtggcccccaccgagtgcagc	**SEQ ID NO: 65**
Heavy chain B	**HC :** gaggtgcagctgaaagagtccggccctggactggtggcccctggcggcagcctgagcatcacct gtaccgtgtccggcttcagcctgaccgacagcagcatcaactgggtccgacagcccccctggcaag ggcctggaatggctgggcatgatctggggcgacggccggatcgactacgccgacgccctgaagt cccggctgagcatcagcaaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcg gaccgacgacaccgccacctactactgcgccagggacggctacttcccctacgccatggatttctg gggccagggcaccagcgtgaccgtgtccagtcaggtccagctgcagcagagcggccctgagct ggtcaagcctggcgccagcgtgaagatcagctgcaaggccagcggctacagcttcaccagctact ggatccactggatcaagcagcggcctggccagggcctcgagtggatcggaatgatcgaccccag cgacggcgagacacggctgaaccagagattccagggcagagccaccctgaccgtggacgagag caccagcaccgcctacatgcagctgcggagccccaccagcgaggacagcgccgtgtactactgc acccggctgaaagaatacggcaactacgacagcttctacttcgacgtgtggggagccggcaccct ggtcaccgtgtctagcgcttccaccaagggccccagcgtgttccctctggccectagcagcaagag cacatctggcggaacagccgccctgggctgcctggtcaaggactactttccgagccccgtgaccgt gtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcgg cctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctg caacgtgaaccacaagccctccaacaccaaggtggacaagaaggtggaacccaagagctgcga caagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttcc ctccaaagcccaaggatacccctgatgatcagccggaccccctgaagtgacctgcgtggtggtggac gtgtcccacgaggatccccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgcc aagaccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgc tgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagc ccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactg cctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctac ccctccgatatcgccgtggaatgggagagcaacggccagccccgagaacaactacaagaccaccc ctcccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtcccggt	**SEQ ID NO: 97**

	ggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccag aagtccctgagcctgagccctggc	
Light chain B	**LC:** gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggcccacagctaccccttcaccttcggcggaggcaccaagctggaaatcaagggc ggcagcggcagctccggctctggcggcgatatcgtgctgacccagtctccccgcctccctggccgt gtctctgggccagagagccaccatcagctgccgggccagcgagagcgtggacagctacggcca gagctacatgcactggtatcagcagaaggccggacagccccctaaactgctcatctacctggcctc caacctggaaagcggcgtgccccgccaggttttccggcagcggctccagaaccgacttcaccctga caatcgaccccgtgcaggccgaggacgccgccacatattactgtcagcagaacgccgaggacag cagaacctttggcggcggaacaaagctcgagattaagggcggctccggctccagcggatctggc ggacgtacggtggccgctccttccgtgttcatcttccctccctccgacgagcagctgaagtccggca ccgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtgg acaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagcac ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgt gaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 70**
Binding Protein 11 Amino Acid Sequences		
Heavy chain A	**HC :** EVQLVESGGGLVQPGRSLRLSCAAS*GFTFDDYAMH*WVRQAP GKGLEWVS*AITWNSGHID*YADSVEGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAK*VSYLSTASSLDY*WGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	**SEQ ID NO: 60**
Light chain A	**LC:** DIQMTQSPSSLSASVGDRVTITC*RASQGIRNYLA*WYQQKPGKA PKLLIY*AASTLQS*GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC *QRYNRAPYT*FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 71**
Heavy chain B	**HC:** EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSQVQLQQSGPE LVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQGLEWIG*MIDP SDGET*RLNQRFQGRATLTVDESTSTAYMQLRSPTSEDSAVYYC TR*LKEYGNYDSFYFDV*WGAGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 68**
Light	**LC:**	**SEQ ID NO:**

chain B	DIQMTQSPASLSVSVGDTITLTC*HASQNIDVWLS*WFQQKPGNIP KLLIY*KASNLHT*GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC*Q QAHSYPFT*FGGGTKLEIKGGSGSSGSGGDIVLTQSPASLAVSLG QRATISC*RASESVDSYGQSYMH*WYQQKAGQPPKLLIY*LASNLE S*GVPARFSGSGSRTDFTLTIDPVQAEDAATYYC*QQNAEDSRT*F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	69
Binding Protein 11 _Nucleotide Sequences		
Heavy chain A	**HC:** gaggtgcagctggtggaaagcggcggaggactggtgcagcccggcagaagcctgagactgagc tgcgccgccagcggcttcaccttcgacgactacgccatgcactgggtccgccaggccccctggcaa gggcctggaatgggtgtccgccatcacctggaacagcggccacatcgactacgccgacagcgtg gaaggccggttcaccatcagccgggacaacgccaagaacagcctgtacctgcagatgaacagcc tgcgggccgaggacaccgccgtgtactactgcgccaaggtgtcctacctgagcaccgccagcag cctggactactggggccagggcaccctggtgacagtgtccagcgcttccaccaagggccccagc gtgttccccctggccccctagcagcaagagcacatctggcggcacagccgccctgggctgcctggt caaggactacttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcggagtgc ataccttccctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacagtgccca gcagcagcctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacaccaaggt ggacaagaaggtggaacccaagagctgcgacaagacccacacctgtccccctgccctgccct gaactgctgggcggaccctccgtgttcctgttcccccaaagcccaaggacaccctgatgatcagc cggacccccgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaagttcaa ttggtacgtggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagtacaac agcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagta caagtgcaaggtgtccaacaaggccctgcctgcccccatcgagaaaaccatcagcaaggccaag ggccagcctagagagccccaagtctgcaccctgccccccagcagagatgagctgaccaagaacc aggtgtccctgagctgcgccgtgaagggcttctacccccagcgatatcgccgtggaatgggagagc aacggccagcccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattctt cctggtgtccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctgcagc gtgatgcacgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	**SEQ ID NO: 64**
Light chain A	**LC:** gacatccagatgacccagagccccagcagcctgagcgccagcgtgggcgacagagtgaccatc acctgtcgggccagccagggcatccggaactacctggcctggtatcagcagaagccccggcaagg ccccccaagctgctgatctacgccgccagcacactgcagagcggcgtgccccagcagattcagcgg cagcggctccggcaccgacttcaccctgaccatcagcagcctgcagccccgaggacgtggccacc tactactgccagcggtacaacagagccccctacaccttcggccagggcaccaaggtggaaatcaa gcgtacggtggccgctccttccgtgttcatcttccctccctccgacgagcagctgaagtccggcacc gcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtggac aacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagcacct actccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgtg aggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 72**
Heavy chain B	**HC :** gaggtgcagctgaaagagtccggccctggactggtggccccctggcggcagcctgagcatcacct gtaccgtgtccggcttcagcctgaccgacagcagcatcaactgggtccgacagccccctggcaag ggcctggaatggctgggcatgatctggggcgacggccggatcgactacgccgacgccctgaagt cccggctgagcatcagcaaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcg gaccgacgacaccgccacctactactgcgccagggacggctacttccccctacgccatggatttctg gggccagggcaccagcgtgaccgtgtccagtcaggtccagctgcagcagagcggccctgagct ggtcaagcctggcgccagcgtgaagatcagctgcaaggccagcggctacagcttcaccagctact ggatccactggatcaagcagcggcctggccagggcctcgagtggatcggaatgatcgaccccag cgacggcgagacacggctgaaccagagattccagggcagagccaccctgaccgtggacgagag caccagcaccgcctacatgcagctgcggagccccaccagcgaggacagcgccgtgtactactgc acccggctgaaagaatacggcaactacgacagcttctacttcgacgtgtggggagccggcaccct	**SEQ ID NO: 97**

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Light chain B	**LC:** gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggccccacagctaccccttcaccttcggcggaggcaccaagctggaaatcaagggc ggcagcggcagctccggctctggcggcgatatcgtgctgacccagtctccccgcctccctggccgt gtctctgggccagagagccaccatcagctgccgggccagcgagagcgtggacagctacggcca gagctacatgcactggtatcagcagaaggccggacagccccctaaactgctcatctacctggcctc caacctggaaagcggcgtgccccgccaggttttccggcagcggctccagaaccgacttcaccctga caatcgaccccgtgcaggccgaggacgccgccacatattactgtcagcagaacgccgaggacag cagaacctttggcggcggaacaaagctcgagattaagggcggctccggctccagcggatctggc ggacgtacggtggccgctccttccgtgttcatcttccctccctccgacgagcagctgaagtccggca ccgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtgg acaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagcac ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgt gaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 70**
Binding Protein 12 Amino Acid Sequences		
Heavy chain A	**HC :** EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	**SEQ ID NO: 73**
Light chain A	**LC:** DIVLTQSPASLAVSLGQRATISC*RASESVDSYGQSYMH*WYQQK AGQPPKLLIY*LASNLES*GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC*QQNAEDSRT*FGGGTKLEIKGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC S	**SEQ ID NO: 74**
Heavy	**HC:**	**SEQ ID NO:**

chain B	QVQLQQSGPELVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQ GLEWIG*MIDPSDGET*RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR*LKEYGNYDSFYFDV*WGAGTLVTVSSEVQLV ESGGGLVQPGRSLRLSCAAS*GFTFDDYAMH*WVRQAPGKGLE WVS*AITWNSGHID*YADSVEGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAK*VSYLSTASSLDY*WGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNRFTQKSLSLSPG	75
Light chain B	LC: DIQMTQSPSSLSASVGDRVTITC*RASQGIRNYLA*WYQQKPGKA PKLLIY*AASTLQS*GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC *QRYNRAPYT*FGQGTKVEIKGGSGSSGSGGDIQMTQSPASLSVS VGDTITLTC*HASQNIDVWLS*WFQQKPGNIPKLLIY*KASNLHT*G VPSRFSGSGSGTGFTLTISSLQPEDIATYYC*QQAHSYPFT*FGGGT KLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 76
Binding Protein 12 Nucleotide Sequences		
Heavy chain A	HC: gaggtgcagctgaaggagagcggccccggcctggtggccccctggcggcagcctgagcatcacc tgcaccgtgagcggcttcagcctgaccgacagcagcatcaactgggtgcgccagccccccggca agggcctggagtggctgggcatgatctggggcgacggccgcatcgactacgccgacgccctgaa gagccgcctgagcatcagcaaggacagcagcaagagccaggtgttcctggagatgaccagcctg cgcaccgacgacaccgccacctactactgcgccccgcgacggctacttccctacgccatggacttc tggggccagggcaccacgcgtgaccgtgagcagcgccagcaccaagggccccagcgtgttcccc ctggccctagcagcaagagcacatctggcggcacagccgccctgggctgcctggtcaaggact acttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcggagtgcatacctttcc ctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacagtgcccagcagcagc ctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacaccaaggtggacaaga aggtggaacccaagagctgcgacaagacccacacctgtccccctgccctgccctgaactgctg ggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatgatcagccggacccc cgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaagttcaattggtacgt ggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagtacaacagcacctca ccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgca aggtgtccaacaaggccctgcctgcccccatcgagaaaaccatcagcaaggccaagggccagcc tagagagccccaagtctgcaccctgccccccagcagagatgagctgaccaagaaccaggtgtcc ctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgggagagcaacggcc agcccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctggtgt ccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctgcagcgtgatgca cgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	SEQ ID NO: 77
Light chain A	LC: gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatcag ctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaag gccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgccccgcca gattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagga cgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcaccaa gctggaaatcaagggacagcccaaggctgccccctcggtcaccctgttcccccaagcagcgag gaactgcaggccaacaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgac	SEQ ID NO: 78

