

TRISPECIFIC BINDING PROTEINS, METHODS, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/831,572, filed April 9, 2019, and EP Application No. EP19306311.2, filed October 8, 2019, the disclosures of each of 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: 183952032040SEQLIST.TXT, date recorded: April 6, 2020, size: 526 KB).

FIELD

[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. 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.

[0005] Immuno-oncology is a promising, emerging therapeutic approach to disease management in cancer. The immune system is the first line of defense against cancer development and progression. There is now large evidence that T cells are able to control

tumor growth and prolong the survival of cancer patients in both early and late stages of disease. However, T cells specific for tumors can be limited in a number of ways preventing them from controlling the disease.

[0006] As part of the human adaptive immunity, T cell immunity plays crucial role in controlling viral infection and cancer, possibly eliminating infected cells and malignant cells which result in clearance of viral infection or cure of cancer. In chronic infectious diseases such as Herpes viral infection (HSV, CMV, EBV, etc.), HIV, and HBV, viruses establish their persistence in humans by various mechanisms including immune suppression, T cell exhaustion, and latency establishment. Nevertheless, viral infection generally induces viral antigen specific immunity including antigen specific CD8 T cells that can readily recognize infected cells for controlling or killing through cytokine release or cytotoxic T cell (CTL) mediated killing processes.

[0007] Thus, viral antigen specific T cell activation and/or amplification *in vivo* and/or *ex vivo* may provide therapeutic strategies against chronic viral infections.

[0008] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

BRIEF SUMMARY

[0009] To meet these and other needs, provided herein are trispecific 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, such as CD28, CD3, and a tumor target protein. Some tumors express specific antigens. For example, HER2 amplification and overexpression can be found in molecular subtypes of breast cancer, and also in gastric, ovarian, lung and prostate carcinomas. Optimal activation of T cells requires two factors: 1. Antigen recognition and 2. Co-stimulation. Using the trispecific HER2/CD28xCD3 trispecific binding proteins described herein, Signal 1 is provided by an agonist anti-CD3 binding site, and Signal 2 is provided by an agonist anti-CD28 binding site. The trispecific binding protein recruits T cells to the tumor via HER2, CD38, or a binding site recognizing another tumor target protein and activates the engaged T cells via anti-CD3 and –CD28. The resulting activation induces the killing potential of the immune cells against the nearby tumor cells. In addition, anti-CD3 binding sites are described with

high affinity binding to human CD3 polypeptides and potential manufacturing liabilities (*e.g.*, deamidation sites) removed.

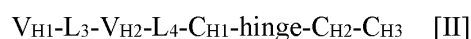
[0010] Further provided herein are anti-CD38/CD28xCD3 trispecific antibodies that were developed and evaluated for their potential in activating T cells, and subsequent proliferation and/or amplification of antigen specific T cells. These trispecific Abs can effectively expand CD4 and CD8 effector and memory populations, including antigen specific CD8 T central memory and effector memory cells *in vitro*. Specifically, *in vitro* expansion of CMV, EBV, HIV-1, Influenza specific CD8 central memory and effector memory cells were demonstrated. The anti-CD38/CD28xCD3 trispecific antibodies described herein exhibited novel properties by engaging CD3/CD28/CD38, providing signaling pathways to stimulate and expand T cells, which may offer an effective strategy treating chronic infectious diseases such as HSV, CMV, EBV, HIV-1, and HBV infections.

[0011] To meet these and other needs, provided herein are binding proteins that bind CD38 polypeptides (*e.g.*, human and cynomolgus monkey CD38 polypeptides), including monospecific, bispecific, or trispecific binding proteins with at least one antigen binding site that binds a CD38 polypeptide. Advantageously, these binding proteins have the ability to recruit T cells to the proximity of cancer cells, subsequently to activate T cells and promote the activated T cells killing of adjacent cancer cells through a Granzyme/Perforin mechanism, providing a different mode of action for anti-tumor activity from anti-CD38 antibodies such as DARZALEX® (daratumumab). Moreover, the ability to bind both human and cynomolgus monkey CD38 polypeptides allows binding proteins to be readily tested in preclinical toxicological studies, *e.g.*, to evaluate their safety profiles for later clinical use.