	cgtggcctggaaggccgatagctctcccgtgaaggccggcgtggaaaccaccacccccagcaag cagagcaacaacaaatacgccgccagcagctacctgagcctgacccccgagcagtggaagtccc accggtcctacagctgccaggtcacacacgagggcagcaccgtggaaaagaccgtggcccccca ccgagtgcagc	
Heavy chain B	**HC :** caggtgcagctgcagcagagcggccctgagctggtcaagcctggcgccagcgtgaagatcagct gcaaggccagcggctacagcttcaccagctactggatccactggatcaagcagcggcctggcca gggcctggaatggatcggcatgatcgaccccagcgacggcgagacacggctgaaccagagattc cagggcagagccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcggagc ccacccagcgaggacagcgccgtgtactactgcacccggctgaaagagtacggcaactacgaca gcttctacttcgacgtgtggggagccggcaccctggtcaccgtgtccagcgaagtgcagctggtgg aaagcggcggaggcctggtgcagccccggcagaagcctgagactgagctgcgccgccagcggct tcaccttcgacgactacgccatgcactgggtccgacaggccccctggcaaaggactggaatgggtg tccgccatcacctggaacagcggccacatcgactacgccgacagcgtggaaggccggttcaccat cagccgggacaacgccaagaacagcctgtacctgcagatgaacagcctgcgggccgaggatac cgccgtgtattattgcgccaaggtgtcctacctgagcaccgccagcagcctggactactggggcca gggcaccctcgtgacagtgtcctccgcttccaccaagggccccagcgtgttccctctggccctag cagcaagagcacatctggcggaacagccgccctgggctgcctggtcaaggactactttccgagc ccgtgaccgtgtcctggaactctggtgccctgacaagcggagtgcatacttccctgccgtgctgca gagcagcggcctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccag acctacatctgcaacgtgaaccacaagccctccaacaccaaggtggacaagaaggtggaaccca agagctgcgacaagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccg tgttcctgttccctccaaagcccaaggataccctgatgatcagccggacccctgaagtgacctgcgt ggtggtggacgtgtcccacgaggatccccgaagtgaagttcaattggtacgtggacggcgtggaag tgcataacgccaagaccaagccccagagaggaacagtacaacagcacctaccgggtggtgtccgt gctgacagtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaag gccctgccagccccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcag gtgtacacactgccctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtg aagggcttctaccctccgatatcgccgtggaatgggagagcaacggccagcccgagaacaacta caagaccacccctccccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtgga caagtccccggtggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaacc ggttcacccagaagtccctgagcctgagccctggc	**SEQ ID NO: 79**
Light chain B	**LC:** gacatccagatgacccagagccccagcagcctgagcgccagcgtgggcgacagagtgaccatc acctgtcgggccagccagggcatccggaactacctggcctggtatcagcagaagccccggcaaagg cccccaagctgctgatctacgccgccagcacactgcagagcggcgtgccccagcagattcagcgg cagcggctccggcaccgacttcaccctgaccatcagcagcctgcagccccgaggacgtggccacc tactactgccagcggtacaacagagccccctacaccttcggccagggcaccaaggtggaaatcaa gggcggctctggcagctccggcagcggcggagacattcagatgacacagtcccccgccagcctg tccgtgtccgtgggcgatacatcaccctgacatgccacgccagccagaacatcgacgtgtggctg agctggttccagcagaaacctggcaacatccctaagctgctcatctataaggccagcaacctgcac acaggcgtgccctccagattctccggctctggctctggcaccggctttacactgacaatcagttctct gcagcctgaggatatcgccacatattactgtcagcaggcccacagctacccttttcaccttcggaggc ggcaccaagctcgagattaagggcggaagcggctcctccggctccggcggacgtacggtggcc gctccttccgtgttcatcttccctccctccgacgagcagctgaagtccggcaccgcctccgtggtgtg tctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtggacaacgccctgcagt ccggcaactcccaggagtccgtcaccgagcaggactccaaggacagcacctactccctgtcctcc accctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgtgaggtgacccacca gggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 80**
Binding Protein 13 Amino Acid Sequences		
Heavy chain A	**HC :** EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSASTKGPSVFPL	**SEQ ID NO: 73**

	APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	
Light chain A	**LC:** DIVLTQSPASLAVSLGQRATISC***RASESVDSYGQSYMH***WYQQK AGQPPKLLIY***LASNLES***GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC***QQNAEDSRT***FGGGTKLEIKGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC S	**SEQ ID NO: 74**
Heavy chain B	**HC:** EVQLVESGGGLVQPGRSLRLSCAAS***GFTFDDYAMH***WVRQAP GKGLEWVS***AITWNSGHID***YADSVEGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAK***VSYLSTASSLDY***WGQGTLVTVSSQVQL QQSGPELVKPGASVKISCKAS***GYSFTSYWIH***WIKQRPGQGLEW IG***MIDPSDGET***RLNQRFQGRATLTVDESTSTAYMQLRSPTSED SAVYYCTR***LKEYGNYDSFYFDV***WGAGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNRFTQKSLSLSPG	**SEQ ID NO: 81**
Light chain B	**LC:** DIQMTQSPASLSVSVGDTITLTC***HASQNIDVWLS***WFQQKPGNIP KLLIY***KASNLHT***GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC***Q*** ***QAHSYPFT***FGGGTKLEIKGGSGSSGSGGDIQMTQSPSSLSASVG DRVTITC***RASQGIRNYLA***WYQQKPGKAPKLLIY***AASTLQS***GVPS RFSGSGSGTDFTLTISSLQPEDVATYYC***QRYNRAPYT***FGQGTKV EIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 82**
Binding Protein 13_Nucleotide Sequences		
Heavy chain A	**HC:** gaggtgcagctgaaggagagcggccccggcctggtggccccctggcggcagcctgagcatcacc tgcaccgtgagcggcttcagcctgaccgacagcagcatcaactgggtgcgccagccccccggca agggcctggagtggctgggcatgatctggggcgacggccgcatcgactacgccgacgccctgaa gagccgcctgagcatcagcaaggacagcagcaagagccaggtgttcctggagatgaccagcctg cgcaccgacgacaccgccacctactactgcgccccgcgacggctacttccctacgccatggacttc tggggccagggcaccagcgtgaccgtgagcagcgccagcaccaagggccccagcgtgttcccc ctggccctagcagcaagagcacatctggcggcacagccgccctgggctgcctggtcaaggact acttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcggagtgcataccttcc ctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacagtgcccagcagcagc ctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacaccaaggtggacaaga aggtggaacccaagagctgcgacaagacccacacctgtccccctgccctgccctgaactgctg ggcggaccctccgtgttcctgttcccccaaagcccaaggacaccctgatgatcagccggacccc cgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaagttcaattggtacgt	**SEQ ID NO: 77**

	ggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagtacaacagcaccta ccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgca aggtgtccaacaaggccctgcctgccccatcgagaaaaccatcagcaaggccaagggccagcc tagagagccccaagtctgcaccctgccccccagcagagatgagctgaccaagaaccaggtgtcc ctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgggagagcaacggcc agccccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctggtgt ccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctgcagcgtgatgca cgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	
Light chain A	**LC:** gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatcag ctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaag gccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgccccgcca gattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgaggca cgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcaccaa gctggaaatcaagggacagcccaaggctgccccctcggtcaccctgttcccccaagcagcgag gaactgcaggccaacaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgac cgtggcctggaaggccgatagctctccgtgaaggccggcgtggaaaccaccacccccagcaag cagagcaacaacaaatacgccgccagcagctacctgagcctgacccccgagcagtggaagtccc accggtcctacagctgccaggtcacacacgagggcagcaccgtggaaaagaccgtggcccccca ccgagtgcagc	**SEQ ID NO: 78**
Heavy chain B	**HC :** gaggtgcagctggtggaaagcggcggaggactggtgcagcccggcagaagcctgagactgagc tgcgccgccagcggcttcaccttcgacgactacgccatgcactgggtccgacaggccccctggcaa gggcctggaatgggtgtccgccatcacctggaacagcggccacatcgactacgccgacagcgtg gaaggccggttcaccatcagccgggacaacgccaagaacagcctgtacctgcagatgaacagcc tgcgggccgaggacaccgccgtgtactactgcgccaaggtgtcctacctgagcaccgccagcag cctggactactggggccagggcaccctggtcaccgtgtccagtcaggtccagctgcagcagagc ggccctgagctggtcaagcctggcgccagcgtgaagatcagctgcaaggccagcggctacagct tcaccagctactggatccactggatcaagcagcggcctggccagggcctcgagtggatcggcatg atcgaccccagcgacggcgagacacggctgaaccagagattccagggcagagccaccctgacc gtggacgagagcaccagcaccgcctacatgcagctgcggagccccaccagcgaggatagcgcc gtgtattattgcacccggctgaaagagtacggcaactacgacagcttctacttcgacgtgtggggag ccggcaccctcgtgacagtgtcctccgcttccaccaagggccccagcgtgttccctctggccccta gcagcaagagcacatctggcggaacagccgccctgggctgcctggtcaaggactactttccgag ccgtgaccgtgtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgc agagcagcggcctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcaccca gacctacatctgcaacgtgaaccacaagccctccaacaccaaggtggacaagaaggtggaaccc aagagctgcgacaagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctcc gtgttcctgttccctccaaagcccaaggataccctgatgatcagccggacccctgaagtgacctgcg tggtggtggacgtgtcccacgaggatccgaagtgaagttcaattggtacgtggacggcgtggaa gtgcataacgccaagaccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccg tgctgacagtgctgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaag gccctgccagccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcag gtgtacacactgcctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtg aagggcttctaccctccgatatcgccgtggaatgggagagcaacggccagccgagaacaacta caagaccacccctccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtgga caagtcccggtggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaacc ggttcacccagaagtccctgagcctgagccctggc	
Light chain B	**LC:** gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagcccggcaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgcccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccgaggatatcgccacctacta ctgccagcaggcccacagctaccccttcaccttcggcggaggcaccaagctggaaatcaagggc	**SEQ ID NO; 84**