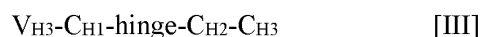
[0012] In some embodiments, provided herein are binding proteins comprising four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide,

wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X_1 is E or Q, X_2 is A or L, and X_3 is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site.

[0013] In some embodiments, the first binding site binds a CD28 polypeptide. In some embodiments, the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYY (SEQ ID NO:49), a CDR-H2 sequence comprising the amino acid sequence of IYPGNVNT (SEQ ID NO:50), and a CDR-H3 sequence comprising the amino acid sequence of TRSHYGLDWNFDV (SEQ ID NO:51), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QNIYVW (SEQ ID NO:52), a CDR-L2 sequence comprising the amino acid sequence of KAS (SEQ ID NO:53), and a CDR-L3 sequence comprising the amino acid sequence of QQGQTYPY

(SEQ ID NO:54). In some embodiments, the V_{H1} domain comprises the amino acid sequence of

QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGN
VNTNYAQKFQGRATLTVDTSISTAYMELSRLSDDTAVYYCTRSHYGLDWNFDV
WGKGTTVTVSS (SEQ ID NO:91), and/or the V_{L1} domain comprises the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCQASQNIYVWLNWYQQKPGKAPKLLIYKASNLHT
GVPSRFGSGSGTDFTLTISLQPEDATYYCQQGQTYPTYTFGQGTKLEIK (SEQ ID NO:92).

[0014] In some embodiments, the CDR-L1 sequence of the V_{L2} domain comprises an amino acid sequence selected from the group consisting of QSLVHQNAQTY (SEQ ID NO:59), QSLVHENLQTY (SEQ ID NO:60), QSLVHENLFTY (SEQ ID NO:61), and QSLVHENLRTY (SEQ ID NO:62). In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHQNAQTY (SEQ ID NO:59), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLQTY (SEQ ID NO:60), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-

H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLFTY (SEQ ID NO:61), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding protein of the present disclosure comprises an antigen binding site comprising: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLRTY (SEQ ID NO:62), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, the V_{H2} domain comprises the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKD
KSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPF
DYWGQGTLVTVSS (SEQ ID NO:93), and/or the V_{L2} domain comprises an amino acid sequence selected from the group consisting of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:98). In some embodiments, the V_{H2} domain comprises the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKD
KNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPF
DYWGQGTLVTVSS (SEQ ID NO:93) or

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKD
KNSYATYYASSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPF
DYWGQGTLVTVSS (SEQ ID NO:302), and/or the V_{L2} domain comprises an amino acid
sequence selected from the group consisting of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:98). In some embodiments, a binding protein of the present disclosure

comprises an antigen binding site comprising: an antibody heavy chain variable (VH)
domain comprising the amino acid sequence of SEQ ID NO:93, and/or an antibody light
chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:95. In
some embodiments, a binding protein of the present disclosure comprises an antigen
binding site comprising: an antibody heavy chain variable (VH) domain comprising the
amino acid sequence of SEQ ID NO:302, and/or an antibody light chain variable (VL)
domain comprising the amino acid sequence of SEQ ID NO:95. In some embodiments, a
binding protein of the present disclosure comprises an antigen binding site comprising: an
antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ
ID NO:93, and/or an antibody light chain variable (VL) domain comprising the amino acid
sequence of SEQ ID NO:96. In some embodiments, a binding protein of the present
disclosure comprises an antigen binding site comprising: an antibody heavy chain variable
(VH) domain comprising the amino acid sequence of SEQ ID NO:93, and/or an antibody
light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:97. In
some embodiments, a binding protein of the present disclosure comprises an antigen

binding site comprising: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:98.

[0015] In some embodiments, the third antigen binding site binds a tumor target protein. In some embodiments, the tumor target protein is a CD38 polypeptide (*e.g.*, a human CD38 polypeptide). In some embodiments, the tumor target protein is a HER2 polypeptide (*e.g.*, a human HER2 polypeptide). In some embodiments, a tumor target protein of the present disclosure includes, without limitation, 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, IFN α , 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, MUC-1, 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, TNF α , 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.

[0016] In some embodiments, the third antigen binding site binds a human CD38 polypeptide. In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:13), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:14), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:15), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:16), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:17), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:18). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTLTEFS (SEQ ID NO:19), a CDR-H2 sequence comprising the amino acid sequence of FDPEDGET (SEQ ID NO:20), and a CDR-H3 sequence comprising the amino acid sequence of TTGRFFDWF (SEQ ID NO:21), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVISRF (SEQ ID NO:22), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:23), and a CDR-L3 sequence comprising the amino acid sequence of QQDSNLPIT (SEQ ID NO:24). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYAFTTYL (SEQ ID NO:25), a CDR-H2 sequence comprising the amino acid sequence of INPGSGST (SEQ ID NO:26), and a CDR-H3 sequence comprising the amino acid sequence of ARYAYGY (SEQ ID NO:27), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QNVGTA (SEQ ID NO:28), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:29), and a CDR-L3 sequence comprising the amino acid sequence of QQYSTYPFT (SEQ ID NO:30). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYSFTNYA (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of ISPYYGDT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARRFEGFYYSMDY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHSNGNTY (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of SQSTHVPLT (SEQ ID NO:36).

[0017] In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARDPGLRYFDGGMDV (SEQ ID NO:39), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGISSY (SEQ ID NO:40), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:41), and a CDR-L3 sequence comprising the amino acid sequence of QQLNSFPYT (SEQ ID NO:42). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:43), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:44), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:45), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:46), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:47), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:48). In some embodiments, the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYAMHWVKEAPGQRLEWIGYIYPG QGGTNYNQKFQGRATLTADTSASTAYMELSSLRSEDTAVYFCARTGGLRRAYFTY WGQGTLLTVSS (SEQ ID NO:79), and/or the V_{L3} domain comprises the amino acid sequence of DIVLTQSPATLSLSPGERATISCRASQSVSSYGQGFMHWYQQKPGQPPRLLIYGASS RATGIPARFSGSGSGTDFTLTISPLEDFAVYYCQQNKEDPWTFGGGKLEIK (SEQ ID NO:80). In some embodiments, the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEFSIHWRQAPGQGLEWMGGFDPE DGETIYAQKFQGRVIMTEDTSTDATYMEMNSLRSEDTAIYYCTTGRFFDWFWGQGTLLTVSS (SEQ ID NO:81), and/or the V_{L3} domain comprises the amino acid sequence of EIILTQSPAILSLSPGERATLSCRASQSVISRFLSWYQVKPGLAPRLLIYGASTRATGIP VRFSGSGSGTDFTSLTISSLPEDCAVYYCQQDSNLPITFGQGTRLEIK (SEQ ID NO:82). In some embodiments, the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYAFTTYLVEWIRQRPGQGLEWMGVINPG SGSTNYAQKFQGRVTMTVDRSSTTAYMELSRLSDDTAVYYCARYAYGYWGQGTLLTVSS (SEQ ID NO:83), and/or the V_{L3} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRYT

GVPSRFSGSGSGTDFTLTISLQPEDLATYYCQQYSTYPFTFGQGTKLEIK (SEQ ID NO:84). In some embodiments, the V_{H3} domain comprises the amino acid sequence of QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMWVRQAPGKGLEWVAVIWYD GSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDGG MDVWGQGTTVTVSS (SEQ ID NO:87), and/or the V_{L3} domain comprises the amino acid sequence of

DIQLTQSPSFLSASVGDRVITITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSG VPSRFSGSGSGTEFTLTISLQPEDFATYYCQQLNSFPYTFGQGTKLEIK (SEQ ID NO:88). In some embodiments, the V_{H3} domain comprises the amino acid sequence of QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYD GSNKYYADSVKGRFTISGDNSKNTLYLQMNSLRAEDTAVYYCARMFRGAFDYWG QGTLVTVSS (SEQ ID NO:89), and/or the V_{L3} domain comprises the amino acid sequence of

AIQMTQSPSSLSASVGDRVITITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISGLQPEDSATYYCLQDYIYYPTFGQGTKVEIK (SEQ ID NO:90). In some embodiments, the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYSFTNYAVHWVRQAPGQGLEWMGVISPY YGDTTYAQKFQGRVTMTVDKSSSTAYMELSR LRSDDTAVYYCARRFEGFYYSMD YWGQGT LTVTVSS (SEQ ID NO:85), and/or the V_{L3} domain comprises the amino acid sequence of

DVVM TQSPLSLPVT LGQPASISCRPSQSLVHSNGNTYLNWYQQRPGQSPKLLIYKV SKRFSGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGTKVEIK (SEQ ID NO:86).