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Binding Protein 14 Amino Acid Sequences		
Heavy chain A	**HC :** QVQLQQSGPELVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQ GLEWIG*MIDPSDGET*RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR*LKEYGNYDSFYFDV*WGAGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	**SEQ ID NO: 85**
Light chain A	**LC:** DIQMTQSPASLSVSVGDTITLTC*HASQNIDVWLS*WFQQKPGNIP KLLIY*KASNLHT*GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC*Q* *QAHSYPFT*FGGGTKLEIKGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	**SEQ ID NO: 86**
Heavy chain B	**HC:** EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSEVQLVESGGG LVQPGRSLRLSCAAS*GFTFDDYAMH*WVRQAPGKGLEWVS*AIT* *WNSGHID*YADSVEGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCAK*VSYLSTASSLDY*WGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 87**
Light chain B	**LC:** IQMTQSPSSLSASVGDRVTITC*RASQGIRNYLA*WYQQKPGKAP KLLIY*AASTLQS*GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC*Q* *RYNRAPYT*FGQGTKVEIKGGSGSSGSGGDIVLTQSPASLAVSLG QRATISC*RASESVDSYGQSYMH*WYQQKAGQPPKLLIY*LASNLE* *S*GVPARFSGSGSRTDFTLTIDPVQAEDAATYYC*QQNAEDSRT*F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 88**

Binding Protein 14 _Nucleotide Sequences		
Heavy chain A	**HC:** caggtgcagctgcagcagagcggccccgagctggtgaagcccggcgccagcgtgaagatcagc tgcaaggccagcggctacagcttcaccagctactggattcactggatcaagcagcgccccggcca gggcctggagtggatcggcatgatcgaccccagcgacggcgagacccgcctgaaccagcgcttc cagggccgcgccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcgcagc ccccaccagcgaggacagcgccgtgtactactgcacccgcctgaaggagtacggcaactacgaca gcttctacttcgacgtgtggggcgccggcaccctggtgaccgtgagcagcgccagcaccaaggg ccccagcgtgttccccctggccctagcagcaagagcacatctggcggcacagccgccctgggct gcctggtcaaggactacttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcg gagtgcataccttccctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacag tgccccagcagcagcctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacac caaggtggacaagaaggtggaacccaagagctgcgacaagacccacacctgtccccctgccct gccccctgaactgctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatg atcagccggacccccgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaa gttcaattggtacgtggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagt acaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaa gagtacaagtgcaaggtgtccaacaaggccctgcctgccccatcgagaaaaccatcagcaaggc caagggccagcctagagagccccaagtctgcaccctgccccccagcagagatgagctgaccaag aaccaggtgtccctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgggga gagcaacggccagcccgagaacaactacaagaccacccccccctgtgctggacagcgacggctc attcttcctggtgtccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctg cagcgtgatgcacgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	**SEQ ID NO: 89**
Light chain A	**LC:** gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagcccggcaaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgcccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggccccacagctacccccttcaccttcggcggaggcaccaagctggaaatcaaggga cagcccaaggctgccccctcggtcaccctgttcccccccaagctctgaggaactgcaggccaacaa ggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggccg atagctctccccgtgaaggccggcgtggaaaccaccaccccccagcaagcagagcaacaacaaata cgccgccagcagctacctgagcctgacccccgagcagtggaagtcccaccggtcctacagctgc caggtcacacacgagggcagcaccgtggaaaagaccgtggcccccaccgagtgcagc	**SEQ ID NO: 90**
Heavy chain B	**HC :** gaggtgcagctgaaagagtccggccctggactggtggcccctggcggcagcctgagcatcacct gtaccgtgtccggcttcagcctgaccgacagcagcatcaactgggtccgacagcccccctggcaag ggcctggaatggctgggcatgatctggggcgacggccggatcgactacgccgacgccctgaagt cccggctgagcatcagcaaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcg gaccgacgacaccgccacctactactgcgccagggacggctacttcccctacgccatggatttctg gggccagggcaccagcgtgaccgtgtcctccgaagtgcagctggtggaaagcggcggaggcct ggtgcagcccggcagaagcctgagactgagctgcgccgccagcggcttcaccttcgacgactac gccatgcactgggtccgccaggctcccggaaagggactcgagtgggtgtccgccatcacctggaa cagcggccacatcgattacgccgatagcgtggaaggccggttcaccatcagccgggacaacgcc aagaacagcctgtacctgcagatgaacagcctgagagccgaggataccgccgtgtactactgtgc caaggtgtcctacctgagcaccgccagcagcctggactactggggacagggaaccctggtcacc gtgtccagcgcttccaccaagggccccagcgtgttccctctggccccctagcagcaagagcacatct ggcggaacagccgccctgggctgcctggtcaaggactactttccccgagccgtgaccgtgtcctg gaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcggcctgta ctctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctgcaacgt gaaccacaagcccctccaacaccaaggtggacaagaaggtggaacccaagagctgcgacaagac ccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttccctccaa agcccaaggataccctgatgatcagccggacccctgaagtgacctgcgtggtggtggacgtgtcc cacgaggatcccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgccaagac	**SEQ ID NO: 91**

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Light chain B	**LC:** gacatccagatgacccagagccccagcagcctgagcgccagcgtgggcgacagagtgaccatc acctgtcgggccagccagggcatccggaactacctggcctggtatcagcagaagccccggcaagg cccccaagctgctgatctacgccgccagcacactgcagagcggcgtgccccagcagattcagcgg cagcggctccggcaccgacttcaccctgaccatcagcagcctgcagccccgaggacgtggccacc tactactgccagcggtacaacagagccccctacaccttcggccagggcaccaaggtggaaatcaa gggcggctctggcagctccggctctggcggcgatatcgtgctgacccagtctccccgccagcctgg ccgtgtctctgggccagagagccaccatcagctgcagagccagcgagagcgtggacagctacggc ccagagctacatgcattggtatcagcagaaagccggccagcctcctaaactgctcatctacctggcc agcaacctggaatccggcgtgcccgccaggttttccggcagcggcagcagaaccgatttcacact gacaatcgaccccgtgcaggccgaggatgccgccacatattactgtcagcagaacgccgaggac agccggaccttcggcggaggcaccaagctcgagattaagggcggaagcggctccagcggcagt ggcggacgtacggtggccgctccttccgtgttcatcttccctccctccgacgagcagctgaagtccg gcaccgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaagg tggacaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacag cacctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgc ctgtgaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 92**
Binding Protein 15 Amino Acid Sequences		
Heavy chain A	**HC :** QVQLQQSGPELVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQ GLEWIG*MIDPSDGET*RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR*LKEYGNYDSFYFDV*WGAGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	**SEQ ID NO: 85**
Light chain A	**LC:** DIQMTQSPASLSVSVGDTITLTC*HASQNIDVWLS*WFQQKPGNIP KLLIY*KASNLHT*GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC*Q QAHSYPFT*FGGGTKLEIKGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	**SEQ ID NO: 86**
Heavy chain B	**HC:** EVQLVESGGGLVQPGRSLRLSCAAS*GFTFDDYAMH*WVRQAP GKGLEWVS*AITWNSGHID*YADSVEGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAK*VSYLSTASSLDY*WGQGTLVTVSSEVQL KESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKGLEWL G*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRTDDTA TYYCAR*DGYFPYAMDF*WGQGTSVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC	**SEQ ID NO: 93**

	VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNRFTQKSLSLSPG	
Light chain B	LC: DIVLTQSPASLAVSLGQRATISC*CRASESVDSYGQSYMH*WYQQK AGQPPKLLIY*LASNLES*GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC*QQNAEDSRT*FGGGTKLEIKGGSGSSGSGGDIQMTQSPS SLSASVGDRVTITC*RASQGIRNYLA*WYQQKPGKAPKLLIY*AAST LQS*GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC*QRYNRAPYT* FGQGTKVEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 94
Binding Protein 15 Nucleotide Sequences		
Heavy chain A	HC: caggtgcagctgcagcagagcggccccgagctggtgaagccccggcgccagcgtgaagatcagc tgcaaggccagcggctacagcttcaccagctactggattcactggatcaagcagcgccccggcca gggcctggagtggatcggcatgatcgaccccagcgacggcgagaccgcctgaaccagcgcttc cagggccgcgccacccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcgcagc ccccaccagcgaggacagcgccgtgtactactgcacccgcctgaaggagtacggcaactacgaca gcttctacttcgacgtgtggggcgccggcaccctggtgaccgtgagcagcgccagcaccaaggg ccccagcgtgttccccctggccccctagcagcaagagcacatctggcggcacagccgccctgggct gcctggtcaaggactacttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcg gagtgcatacttccctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacag tgcccagcagcagcctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacac caaggtggacaagaaggtggaacccaagagctgcgacaagacccacacctgtccccccctgccct gccccctgaactgctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatg atcagccggacccccgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtga agttcaattggtacgtggacggcgtggaagtgcataacgccaagaccaagcccagagaggaaca gtacaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggca aagagtacaagtgcaaggtgtccaacaaggccctgcctgccccccatcgagaaaaccatcagcaag gccaagggccagcctagagagccccaagtctgcaccctgcccccccagcagagatgagctgacca agaaccaggtgtccctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgg gagagcaacggccagccccgagaacaactacaagaccacccccccctgtgctggacagcgacggc tcattcttcctggtgtccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagc tgcagcgtgatgcacgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc c	SEQ ID NO: 89
Light chain A	LC: gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggcccacagctaccccttcaccttcggcggaggcaccaagctggaaatcaagggca cagcccaaggctgcccccctcggtcaccctgttcccccccaagctctgaggaactgcaggccaacaa ggccacccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggccg atagctctcccgtgaaggccggcgtggaaaccaccaccccccagcaagcagagcaacaacaaaata cgccgccagcagctacctgagcctgacccccgagcagtggaagtcccaccggtcctacagctgc caggtcacacacgagggcagcaccgtggaaaagaccgtggcccccaccgagtgcagc	SEQ ID NO: 90
Heavy chain B	HC : gaggtgcagctggtggaaagcggcggaggactggtgcagcccggcagaagcctgagactgagc tgcgccgccagcggcttcaccttcgacgactacgccatgcactgggtccgacaggcccctggcaa gggcctggaatgggtgtccgccatcacctggaacagcggccacatcgactacgccgacagcgtg gaaggccggttcaccatcagccgggacaacgccaagaacagcctgtacctgcagatgaacagcc	SEQ ID NO: 95