[0018] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:156 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:156; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:157 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:157; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:158 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:158; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:159 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:159. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:160 or an amino acid sequence that is at least 95% identical to the amino acid

sequence of SEQ ID NO:160; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:161 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:161; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:162 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:162; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:163 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:163. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:164 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:164; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:165 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:165; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:166 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:166; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:167 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:167. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:168 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:168; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:169 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:169; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:170 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:170; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:171 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:171. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:172 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:172; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:173 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:173; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:174 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:174; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:175 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:175. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:176 or an amino acid

sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:176; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:177 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:177; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:178 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:178; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:179 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:179. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:181 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:181; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:182 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:182; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:183 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:183; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:184 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:184. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:185 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:185; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:186 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:186; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:187 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:187; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:188 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:188.

[0019] In some embodiments, the third antigen binding site binds a human HER2 polypeptide. In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1) or GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), IYPTQGYT (SEQ ID NO:4), or IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), SRWGGEGFYAMDY (SEQ ID NO:7), or SRWGGSGFYAMDY (SEQ ID NO:8), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9) or QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino

acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID

NO:7), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, the V_{H3} domain comprises the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDY WGQGTLLTVSS (SEQ ID NO:72), EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMDY WGQGTLLTVSS (SEQ ID NO:73), EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSFGFYAMDY WGQGTLLTVSS (SEQ ID NO:74), EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTN AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSFGFYAMDY WGQGTLLTVSS (SEQ ID NO:75), or EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTN AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMDY WGQGTLLTVSS (SEQ ID NO:76), and/or the V_{L3} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID NO:77) or DIQMTQSPSSLSASVGDRVTITCRASQDVQTA VAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID NO:78). In some embodiments, the V_{H3} domain comprises the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDY
WGQGTLVTVSS (SEQ ID NO:72), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS
GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77). In some embodiments, the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDY
WGQGTLVTVSS (SEQ ID NO:73), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS
GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77). In some embodiments, the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTN
AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDY
WGQGTLVTVSS (SEQ ID NO:75), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS
GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77). In some embodiments, the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDY
WGQGTLVTVSS (SEQ ID NO:74), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS
GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77). In some embodiments, the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTN
AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDY
WGQGTLVTVSS (SEQ ID NO:76), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS
GVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID

NO:77). In some embodiments, the V_{H3} domain comprises the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDY WGQGTLLVTVSS (SEQ ID NO:72), and/or the V_{L3} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVQTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID NO:78).

[0020] In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:100 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:100; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:101 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:101; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:102 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:102; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:103 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:103. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:104 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:104; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:105 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:105; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:106 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:106; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:107 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:107. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:112 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:112; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:113 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:113; 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. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:116 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:116; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:117 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:117; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:118 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:118; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:119 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:119. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:120 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:120; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:121 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:121; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:122 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:122; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:123 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:123. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:124 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:124; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:125 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:125; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:126 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:126; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:127 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:127. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:128 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:128; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:129 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:129; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:130 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:130; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:131 or an amino acid

sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:131. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:132 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:132; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:133 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:133; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:134 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:134; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:135 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:135. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:136 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:136; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:137 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:137; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:138 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:138; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:139 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:139. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:140 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:140; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:141 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:141; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:142 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:142; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:143 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:143. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:144 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:144; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:145 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:145; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:146 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:146; and the fourth polypeptide chain comprises

the amino acid sequence of SEQ ID NO:147 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:147. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:148 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:148; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:149 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:149; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:150 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:150; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:151 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:151. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:152 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:152; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:153 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:153; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:154 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:154; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:155 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:155. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:286 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:286; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:287 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:287; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:288 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:288; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:289 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:289. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:290 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:290; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:291 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:291; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:292 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ

ID NO:292; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:293 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:293. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:294 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:294; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:295 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:295; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:296 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:296; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:297 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:297. In some embodiments, the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:298 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:298; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:299 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:299; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:300 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:300; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:301 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:301.