	tgcgggccgaggacaccgccgtgtactactgcgccaaggtgtcctacctgagcaccgccagcag cctggactactggggccagggcaccctggtcaccgtgtcctccgaagtgcagctgaaagagtccg gccctggcctggtggccccctggcggcagcctgagcatcacctgtaccgtgtccggcttcagcctga ccgacagcagcatcaactgggtccgccagcctcccggaaagggactcgagtggctgggcatgat ctggggcgacggccggatcgattacgccgatgccctgaagtcccggctgagcatcagcaaggac agcagcaagagccaggtgttcctggaaatgaccagcctgagaaccgacgacaccgccacctact actgtgcccgggacggctacttccctacgccatggatttctggggacagggaaccagcgtgacc gtgtccagcgcttccaccaagggccccagcgtgttccctctggccccctagcagcaagagcacatct ggcggaacagccgccctgggctgcctggtcaaggactactttccccgagccccgtgaccgtgtcctg gaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcggcctgta ctctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctgcaacg tgaaccacaagccctccaacaccaaggtggacaagaaggtggaacccaagagctgcgacaaga cccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttccctcca aagcccaaggataccctgatgatcagccggaccccctgaagtgacctgcgtggtggtggacgtgtc ccacgaggatcccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgccaaga ccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgctgca ccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagcccct atcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactgccctc catgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctacccct ccgatatcgccgtggaatgggagagcaacggccagccccgagaacaactacaagaccacccctcc cgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtcccggtggca gcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccagaagtc cctgagcctgagccctggc	
Light chain B	**LC:** gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatcag ctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaag gccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgccccgcca gattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagga cgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcaccaa gctggaaatcaagggcggctccggcagcagcggctctggcggcgatatccagatgacccagtcc cccagcagcctgagcgccagcgtgggcgacagagtgaccatcacctgtagagccagccagggc atccggaactacctggcttggtatcagcagaaaccccggaaaggccccctaaactgctcatctacgcc gccagcaccctgcagtccggcgtgccaagcagattctccggctctggcagcggcaccgatttcac actgacaatcagcagcctgcagccccgaggatgtggccacctattattgccagagatacaacagagc cccctacaccttcggccagggcaccaaggtcgagattaagggcggaagcggcagctccggctcc ggcggacgtacggtggccgctccttccgtgttcatcttcctcctccgacgagcagctgaagtccg gcaccgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaagg tggacaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacag cacctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgc ctgtgaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 96**
Binding Protein 16 Amino Acid Sequences		
Heavy chain A	**HC :** EVQLKESGPGLVAPGGSLSITCTVS***GFSLTDSSIN***WVRQPPGKG LEWLG***MIWGDGRID***YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR***DGYFPYAMDF***WGQGTSVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	**SEQ ID NO: 73**
Light	**LC:**	**SEQ ID NO:**

chain A	DIVLTQSPASLAVSLGQRATISC*RASESVDSYGQSYMH*WYQQK AGQPPKLLIY*LASNLES*GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC*QQNAEDSRT*FGGGTKLEIKGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC S	74
Heavy chain B	**HC:** EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSQVQLQQSGPE LVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQGLEWIG*MIDP SDGET*RLNQRFQGRATLTVDESTSTAYMQLRSPTSEDSAVYYC TR*LKEYGNYDSFYFDV*WGAGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 68**
Light chain B	**LC:** DIQMTQSPASLSVSVGDTITLTC*HASQNIDVWLS*WFQQKPGNIP KLLIY*KASNLHT*GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC*Q QAHSYPFT*FGGGTKLEIKGGSGSSGSGGDIVLTQSPASLAVSLG QRATISC*RASESVDSYGQSYMH*WYQQKAGQPPKLLIY*LASNLE S*GVPARFSGSGSRTDFTLTIDPVQAEDAATYYC*QQNAEDSRT*F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 69**
Binding Protein 16 Nucleotide Sequences		
Heavy chain A	**HC:** gaggtgcagctgaaggagagcggccccggcctggtggccccgggcggcagcctgagcatcacc tgcaccgtgagcggcttcagcctgaccgacagcagcatcaactgggtgcgccagccccccggca agggcctggagtggctgggcatgatctgggggcgacggccgcatcgactacgccgacgccctgaa gagccgcctgagcatcagcaaggacagcagcaagagccaggtgttcctggagatgaccagcctg cgcaccgacgacaccgccacctactactgcgcccgcgacggctacttccccctacgccatggacttc tggggccagggcaccagcgtgaccgtgagcagccgccagcaccaagggccccagcgtgttcccc ctggccctagcagcaagagcacatctggcggcacagccgccctgggctgcctggtcaaggact acttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcggagtgcataccttcc ctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacagtgcccagcagcagc ctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacaccaaggtggacaaga aggtggaacccaagagctgcgacaagacccacacctgtccccctgccctgccctgaactgctg ggcggaccctccgtgttcctgttcccccaaagcccaaggacaccctgatgatcagccggacccc cgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaagttcaattggtacgt ggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagtacaacagcaccta ccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgca aggtgtccaacaaggccctgcctgcccccatcgagaaaaccatcagcaaggccaagggccagcc tagagagccccaagtctgcaccctgcccccccagcagagatgagctgaccaagaaccaggtgtcc ctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgggagagcaacggcc agcccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctggtgt ccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctgcagcgtgatgca cgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	**SEQ ID NO: 77**
Light	**LC:**	**SEQ ID NO:**

chain A	gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatcag ctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaag gccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgcccgcca gattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagga cgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcaccaa gctggaaatcaagggacagcccaaggctgccccctcggtcaccctgttcccccccaagcagcgag gaactgcaggccaacaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgac cgtggcctggaaggccgatagctctcccgtgaaggccggcgtggaaaccaccaccccccagcaag cagagcaacaacaaatacgccgccagcagctacctgagcctgacccccgagcagtggaagtccc accggtcctacagctgccaggtcacacacgagggcagcaccgtggaaaagaccgtggcccccca ccgagtgcagc	78
Heavy chain B	**HC :** gaggtgcagctgaaagagtccggccctggactggtggcccctggcggcagcctgagcatcacct gtaccgtgtccggcttcagcctgaccgacagcagcatcaactgggtccgacagcccccctggcaag ggcctggaatggctgggcatgatctggggcgacggccggatcgactacgccgacgccctgaagt cccggctgagcatcagcaaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcg gaccgacgacaccgccacctactactgcgccagggacggctacttcccctacgccatggatttctg gggccagggcaccagcgtgaccgtgtccagtcaggtccagctgcagcagagcggccctgagct ggtcaagcctggcgccagcgtgaagatcagctgcaaggccagcggctacagcttcaccagctact ggatccactggatcaagcagcggcctggccagggcctcgagtggatcggaatgatcgacccccag cgacggcgagacacggctgaaccagagattccagggcagagccaccctgaccgtggacgagag caccagcaccgcctacatgcagctgcggagccccaccagcgaggacagcgccgtgtactactgc acccggctgaaagaatacggcaactacgacagcttctacttcgacgtgtggggagccggcaccct ggtcaccgtgtctagcgcttccaccaagggccccagcgtgttccctctggccccctagcagcaagag cacatctggcggaacagccgccctgggctgcctggtcaaggactactttccccgagccccgtgaccgt gtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcgg cctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctg caacgtgaaccacaagcccctccaacaccaaggtggacaagaaggtggaacccaagagctgcga caagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttcc ctccaaagcccaaggataccctgatgatcagccggacccctgaagtgacctgcgtggtggtggac gtgtcccacgaggatcccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgcc aagaccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgc tgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagc ccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactg cctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctac ccctccgatatcgccgtggaatgggagagcaacggccagccgagaacaactacaagaccaccc ctcccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtcccggt ggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccag aagtccctgagcctgagccctggc	**SEQ ID NO: 97**
Light chain B	**LC:** gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggccccacagctacccccttcaccttcggcggaggcaccaagctggaaatcaagggc ggcagcggcagctccggctctggcggcgatatcgtgctgacccagtctccccgcctccctggccgt gtctctgggccagagagccaccatcagctgccgggccagcgagagcgtggacagctacggcca gagctacatgcactggtatcagcagaaggccggacagccccctaaactgctcatctacctggcctc caacctggaaagcggcgtgccccgccaggttttccggcagcggctccagaaccgacttcaccctga caatcgaccccgtgcaggccgaggacgccgccacatattactgtcagcagaacgccgaggacag cagaacctttggcggcggaacaaagctcgagattaagggcggctccggctccagcggatctggc ggacgtacggtggccgctccttccgtgttcatcttccctccctccgacgagcagctgaagtccggca ccgcctccgtggtgtgtctgctgaacaacttctacccctcgggaggccaaggtgcagtggaaggtgg acaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagcac ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgt	**SEQ ID NO: 70**

	gaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	
Binding Protein 17 Amino Acid Sequences		
Heavy chain A	**HC :** QVQLQQSGPELVKPGASVKISCKAS***GYSFTSYWIH***WIKQRPGQ GLEWIG***MIDPSDGET***RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR***LKEYGNYDSFYFDV***WGAGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	**SEQ ID NO: 85**
Light chain A	**LC:** DIQMTQSPASLSVSVGDTITLTC***HASQNIDVWLS***WFQQKPGNIP KLLIY***KASNLHT***GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC***Q*** ***QAHSYPFT***FGGGTKLEIKGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	**SEQ ID NO: 86**
Heavy chain B	**HC:** EVQLKESGPGLVAPGGSLSITCTVS***GFSLTDSSIN***WVRQPPGKG LEWLG***MIWGDGRID***YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR***DGYFPYAMDF***WGQGTSVTVSSQVQLQQSGPE LVKPGASVKISCKAS***GYSFTSYWIH***WIKQRPGQGLEWIG***MIDP*** ***SDGET***RLNQRFQGRATLTVDESTSTAYMQLRSPTSEDSAVYYC TR***LKEYGNYDSFYFDV***WGAGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 68**
Light chain B	**LC:** DIQMTQSPASLSVSVGDTITLTC***HASQNIDVWLS***WFQQKPGNIP KLLIY***KASNLHT***GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC***Q*** ***QAHSYPFT***FGGGTKLEIKGGSGSSGSGGDIVLTQSPASLAVSLG QRATISC***RASESVDSYGQSYMH***WYQQKAGQPPKLLIY***LASNLE*** ***S***GVPARFSGSGSRTDFTLTIDPVQAEDAATYYC***QQNAEDSRT***F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 69**
Binding Protein 17 Nucleotide Sequences		
Heavy chain A	**HC:** caggtgcagctgcagcagagcggccccgagctggtgaagccccggcgccagcgtgaagatcagc tgcaaggccagcggctacagcttcaccagctactggattcactggatcaagcagcgccccggcca gggcctggagtggatcggcatgatcgaccccagcgacggcgagaccccgcctgaaccagcgcttc cagggccgcgccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcgcagc cccaccagcgaggacagcgccgtgtactactgcacccgcctgaaggagtacggcaactacgaca gcttctacttcgacgtgtggggcgccggcaccctggtgaccgtgagcagcgccagcaccaaggg ccccagcgtgttccccctggccctagcagcaagagcacatctggcggcacagccgccctgggct gcctggtcaaggactacttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcg	**SEQ ID NO: 89**

	gagtgcatacctccctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacag tgcccagcagcagcctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacac caaggtggacaagaaggtggaacccaagagctgcgacaagacccacacctgtcccccctgccct gccccctgaactgctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatg atcagccggacccccgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtga agttcaattggtacgtggacggcgtggaagtgcataacgccaagaccaagcccagagaggaaca gtacaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggca aagagtacaagtgcaaggtgtccaacaaggccctgcctgccccccatcgagaaaaccatcagcaag gccaagggccagcctagagagccccaagtctgcaccctgccccccagcagagatgagctgacca agaaccaggtgtccctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgg gagagcaacggccagccccgagaacaactacaagaccacccccccctgtgctggacagcgacggc tcattcttcctggtgtccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagc tgcagcgtgatgcacgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc c	
Light chain A	**LC:** Gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctga cctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaacatc cccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctc tggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggccccacagctaccccttcaccttcggcggaggcaccaagctggaaatcaaggga cagcccaaggctgcccccteggtcaccctgttcccccccaagctctgaggaactgcaggccaacaa ggccacccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggccg atagctctcccgtgaaggccggcgtggaaaccaccacccccagcaagcagagcaacaacaaata cgccgccagcagctacctgagcctgacccccgagcagtggaagtcccaccggtcctacagctgc caggtcacacacgagggcagcaccgtggaaaagaccgtggcccccaccgagtgcagc	**SEQ ID NO: 90**
Heavy chain B	**HC :** gaggtgcagctgaaagagtccggccctggactggtggcccctggcggcagcctgagcatcacct gtaccgtgtccggcttcagcctgaccgacagcagcatcaactgggtccgacagcccccctggcaag ggcctggaatggctgggcatgatctggggcgacggccggatcgactacgccgacgccctgaagt cccggctgagcatcagcaaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcg gaccgacgacaccgccacctactactgcgccagggacggctacttcccctacgccatggatttctg gggccagggcaccagcgtgaccgtgtccagtcaggtccagctgcagcagagcggccctgagct ggtcaagcctggcgccagcgtgaagatcagctgcaaggccagcggctacagcttcaccagctact ggatccactggatcaagcagcggcctggccagggcctcgagtggatcggaatgatcgacccccag cgacggcgagacacggctgaaccagagattccagggcagagccaccctgaccgtggacgagag caccagcaccgcctacatgcagctgcggagccccaccagcgaggacagcgccgtgtactactgc acccggctgaaagaatacggcaactacgacagcttctacttcgacgtgtggggagccggcaccct ggtcaccgtgtctagcgcttccaccaagggccccagcgtgttccctctggccctagcagcaagag cacatctggcggaacagccgccctgggctgcctggtcaaggactactttccgagccgtgaccgt gtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcgg cctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctg caacgtgaaccacaagcccctccaacaccaaggtggacaagaaggtggaacccaagagctgcga caagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttcc ctccaaagcccaaggataccctgatgatcagccggacccctgaagtgacctgcgtggtggtggac gtgtcccacgaggatcccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgcc aagaccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgc tgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagc ccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactg cctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctac ccctccgatatcgccgtggaatgggagagcaacggccagccccgagaacaactacaagaccaccc ctcccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtcccggt ggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccag aagtccctgagcctgagccctggc	**SEQ ID NO: 97**
Light	**LC:**	**SEQ ID NO:**

chain B	gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctct ggcagcggcaccggctttaccctgaccatcagcagcctgcagccccgaggatatcgccacctacta ctgccagcaggcccacagctaccccttcaccttcggcggaggcaccaagctggaaatcaagggc ggcagcggcagctccggctctggcggcgatatcgtgctgacccagtctccccgcctccctggccgt gtctctgggccagagagccaccatcagctgccgggccagcgagagcgtggacagctacggcca gagctacatgcactggtatcagcagaaggccggacagccccctaaactgctcatctacctggcctc caacctggaaagcggcgtgccccgccaggttttccggcagcggctccagaaccgacttcaccctga caatcgaccccgtgcaggccgaggacgccgccacatattactgtcagcagaacgccgaggacag cagaacctttggcggcggaacaaagctcgagattaagggcggctccggctccagcggatctggc ggacgtacggtggccgctccttccgtgttcatcttccctcctccgacgagcagctgaagtccggca ccgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtgg acaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagcac ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgt gaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	70
Binding Protein 18 Amino Acid Sequences		
Heavy chain A	HC : EVQLKESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKG LEWLG*MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRT DDTATYYCAR*DGYFPYAMDF*WGQGTSVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	SEQ ID NO: 73
Light chain A	LC: DIVLTQSPASLAVSLGQRATISC*RASESVDSYGQSYMH*WYQQK AGQPPKLLIY*LASNLES*GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC*QQNAEDSRT*FGGGTKLEIKGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC S	SEQ ID NO: 74
Heavy chain B	HC: QVQLQQSGPELVKPGASVKISCKAS*GYSFTSYWIH*WIKQRPGQ GLEWIG*MIDPSDGET*RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR*LKEYGNYDSFYFDV*WGAGTLVTVSSEVQLK ESGPGLVAPGGSLSITCTVS*GFSLTDSSIN*WVRQPPGKGLEWLG *MIWGDGRID*YADALKSRLSISKDSSKSQVFLEMTSLRTDDTAT YYCAR*DGYFPYAMDF*WGQGTSVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	SEQ ID NO: 62

Light chain B	LC: DIVLTQSPASLAVSLGQRATISC*RASESVDSYGQSYMH*WYQQK AGQPPKLLIY*LASNLES*GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC*QQNAEDSRT*FGGGTKLEIKGGSGSSGSGGDIQMTQSPA SLSVSVGDTITLTC*HASQNIDVWLS*WFQQKPGNIPKLLIY*KASN LHT*GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC*QQAHSYPFT*F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 63
Binding Protein 18Nucleotide Sequences		
Heavy chain A	HC: gaggtgcagctgaaggagagcggccccggcctggtggccccgggcggcagcctgagcatcacc tgcaccgtgagcggcttcagcctgaccgacagcagcatcaactgggtgcgccagccccccggca agggcctggagtggctgggcatgatctggggcgacggccgcatcgactacgccgacgccctgaa gagccgcctgagcatcagcaaggacagcagcaagagccaggtgttcctggagatgaccagcctg cgcaccgacgacaccgccacctactactgcgcccgcgacggctacttccccctacgccatggacttc tggggccagggcaccagcgtgaccgtgagcagccgccagcaccaagggccccagcgtgttcccc ctggccctagcagcaagagcacatctggcggcacagccgccctgggctgcctggtcaaggact acttccccgagccgtgacagtgtcctggaactctggcgccctgaccagcggagtgcataccttcc ctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacagtgcccagcagcagc ctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacaccaaggtggacaaga aggtggaacccaagagctgcgacaagacccacacctgtccccctgccctgccctgaactgctg ggcggaccctccgtgttcctgttcccccaaagcccaaggacaccctgatgatcagccggacccc cgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtgaagttcaattggtacgt ggacggcgtggaagtgcataacgccaagaccaagcccagagaggaacagtacaacagcaccta ccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggcaaagagtacaagtgca aggtgtccaacaaggccctgcctgccccatcgagaaaaccatcagcaaggccaagggccagcc tagagagccccaagtctgcaccctgccccccagcagagatgagctgaccaagaaccaggtgtcc ctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgggagagcaacggcc agccccgagaacaactacaagaccacccccccctgtgctggacagcgacggctcattcttcctggtgt ccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagctgcagcgtgatgca cgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc	SEQ ID NO: 77
Light chain A	LC: gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatcag ctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaag gccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgcccgcca gattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagga cgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcaccaa gctggaaatcaagggacagcccaaggctgcccccctcggtcaccctgttcccccaagcagcgag gaactgcaggccaacaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgac cgtggcctggaaggccgatagctctcccgtgaaggccggcgtggaaaccaccaccccagcaag cagagcaacaacaaatacgccgccagcagctacctgagcctgacccccgagcagtggaagtccc accggtcctacagctgccaggtcacacacgagggcagcaccgtggaaaagaccgtggcccccca ccgagtgcagc	SEQ ID NO:78
Heavy chain B	HC : caggtgcagctgcagcagagcggccctgagctggtcaagcctggcgccagcgtgaagatcagct gcaaggccagcggctacagcttcaccagctactggatccactggatcaagcagcggcctggcca gggcctggaatggatcggcatgatcgaccccagcgacggcgagacacggctgaaccagagattc cagggcagagccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcggagc cccaccagcgaggacagcgccgtgtactactgcacccggctgaaagagtacggcaactacgaca gcttctacttcgacgtgtggggagccggcaccctggtcaccgtgtccagcgaagtgcagctgaaag aaagcggccctggcctggtggccccctggcggcagcctgagcatcacctgtaccgtgtccggcttc	SEQ ID NO: 66