[0021] In some embodiments that may be combined with any other embodiments described herein, at least one of L₁, L₂, L₃ or L₄ is independently 0 amino acids in length. In some embodiments, L₁, L₂, L₃ and L₄ each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO: 70), S, RT, TKGPS (SEQ ID NO: 68), GQPKAAP (SEQ ID NO: 67), and GGS GSSGSGG (SEQ ID NO: 71). In some embodiments, L₁, L₂, L₃ and L₄ each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO:70), S, RT, TKGPS (SEQ ID NO:68), GQPKAAP (SEQ ID NO: 67), and GGS GSSGSGG (SEQ ID NO:71). In some embodiments, L₁ comprises the sequence GQPKAAP (SEQ ID NO: 67), L₂ comprises the sequence TKGPS (SEQ ID NO:68), L₃ comprises the sequence S, and L₄ comprises the sequence RT. In some embodiments, at least one of L₁, L₂, L₃ or L₄ comprises the sequence DKTHT (SEQ ID NO:66). In some embodiments, L₁, L₂, L₃ and L₄ comprise the sequence DKTHT (SEQ ID NO:66).

[0022] In some embodiments that may be combined with any other embodiments described herein, the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG4 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG4 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ domains each comprise amino acid substitutions at positions corresponding to positions 233-236 of human IgG4 according to EU Index, wherein the amino acid substitutions are E233P, F234V, L235A, and a deletion at 236. In some embodiments, the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG4 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG1 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ domains 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 hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG1 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ domains each comprise amino acid substitutions at positions corresponding to positions 298, 299, and 300 of human IgG1 according to EU Index, wherein the amino acid substitutions are S298N, T299A, and Y300S. In some embodiments, the hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ 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.

[0023] In some embodiments, provided herein are isolated nucleic acid molecules comprising a nucleotide sequence encoding the binding protein of any one of the above embodiments. In some embodiments, provided herein are expression vectors comprising the nucleic acid molecule of any one of the above embodiments. In some embodiments, provided herein are isolated host cells comprising the nucleic acid molecule of any one of the above embodiments or the expression vector of any one of the above embodiments. In some embodiments, the host cell is a mammalian or insect cell.

[0024] In some embodiments, provided herein are pharmaceutical compositions comprising the binding protein of any one of the above embodiments and a pharmaceutically acceptable carrier.

[0025] In some embodiments, provided herein are methods 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 of any one of the above embodiments. In some embodiments, provided herein is a binding protein or pharmaceutical composition according to any one of the above embodiments for use in a method of preventing and/or treating cancer in a patient, wherein the method comprises administering to the patient a therapeutically effective amount of the binding protein or pharmaceutical composition. In some embodiments, provided herein is a binding protein or pharmaceutical composition according to any one of the above embodiments for use in manufacturing a medicament for preventing and/or treating cancer in a patient.

[0026] In some embodiments, the at least one binding protein is co-administered with a chemotherapeutic agent. In some embodiments, the patient is a human.

[0027] In some embodiments, the third antigen binding site binds a human CD38 polypeptide, and wherein cancer cells from the individual or patient express CD38. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or a B cell lymphoma. In some embodiments, prior to administration of the binding protein, the patient has been treated with daratumumab without a wash-out period.

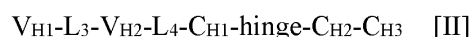
[0028] In some embodiments, the third antigen binding site binds a human HER2 polypeptide, and wherein cancer cells from the individual or patient express HER2. In

some embodiments, the cancer is breast cancer, colorectal cancer, gastric cancer, or non-small cell lung cancer (NSCLC).

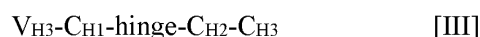
[0029] In some embodiments, provided herein is a method for expanding virus-specific memory T cells, comprising contacting a virus-specific memory T cell with a binding protein, wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

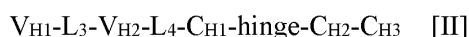
wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid

sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65), and wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide

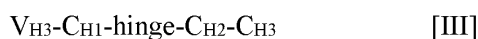
[0030] In some embodiments, provided herein is a binding protein that comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of

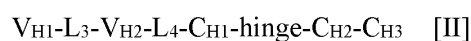
GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65), and wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide for use in expanding virus-specific memory T cells.

[0031] In some embodiments, the virus-specific memory T cell is contacted with the binding protein *in vitro* or *ex vivo*. In some embodiments, contacting the virus-specific memory T cell with the binding protein causes activation and/or proliferation of virus-specific memory T cells.

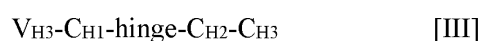
[0032] In some embodiments, provided herein is a method for expanding T cells, comprising contacting a T cell with a binding protein *in vitro* or *ex vivo*, wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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;

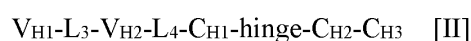
wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X_1 is E or Q, X_2 is A or L, and X_3 is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65), and wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

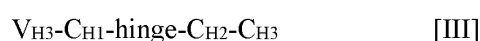
[0033] In some embodiments, provided herein is a binding protein that comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

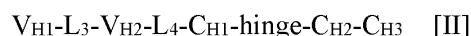
wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X_1 is E or Q, X_2 is A or L, and X_3 is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65), and wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide for use in a method for expanding T cells.

[0034] In some embodiments, the T cell is a memory T cell or an effector T cell. In some embodiments, the T cell expresses a chimeric antigen receptor (CAR) on its cell surface or comprises a polynucleotide encoding a CAR.

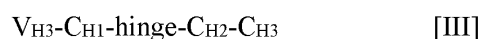
[0035] In some embodiments, provided herein is a method for treating chronic viral infection, comprising administering to an individual or patient in need thereof an effective amount of a binding protein, wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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
 L₁, L₂, L₃ and L₄ are amino acid linkers;

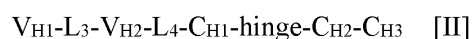
wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65), and wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

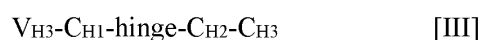
[0036] In some embodiments, provided herein is a binding protein that comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65), and wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide for use in a method for treating chronic viral infection, wherein said method comprises administering to an individual or patient in need thereof an effective amount of the binding protein.

[0037] In some embodiments, the individual or patient is a human. In some embodiments, the binding protein is administered to the individual or patient in pharmaceutical formulation comprising the binding protein and a pharmaceutically

acceptable carrier. In some embodiments, administration of the binding protein results in activation and/or proliferation of virus-specific memory T cells in the individual or patient.

[0038] In some embodiments that may be combined with any other embodiments described herein, the memory T cells are CD8⁺ or CD4⁺ memory T cells. In some embodiments, the memory T cells are central memory T cells (T_{CM}) or effector memory T cells (T_{EM}).

[0039] In some embodiments that may be combined with any other embodiments described herein, the virus is a human immunodeficiency virus (HIV), influenza virus, cytomegalovirus (CMV), hepatitis B virus (HBV), human papillomavirus (HPV), Epstein-barr virus (EBV), human foamy virus (HFV), herpes simplex virus 1 (HSV-1), or herpes simplex virus 2 (HSV-2).

[0040] In some embodiments that may be combined with any other embodiments described herein, the CD28 polypeptide is a human CD28 polypeptide, wherein the CD3 polypeptide is a human CD3 polypeptide, and wherein the CD38 polypeptide is a human CD38 polypeptide.

[0041] In some embodiments, provided herein is a vector system comprising one or more vectors encoding a first, second, third, and fourth polypeptide chain of a binding protein of any one 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.

[0042] In some embodiments, provided herein are kits comprising one, two, three, or four polypeptide chains of a binding protein according to any one of the above embodiments. In some embodiments, the kits further comprise instructions for using the polypeptide chain or binding protein according to any of the methods or uses described herein, *e.g.*, *supra*.

[0043] In some embodiments, provided herein are kits comprising one, two, three, or four polynucleotides according to any one of the above embodiments. In some embodiments, provided herein are kits of polynucleotides comprising one, two, three, or four polynucleotides of a kit of polynucleotides comprising: (a) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:189, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:190, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:191, and a fourth polynucleotide

comprising the polynucleotide sequence of SEQ ID NO:192; (b) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:193, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:194, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:195, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:196; (c) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:197, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:198, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:199, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:200; (d) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:201, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:202, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:203, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:204; (e) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:205, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:206, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:207, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:208; (f) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:209, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:210, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:211, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:212; (g) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:213, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:214, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:215, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:216; (h) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:217, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:218, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:219, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:220; (i) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:221, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:222, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:223, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:224; (j) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:225, a second polynucleotide