	agcctgaccgacagcagcatcaactgggtccgacagccccctggcaagggcctcgagtggctgg gaatgatctggggcgacggccggatcgactacgccgacgccctgaagtccccggctgagcatcag caaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcggaccgacgacaccgc cacctactactgcgccagggacggctacttccccctacgccatggatttctggggccagggcaccag cgtgaccgtgtcctctgcttccaccaagggccccagcgtgttccctctggccccctagcagcaagag cacatctggcggaacagccgccctgggctgcctggtcaaggactactttccccgagccccgtgaccgt gtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcgg cctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctg caacgtgaaccacaagcccctccaacaccaaggtggacaagaaggtggaacccaagagctgcga caagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttcc ctccaaagcccaaggataccctgatgatcagccggacccctgaagtgacctgcgtggtggtggac gtgtcccacgaggatcccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgcc aagaccaagccccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgc tgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagc ccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactg cctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctac ccctccgatatcgccgtggaatgggagagcaacggccagccccgagaacaactacaagaccaccc ctcccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtccccggt ggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccag aagtccctgagcctgagccctggc	
Light chain B	**LC:** Gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatca gctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaa ggccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgccccgcc agattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagg acgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcacca agctggaaatcaagggcggctccggcagcagcggctctggcggcgatatccagatgacccagtc ccccgcctccctgagcgtgtccgtgggcgacaccatcaccctgacatgccacgccagccagaaca tcgacgtgtggctgagctggttccagcagaagcctggcaacatccctaagctgctcatctataaggc ctccaacctgcacaccggcgtgccccagcaggttttccggctctggcagcggcaccggctttaccct gacaatcagcagcctgcagccccgaggatatcgccacatattactgtcagcaggccccacagctacc ccttcacctttggcggcggaacaaagctcgagattaagggcggcagcggaagctccggctccgg cggacgtacggtggccgctccttccgtgttcatcttccctccctccgacgagcagctgaagtccggc accgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtg gacaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagca cctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcct gtgaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 67**
Binding Protein 19 Amino Acid Sequences		
Heavy chain A	**HC :** QVQLQQSGPELVKPGASVKISCKAS***GYSFTSYWIH***WIKQRPGQ GLEWIG***MIDPSDGET***RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR***LKEYGNYDSFYFDV***WGAGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	**SEQ ID NO: 85**
Light chain A	**LC:** DIQMTQSPASLSVSVGDTITLTC***HASQNIDVWLS***WFQQKPGNIP KLLIY***KASNLHT***GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC***Q*** ***QAHSYPFT***FGGGTKLEIKGQPKAAPSVTLFPPSSEELQANKATL	**SEQ ID NO: 86**

	VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	
Heavy chain B	**HC:** QVQLQQSGPELVKPGASVKISCKAS***GYSFTSYWIH***WIKQRPGQ GLEWIG***MIDPSDGET***RLNQRFQGRATLTVDESTSTAYMQLRSP TSEDSAVYYCTR***LKEYGNYDSFYFDV***WGAGTLVTVSSEVQLK ESGPGLVAPGGSLSITCTVS***GFSLTDSSIN***WVRQPPGKGLEWLG ***MIWGDGRID***YADALKSRLSISKDSSKSQVFLEMTSLRTDDTAT YYCAR***DGYFPYAMDF***WGQGTSVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNRFTQKSLSLSPG	**SEQ ID NO: 62**
Light chain B	**LC:** DIVLTQSPASLAVSLGQRATISC***RASESVDSYGQSYMH***WYQQK AGQPPKLLIY***LASNLES***GVPARFSGSGSRTDFTLTIDPVQAEDA ATYYC***QQNAEDSRT***FGGGTKLEIKGGSGSSGSGGDIQMTQSPA SLSVSVGDTITLTC***HASQNIDVWLS***WFQQKPGNIPKLLIY***KASN LHT***GVPSRFSGSGSGTGFTLTISSLQPEDIATYYC***QQAHSYPFT***F GGGTKLEIKGGSGSSGSGGRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	**SEQ ID NO: 63**
Binding Protein 19 Nucleotide Sequences		
Heavy chain A	**HC:** caggtgcagctgcagcagagcggccccgagctggtgaagccccggcgccagcgtgaagatcagc tgcaaggccagcggctacagcttcaccagctactggattcactggatcaagcagcgccccggcca gggcctggagtggatcggcatgatcgaccccagcgacggcgagaccccgcctgaaccagcgcttc cagggccgcgccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcgcagc cccaccagcgaggacagcgccgtgtactactgcaccccgcctgaaggagtacggcaactacgaca gcttctacttcgacgtgtggggcgccggcaccctggtgaccgtgagcagccgccagcaccaaggg ccccagcgtgttccccctggccccctagcagcaagagcacatctggcggcacagccgccctgggct gcctggtcaaggactacttccccgagccccgtgacagtgtcctggaactctggcgccctgaccagcg gagtgcataccttccctgccgtgctgcagtccagcggcctgtacagcctgagcagcgtggtcacag tgcccagcagcagcctgggcacccagacctacatctgcaacgtgaaccacaagcccagcaacac caaggtggacaagaaggtggaacccaagagctgcgacaagacccacacctgtccccccctgccct gccccctgaactgctgggcggaccctccgtgttcctgttcccccccaaagcccaaggacaccctgatg atcagccggacccccgaagtgacctgcgtggtggtggacgtgtcccacgaggaccctgaagtga agttcaattggtacgtggacggcgtggaagtgcataacgccaagaccaagcccagagaggaaca gtacaacagcacctaccgggtggtgtccgtgctgaccgtgctgcaccaggactggctgaacggca aagagtacaagtgcaaggtgtccaacaaggccctgcctgccccccatcgagaaaaccatcagcaag gccaagggccagcctagagagccccaagtctgcaccctgcccccccagcagagatgagctgacca agaaccaggtgtccctgagctgcgccgtgaagggcttctaccccagcgatatcgccgtggaatgg gagagcaacggccagcccgagaacaactacaagaccacccccccctgtgctggacagcgacggc tcattcttcctggtgtccaagctgacagtggacaagagccggtggcagcagggcaacgtgttcagc tgcagcgtgatgcacgaggccctgcacaaccattacacccagaagtccctgagcctgagccccggc c	**SEQ ID NO: 89**
Light chain A	**LC:** gacatccagatgacccagagccccgccagcctgagcgtgtccgtgggcgataccatcaccctgac ctgccacgccagccagaacatcgacgtgtggctgagctggttccagcagaagccccggcaacatcc ccaagctgctgatctacaaggccagcaacctgcacaccggcgtgccccagcagattcagcggctct	**SEQ ID NO: 90**

	ggcagcggcaccggctttaccctgaccatcagcagcctgcagcccgaggatatcgccacctacta ctgccagcaggcccacagctacccccttcaccttcggcggaggcaccaagctggaaatcaaggga cagcccaaggctgcccccctcggtcaccctgttcccccccaagctctgaggaactgcaggccaacaa ggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggccg atagctctcccgtgaaggccggcgtggaaaccaccaccccccagcaagcagagcaacaacaaata cgccgccagcagctacctgagcctgacccccgagcagtggaagtcccaccggtcctacagctgc caggtcacacacgagggcagcaccgtggaaaagaccgtggcccccaccgagtgcagc	
Heavy chain B	**HC :** caggtgcagctgcagcagagcggccctgagctggtcaagcctggcgccagcgtgaagatcagct gcaaggccagcggctacagcttcaccagctactggatccactggatcaagcagcggcctggcca gggcctggaatggatcggcatgatcgaccccagcgacggcgagacacggctgaaccagagattc cagggcagagccaccctgaccgtggacgagagcaccagcaccgcctacatgcagctgcggagc cccaccagcgaggacagcgccgtgtactactgcacccggctgaaagagtacggcaactacgaca gcttctacttcgacgtgtggggagccggcaccctggtcaccgtgtccagcgaagtgcagctgaaag aaagcggccctggcctggtggccccctggcggcagcctgagcatcacctgtaccgtgtccggcttc agcctgaccgacagcagcatcaactgggtccgacagccccctggcaagggcctcgagtggctgg gaatgatctggggcgacggccggatcgactacgccgacgccctgaagtccccggctgagcatcag caaggacagcagcaagagccaggtgttcctggaaatgaccagcctgcggaccgacgacaccgc cacctactactgcgccagggacggctacttccccctacgccatggatttctggggccagggcaccag cgtgaccgtgtcctctgcttccaccaagggccccagcgtgttccctctggccccctagcagcaagag cacatctggcggaacagccgccctgggctgcctggtcaaggactactttccccgagccccgtgaccgt gtcctggaactctggtgccctgacaagcggagtgcataccttccctgccgtgctgcagagcagcgg cctgtactctctgagcagcgtggtcaccgtgccaagcagcagcctgggcacccagacctacatctg caacgtgaaccacaagcctccaacaccaaggtggacaagaaggtggaacccaagagctgcga caagacccacacctgtcctccctgtcctgccccctgaactgctgggcggaccctccgtgttcctgttcc ctccaaagcccaaggataccctgatgatcagccggacccctgaagtgacctgcgtggtggtggac gtgtcccacgaggatcccgaagtgaagttcaattggtacgtggacggcgtggaagtgcataacgcc aagaccaagcccagagaggaacagtacaacagcacctaccgggtggtgtccgtgctgacagtgc tgcaccaggactggctgaacggcaaagagtacaagtgcaaggtgtccaacaaggccctgccagc ccctatcgagaaaaccatcagcaaggccaagggccagccccgcgagcctcaggtgtacacactg cctccatgccgggacgagctgaccaagaaccaggtgtccctgtggtgcctcgtgaagggcttctac ccctccgatatcgccgtggaatgggagagcaacggccagccgagaacaactacaagaccaccc ctcccgtgctggacagcgacggctcattcttcctgtacagcaagctgaccgtggacaagtcccggt ggcagcagggcaacgtgttcagctgctctgtgatgcacgaggccctgcacaaccggttcacccag aagtccctgagcctgagccctggc	**SEQ ID NO: 66**
Light chain B	**LC:** gacatcgtgctgacccagagccctgccagcctggccgtgtctctgggccagagagccaccatcag ctgccgggccagcgagagcgtggacagctacggccagagctacatgcactggtatcagcagaag gccggccagccccccaagctgctgatctacctggccagcaacctggaaagcggcgtgcccgcca gattcagcggcagcggcagcagaaccgacttcaccctgaccatcgaccccgtgcaggccgagga cgccgccacctactactgccagcagaacgccgaggacagccggaccttcggcggaggcaccaa gctggaaatcaagggcggctccggcagcagcggctctggcggcgatatccagatgacccagtcc cccgcctccctgagcgtgtccgtgggcgacaccatcaccctgacatgccacgccagccagaacat cgacgtgtggctgagctggttccagcagaagcctggcaacatccctaagctgctcatctataaggc ctccaacctgcacaccggcgtgccccagcaggttttccggctctggcagcggcaccggctttaccct gacaatcagcagcctgcagccgaggatatcgccacatattactgtcagcaggccccacagctacc ccttcacctttggcggcggaacaaagctcgagattaagggcggcagcggaagctccggctccgg cggacgtacggtggccgctccttccgtgttcatcttcctccctccgacgagcagctgaagtccggc accgcctccgtggtgtgtctgctgaacaacttctaccctcgggaggccaaggtgcagtggaaggtg gacaacgccctgcagtccggcaactcccaggagtccgtcaccgagcaggactccaaggacagca cctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcct gtgaggtgacccaccagggcctgtccagccctgtgaccaagtccttcaaccggggcgagtgc	**SEQ ID NO: 67**