comprising the polynucleotide sequence of SEQ ID NO:226, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:227, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:228; (k) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:229, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:230, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:231, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:232; (l) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:233, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:234, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:235, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:236; (m) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:237, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:238, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:239, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:240; (n) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:241, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:242, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:243, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:244; (o) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:245, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:246, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:247, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:248; (p) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:249, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:250, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:251, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:252; (q) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:253, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:254, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:255, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:256; (r) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:257, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:258, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:259, and a fourth polynucleotide

comprising the polynucleotide sequence of SEQ ID NO:260; (s) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:261, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:262, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:263, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:264; (t) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:265, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:266, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:267, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:268; (u) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:269, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:270, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:271, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:272; or (v) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:273, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:274, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:275, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:276.

[0044] 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

[0045] **FIG. 1A** provides a schematic representation of a trispecific binding protein comprising four polypeptide chains that form three antigen binding sites that binds three target proteins: CD28, CD3, and HER2. A first pair of polypeptides possess dual variable domains having a cross-over orientation (VH1-VH2 and VL2-VL1) forming two antigen binding sites that recognize CD3 and CD28, and a second pair of polypeptides possess a single variable domain (VH3 and VL3) forming a single antigen binding site that recognizes HER2. The trispecific binding protein shown in **FIG. 1A** uses a constant region with a “knobs-into-holes” mutation, where the knob is on the second pair of polypeptides with a single variable domain.

[0046] **FIG. 1B** provides the fold change (vs. parental) in binding affinities of anti-CD28/CD3/HER2 trispecific antibody variants using the indicated anti-HER2, anti-CD3, and anti-CD28 binding domains. Mutations 3233QQ to QEQ (top to bottom) refer to mutations introduced into residues 32-35 of the VL domain of the anti-CD3 binding site (indicated by *); the remaining mutations were introduced into the VH or VL domain of the trastuzumab anti-HER2 binding site (indicated by #; numbering according to Kabat). For the mutations in the anti-HER2 binding site, mutation 30Q was introduced into the VL domain, and the remaining mutations were introduced into the VH domain. The binding affinities were measured by ELISA, and the values provided are relative to parental trispecific antibody.

[0047] **FIG. 1C** provides binding curves for the indicated trispecific antibodies binding to human HER2, human CD28, and CD3, as determined by ELISA.

[0048] **FIG. 1D** provides a proposed mechanism of action for HER2/CD28xCD3 trispecific antibody-mediated T cell activation and HER2+ cancer cell killing.

[0049] **FIG. 2A** provides a schematic representation of a trispecific binding protein comprising four polypeptide chains that form three antigen binding sites that binds three target proteins: CD28, CD3, and CD38. A first pair of polypeptides possess dual variable domains having a cross-over orientation (VH1-VH2 and VL2-VL1) forming two antigen binding sites that recognize CD3 and CD28, and a second pair of polypeptides possess a single variable domain (VH3 and VL3) forming a single antigen binding site that recognizes CD38. The trispecific binding protein shown in **FIG. 2A** uses an IgG4 constant region with a “knobs-into-holes” mutation, where the knob is on the second pair of polypeptides with a single variable domain.

[0050] **FIGS. 2B-2E** show the binding affinities, as measured by ELISA, of CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated anti-CD38 binding domains for the target antigens human CD38 (**FIG. 2B**), cynomolgus monkey CD38 (**FIG. 2C**), human CD3 (**FIG. 2D**), and human CD28 (**FIG. 2E**).

[0051] **FIG. 3** shows SPR competition assays for binding to CD38 by Daratumumab and anti-CD38 monospecific antibodies with the indicated anti-CD38 binding domains. If an antibody recognized an epitope on CD38 which was different from that of Daratumumab, injection of the antibody resulted in an increased SPR signal. If an antibody recognized an overlapping epitope as Daratumumab, injection of the antibody did not increase SPR signal.

[0052] FIGS. 4A-4B show the *in vitro* cell killing activity of CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated anti-CD38 binding domains against human multiple myeloma NCI-H929 cells (CD38+/CD28+). The assays were carried out in the presence of 5 nM isotype control antibody (FIG. 4A) or Daratumumab (FIG. 4B). In the presence of daratumumab, the trispecific antibodies continued to exhibit cell killing activity.