Table 4: CDR sequences of binding proteins

Ab	CDR_H1	CDR_H2	CDR_H3	CDR_L1	CDR_L2	CDR_L3
Anti-Her2	GFNIKDTY (SEQ ID NO:25)	IYPTNGYT (SEQ ID NO:26)	SRWGGDGFYAMDY (SEQ ID NO:27)	QDVNTA (SEQ ID NO:43)	SAS (SEQ ID NO:44)	QQHYTTPPT (SEQ ID NO:45)
Anti-CD3	GFTFTKAW (SEQ ID NO:34)	IKDKSNS (SEQ ID NO:35)	RGVYYALSPFDY (SEQ ID NO:36)	QSLVHNNANTY (SEQ ID NO:52)	KVS (SEQ ID NO:53)	GQGTQYP (SEQ ID NO:54)
Anti-CD3-2	GFTFTKAW (SEQ ID NO:34)	IKDKSNS (SEQ ID NO:35)	RGVYYALSPFDY (SEQ ID NO:36)	QSLVHNNGNTY (SEQ ID NO:149)	KVS (SEQ ID NO:53)	GQGTQYP (SEQ ID NO:54)
Anti-CD19	GYAFSSYW (SEQ ID NO:37)	IWPGDGDT (SEQ ID NO:38)	ARRETTTVGRYYYAMD (SEQ ID NO:39)	QSVDYDGDSY (SEQ ID NO:55)	DAS (SEQ ID NO:56)	QQSTEDPWT (SEQ ID NO:57)
Anti-CD20	GYTFTSYN (SEQ ID NO:120)	IYPGNGDT (SEQ ID NO:121)	ARSTYYGGDWYFNV (SEQ ID NO:122)	SSVSY (SEQ ID NO:123)	ATS (SEQ ID NO:124)	QQWTSNP (SEQ ID NO:125)
Anti-CD28-1	GYTFTSYY (SEQ ID NO:28)	IYPGNVNT (SEQ ID NO:29)	TRSHYGLDWNFDV (SEQ ID NO:30)	QNIYVW (SEQ ID NO:46)	KAS (SEQ ID NO:47)	QQGQTYPYT (SEQ ID NO:48)
Anti-CD28-2	GFSLSDYG (SEQ ID NO:31)	IWAGGGT (SEQ ID NO:32)	ARDKGYSYYYSMD (SEQ ID NO:33)	ESVEYYVTSL (SEQ ID NO:49)	AAS (SEQ ID NO:50)	QQSRKVPYT (SEQ ID NO:51)
Anti-CD38	GYTFTDYW (SEQ ID NO:40)	IYPGDGDT (SEQ ID NO:41)	ARGDYYGSNSLDY (SEQ ID NO:42)	QDVSTV (SEQ ID NO:58)	SAS (SEQ ID NO:44)	QQHYSPPYT (SEQ ID NO:59)
Anti-LAMP1	GYIFTNYNIH (SEQ ID NO:126)	AIYPGNGDAP (SEQ ID NO:127)	ANWDVAFAY (SEQ ID NO:128)	KASQDIDRYMA (SEQ ID NO:138)	DTSTLQS (SEQ ID NO:139)	LQYDNLWT (SEQ ID NO:140)
Anti-TNFα	GFTFDDYAMH (SEQ ID NO:129)	AITWNSGHID (SEQ ID NO:130)	VSYLSTASSLDY (SEQ ID NO:131)	RASQGIRNYLA (SEQ ID NO:141)	AASTLQS (SEQ ID NO:178)	QRYNRAPYT (SEQ ID NO:142)
Anti-IL4	GYSFTSYWIH (SEQ ID NO:132)	MIDPSDGET (SEQ ID NO:133)	LKEYGNYDSFYFDV (SEQ ID NO:134)	HASQNIDVWLS (SEQ ID NO:143)	KASNLHT (SEQ ID NO:179)	QQAHSYPFT (SEQ ID NO:144)
Anti-IL13	GFSLTDSSIN (SEQ ID NO:135)	MIWGDGRID (SEQ ID NO:136)	DGYFPYAMDF (SEQ ID NO:137)	RASESVDSYGQSYMH (SEQ ID NO:145)	LASNLES (SEQ ID NO:146)	QQNAEDSRT (SEQ ID NO:147)

Table 5: VH/VL sequences of binding proteins

Ab	VH (protein)	VL (protein)
Anti-Her2	EVQLVESGGGLVQPGGSLRLSCAAS*GFNIKDTY* IHWVRQAPGKGLEWVAR*IYPTNGYT*RYADSVK GRFTISADTSKNTAYLQMNSLRAEDTAVYYC*SR WGGDGFYAMDY*WGQGTLVTVSS (SEQ ID NO:150)	DIQMTQSPSSLSASVGDRVTITCRAS*QDV NTA*VAWYQQKPGKAPKLLIY*SAS*FLYSG VPSRFSGSRSGTDFTLTISSLQPEDFATYY C*QQHYTTPPT*FGQGTKVEIK (SEQ ID NO:151)
Anti-CD3	QVQLVESGGGVVQPGRSLRLSCAAS*GFTFTKA WMHWVRQAPGKQLEWVAQIKDKSNS*YATYYA DSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVY YC*RGVYYALSPFDY*WGQGTLVTVSS (SEQ ID NO:152)	DIVMTQTPLSLSVTPGQPASISCKSS*QSLV HNNANTY*LSWYLQKPGQSPQSLIY*KVS*N RFSGVPDRFSGSGSGTDFTLKISRVEAED VGVYYC*GQGTQYP*FTFGSGTKVEIK (SEQ ID NO:153)
Anti-CD3-2	QVQLVESGGGVVQPGRSLRLSCAAS*GFTFTKA WMHWVRQAPGKGLEWVAQIKDKSNS*YATYYA DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YC*RGVYYALSPFDY*WGQGTLVTVSS (SEQ ID NO:154)	DIVMTQTPLSLSVTPGQPASISCKSS*QSLV HNNGNTY*LSWYLQKPGQSPQLLIY*KVS*N RFSGVPDRFSGSGSGTDFTLKISRVEAED VGVYYC*GQGTQYP*FTFGGGTKVEIK (SEQ ID NO:155)
Anti-CD19	QVQLVQSGAEVKKPGSSVKVSCKAS*GYAFSSY WMNWVRQAPGQGLEWIGQIWPGDGDT*NYNQ KFKGRATLTADESTSTAYMELSSLRSEDTAVYY C*ARRETTTVGRYYYAMD*YWGQGTTVTVSS (SEQ ID NO:156)	DLVLTQSPASLAVSPGQRATITCKAS*QSV DYDGDSY*LNWYQQKPGQPPKLLIY*DAS*N LVSGVPARFSGSGSGTDFTLTINPVEAND TANYYC*QQSTEDPWT*FGQGTKLEIK (SEQ ID NO:157)
Anti-CD20	QVQLQQPGAELVKPGASVKMSCKAS*GYTFTSY NMHWVKQTPGRGLEWIGAIYPGNGDT*SYNQKF KGKATLTADKSSSTAYMQLSSLTSEDSAVYYC*A RSTYYGGDWYFNV*WGAGTTVTVSA (SEQ ID NO:158)	QIVLSQSPAILSASPGEKVTMTCRAS*SSVS YIH*WFQQKPGSSPKPWIY*ATS*NLASGVP VRFSGSGSGTSYSLTISRVEAEDAATYYC *QQWTSNP*PTFGGGTKLEIK (SEQ ID NO:159)
Anti-CD28-1	QVQLVQSGAEVVKPGASVKVSCKAS*GYTFTSY YIH*WVRQAPGQGLEWIGS*IYPGNVNT*NYAQKF QGRATLTVDTSISTAYMELSRLRSDDTAVYYC*T RSHYGLDWNFDV*WGKGTTVTVSS (SEQ ID NO:160)	DIQMTQSPSSLSASVGDRVTITCQAS*QNI YVW*LNWYQQKPGKAPKLLIY*KAS*NLHT GVPSRFSGSGSGTDFTLTISSLQPEDIATY YC*QQGQTYPYT*FGQGTKLEIK (SEQ ID NO:161)
Anti-CD28-2	QVQLQESGPGLVKPSQTLSLTCTVS*GFSLSDYG* VHWVRQPPGKGLEWLGV*IWAGGGT*NYNPSLK SRKTISKDTSKNQVSLKLSSVTAADTAVYYC*AR DKGYSYYYSMD*YWGQGTTVTVSS (SEQ ID NO:162)	DIVLTQSPASLAVSPGQRATITCRAS*ESV EYYVTSL*MQWYQQKPGQPPKLLIF*AAS*N VESGVPARFSGSGSGTDFTLTINPVEAND VANYYC*QQSRKVPYT*FGQGTKLEIK (SEQ ID NO:163)
Anti-CD38	QVQLVQSGAEVAKPGTSVKLSCKAS*GYTFTDY WMQ*WVKQRPGQGLEWIGT*IYPGDGDT*GYAQK FQGKATLTADKSSKTVYMHLSSLASEDSAVYY C*ARGDYYGSNSLDY*WGQGTSVTVSS (SEQ ID NO:164)	DIVMTQSHLSMSTSLGDPVSITCKAS*QDV STV*VAWYQQKPGQSPRRLIY*SAS*YRYIG VPDRFTGSGAGTDFTFTISSVQAEDLAVY YC*QQHYSPPYT*FGGGTKLEIK (SEQ ID NO:165)
Anti-LAMP1	QVQLVQSGAEVKKPGSSVKVSCKAS*GYIFTNYN IH*WVKKSPGQGLEWIG*AIYPGNGDAP*YSQKFQ GKATLTADTSTSTTYMELSSLRSEDTAVYYCVR *ANWDVAFAY*WGQGTLVTVSS (SEQ ID NO:166)	DIQMTQSPSSLSASVGDRVTITC*KASQDI DRYMA*WYQDKPGKAPRLLIH*DTSTLQS* GVPSRFSGSGSGRDYTLTISNLEPEDFAT YYC*LQYDNLWT*FGGGTKVEIK (SEQ ID NO:167)
Anti-TNFα	EVQLVESGGGLVQPGRSLRLSCAAS*GFTFDDYA MH*WVRQAPGKGLEWVS*AITWNSGHID*YADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AK*VSYLSTASSLDY*WGQGTLVTVSS (SEQ ID NO:168)	DIQMTQSPSSLSASVGDRVTITC*RASQGI RNYLA*WYQQKPGKAPKLLIY*AASTLQS*G VPSRFSGSGSGTDFTLTISSLQPEDVATY YC*QRYNRAPYT*FGQGTKVEIK (SEQ ID NO:169)
Anti-	QVQLQQSGPELVKPGASVKISCKAS*GYSFTSYW*	DIQMTQSPASLSVSVGDTITLTC*HASQNI*

Ab	VH (protein)	VL (protein)
IL4	***IH***WIKQRPGQGLEWIG***MIDPSDGET***RLNQRFQG RATLTVDESTSTAYMQLRSPTSEDSAVYYCTR***L KEYGNYDSFYFDV***WGAGTLVTVSS (SEQ ID NO:170)	***DVWLS***WFQQKPGNIPKLLIY***KASNLHT***G VPSRFSGSGSGTGFTLTISSLQPEDIATYY C***QQAHSYPFT***FGGGTKLEIK (SEQ ID NO:171)
Anti-IL13	EVQLKESGPGLVAPGGSLSITCTVS***GFSLTDSSI N***WVRQPPGKGLEWLG***MIWGDGRID***YADALKS RLSISKDSSKSQVFLEMTSLRTDDTATYYCAR***D GYFPYAMDF***WGQGTSVTVSS (SEQ ID NO:172)	DIVLTQSPASLAVSLGQRATISC***RASESV DSYGQSYMH***WYQQKAGQPPKLLIY***LAS NLES***GVPARFSGSGSRTDFTLTIDPVQAE DAATYYC***QQNAEDSRT***FGGGTKLEIK (SEQ ID NO:173)

Note: CDR sequences are bolded and italicized in amino acid sequences above.

CLAIMS

1. A binding protein for use in treating an inflammatory disease or disorder in a patient, wherein the binding protein comprises four polypeptide chains that form three antigen binding sites that specifically bind one or more target proteins, wherein a first polypeptide chain of the binding protein comprises a structure represented by the formula:

$$V_{L2}\text{-}L_1\text{-}V_{L1}\text{-}L_2\text{-}C_L \qquad [I]$$

and a second polypeptide chain of the binding protein comprises a structure represented by the formula:

$$V_{H1}\text{-}L_3\text{-}V_{H2}\text{-}L_4\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [II]$$

and a third polypeptide chain of the binding protein comprises a structure represented by the formula:

$$V_{H3}\text{-}C_{H1}\text{-hinge-}C_{H2}\text{-}C_{H3} \qquad [III]$$

and a fourth polypeptide chain of the binding protein comprises a structure represented by the formula:

$$V_{L3}\text{-}C_L \qquad [IV]$$

wherein:

V_{L1} is a first immunoglobulin light chain variable domain;

V_{L2} is a second immunoglobulin light chain variable domain;

V_{L3} is a third immunoglobulin light chain variable domain;

V_{H1} is a first immunoglobulin heavy chain variable domain;

V_{H2} is a second immunoglobulin heavy chain variable domain;

V_{H3} is a third immunoglobulin heavy chain variable domain;

C_L is an immunoglobulin light chain constant domain;

C_{H1} is an immunoglobulin C_{H1} heavy chain constant domain;

C_{H2} is an immunoglobulin C_{H2} heavy chain constant domain;

C_{H3} is an immunoglobulin C_{H3} heavy chain constant domain;

hinge is an immunoglobulin hinge region connecting the C_{H1} and C_{H2} domains; and

L_1, L_2, L_3 and L_4 are amino acid linkers;

wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair; wherein V_{H1} and V_{L1} form a binding pair and a first antigen binding site, V_{H2} and V_{L2} form a binding pair and a second antigen binding site; and V_{H3} and V_{L3} form a binding pair and a third antigen binding site.

2. The binding protein for use of claim 1, wherein the binding protein comprises three antigen binding sites that each specifically bind a cytokine target protein selected from the group consisting of IL-4, IL-13 and TNFa.

3. The binding protein for use of claim 1, wherein the binding protein is capable of inhibiting the function of one or more target proteins selected from the group consisting of A2AR, APRIL, ATPDase, BAFF, BAFFR, BCMA, BlyS, BTK, BTLA, B7DC, B7H1, B7H4, B7H5, B7H6, B7H7, B7RP1, B7-4, C3, C5, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL15, CCL17, CCL19, CCL20, CCL21, CCL24, CCL25, CCL26, CCR3, CCR4, CD3, CD19, CD20, CD23, CD24, CD27, CD28, CD38, CD39, CD40, CD70, CD80, CD86, CD122, CD137, CD137L, CD152, CD154, CD160, CD272, CD273, CD274, CD275, CD276, CD278, CD279, CDH1, chitinase, CLEC9, CLEC91, CRTH2, CSF-1, CSF-2, CSF-3, CX3CL1, CXCL12, CXCL13, CXCR3, DNGR-1, ectonucleoside triphosphate diphosphohydrolase 1, EGFR, ENTPD1, FCER1A, FCER1, FLAP, FOLH1, Gi24, GITR, GITRL, GM-CSF, Her2, HHLA2, HMGB1, HVEM, ICOSLG, IDO, IFNα, IgE, IGF1R, IL2Rbeta, IL1, IL1A, IL1B, IL1F10, IL2, IL4, IL4Ra, IL5, IL5R, IL6, IL7, IL7Ra, IL8, IL9, IL9R, IL10, rhIL10, IL12, IL13, IL13Ra1, IL13Ra2, IL15, IL17, IL17Rb, IL18, IL22, IL23, IL25, IL27, IL33, IL35, ITGB4, ITK, KIR, LAG3, LAMP1, leptin, LPFS2, MHC class II, NCR3LG1, NKG2D, NTPDase-1, OX40, OX40L, PD-1H, platelet receptor, PROM1, S152, SISP1, SLC, SPG64, ST2, STEAP2, Syk kinase, TACI, TDO, T14, TIGIT, TIM3, TLR, TLR2, TLR4, TLR5, TLR9, TMEF1, TNFa, TNFRSF7, Tp55, TREM1, TSLP, TSLPR, TWEAK, VEGF, VISTA, Vstm3, WUCAM, and XCR1.

4. The binding protein for use of claim 1, wherein:

(a) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human TNFa, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL13, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL4;

(b) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human TNFa, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL4, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL13;

(c) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL4, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human TNFa, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL13;

(d) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL4, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL13, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human TNFa;

(e) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL13, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human IL4, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human TNFa; or

(f) V_{H1} and V_{L1} form a first antigen binding site that specifically binds human IL13, V_{H2} and V_{L2} form a second antigen binding site that specifically binds human TNFa, and V_{H3} and V_{L3} form a third antigen binding site that specifically binds human IL4.

5. The binding protein for use of claim 4, wherein the antigen binding site that specifically binds human TNFa comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:168 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:169.

6. The binding protein for use of claim 4 or claim 5, wherein the antigen binding site that specifically binds human IL4 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:170 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:171.

7. The binding protein for use of any one of claims 4-6, wherein the antigen binding site that specifically binds human IL13 comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:172 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:173.

8. The binding protein for use of any one of claims 1-7, wherein the binding protein is co-administered with an anti-inflammatory agent.

9. The binding protein for use of any one of claims 1-8, wherein the patient is a human.

10. The binding protein for use of any one of claims 1-9, wherein (a) L_1, L_2, L_3 and L_4 each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148); or (b) L_1, L_2, L_3 and L_4 each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:104), GGGGSGGGGSGGGGS (SEQ ID NO:105), S, RT, TKGPS (SEQ ID NO:106), GQPKAAP (SEQ ID NO: 175), and GGSGSSGSGG (SEQ ID NO:148).

11. The binding protein for use of claim 10, wherein

(a) L_1 comprises the sequence GQPKAAP (SEQ ID NO: 175), L_2 comprises the sequence TKGPS (SEQ ID NO:106), L_3 comprises the sequence S, and L_4 comprises the sequence RT;

(b) L_1 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_2 comprises the sequence GGGGSGGGGS (SEQ ID NO:104), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length; or

(c) L_1 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_2 comprises the sequence GGSGSSGSGG (SEQ ID NO:148), L_3 is 0 amino acids in length, and L_4 is 0 amino acids in length.

12. The binding protein for use of any one of claims 1-9, wherein L_1, L_2, L_3, and/or L_4 comprise the sequence Asp-Lys-Thr-His-Thr (SEQ ID NO: 525).

13. The binding protein for use of any one of claims 1-12, wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; and wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V.

14. The binding protein for use of any one of claims 1-12, wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid

substitutions are Y349C, T366S, L368A, and Y407V; and wherein the C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W.

15. The binding protein for use of any one of claims 1-14, wherein the C_{H3} domains of the second and the third polypeptide chains both comprise amino acid substitutions at positions corresponding to positions 428 and 434 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are M428L and N434S.

16. The binding protein for use of any one of claims 1-15, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG1 or IgG4 C_{H3} domains, and wherein only one of the C_{H3} domains comprises amino acid substitutions at positions corresponding to positions 435 and 436 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are H435R and Y436F.

17. The binding protein for use of any one of claims 1-16, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG4 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K.

18. The binding protein for use of any one of claims 1-17, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG4 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A.

19. The binding protein for use of any one of claims 1-17, wherein the C_{H3} domains of the second and the third polypeptide chains are human IgG1 C_{H3} domains, and wherein the C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are L234A and L235A.

20. The binding protein for use of any one of claims 1-12, wherein the first polypeptide chain comprises a lambda C_L domain; wherein the C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 according to EU Index, wherein the amino acid substitutions are S354C and T366W; wherein the C_{H3}

domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, 407, 435, and 436 of human IgG1 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, Y407V, H435R, and Y436F; and wherein the fourth polypeptide chain comprises a kappa C_L domain.