[0053] FIGS. 5A-5B show the *in vitro* cell killing activity of CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated anti-CD38 binding domains against human lymphoma OCI-Ly19 cells (CD38+/CD28-). The assays were carried out in the presence of 5 nM isotype control antibody (FIG. 5A) or Daratumumab (FIG. 5B). Daratumumab caused a decrease in the cell killing activity of anti-CD38/CD28xCD3 trispecific antibodies.

[0054] FIGS. 6A-6J show the characterization of *in vitro* T cell subset expansion in PBMCs collected from CMV-infected Donor D in response to CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated alternative anti-CD38 binding domains. A trispecific antibody lacking the CD38VH1 anti-CD38 binding domain was used as a negative control (Δ CD38VH1/ Δ CD28sup x Δ CD3mid IgG4 FALA). T cell populations were measured at indicated time points (D3 refers to day 3; D7 refers to day 7). The indicated trispecific antibodies were tested at the indicated concentrations of 0.2 nM and 1 nM. Flow cytometry was used to quantify CMV-specific CD8+ T cells (FIGS. 6A-6B), CMV-specific T_{cm} CD8+ cells (FIGS. 6C-6D), and CMV-specific T_{em} CD8+ cells (FIGS. 6E-6F). In addition, the percentages of CMV-specific T_{cm} (FIGS. 6G-6H) and T_{em} (FIGS. 6I-6J) CD8+ cells were quantified at the indicated time points. All tested trispecific antibodies promoted the proliferation of CMV-specific memory CD8+ T cells with different potency and kinetics in a dose-responsive manner.

[0055] FIGS. 7A-7J show the characterization of *in vitro* T cell subset expansion in PBMCs collected from CMV-infected Donor E in response to CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated anti-CD38 binding domains. A trispecific antibody lacking the CD38VH1 anti-CD38 binding domain was used as a negative control (Δ CD38VH1/ Δ CD28sup x Δ CD3mid IgG4 FALA). Antibodies shown in legend from top to bottom are shown in the graphs from left to right. T cell populations were measured at indicated time points (D3 refers to day 3; D7 refers to day 7). The indicated trispecific antibodies were tested at the indicated concentrations of 0.2 nM, 1 nM, and 2 nM. Flow cytometry was used to quantify CMV-specific CD8+ T cells

(FIGS. 7A-7B), CMV-specific T_{cm} CD8⁺ cells (FIGS. 7C-7D), and CMV-specific T_{em} CD8⁺ cells (FIGS. 7E-7F). In addition, the percentages of CMV-specific T_{cm} (FIGS. 7G-7H) and T_{em} (FIGS. 7I-7J) CD8⁺ cells were quantified at the indicated time points. All tested trispecific antibodies promoted the proliferation of CMV-specific memory CD8⁺ T cells with different potency and kinetics in dose response manner.

[0056] FIGS. 8A-8J show the characterization of *in vitro* T cell subset expansion in PBMCs collected from EBV-infected Donor C in response to CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated alternative anti-CD38 binding domains. A trispecific antibody lacking the CD38VH1 anti-CD38 binding domain was used as a negative control (Δ CD38VH1/ Δ CD28sup x Δ CD3mid IgG4 FALA). T cell populations were measured at indicated time points (D3 refers to day 3; D7 refers to day 7). The indicated trispecific antibodies were tested at the indicated concentrations of 0.2 nM and 1 nM. Flow cytometry was used to quantify EBV-specific CD8⁺ T cells (FIGS. 8A-8B), CMV-specific T_{cm} CD8⁺ cells (FIGS. 8C-8D), and CMV-specific T_{em} CD8⁺ cells (FIGS. 8E-8F). In addition, the percentages of EBV-specific T_{cm} (FIGS. 8G-8H) and T_{em} (FIGS. 8I-8J) CD8⁺ cells were quantified at the indicated time points. All tested trispecific antibodies promoted the proliferation of CMV-specific memory CD8⁺ T cells with different potency and kinetics in dose response manner.

[0057] FIGS. 9A-12 show the characterization of *in vitro* T cell subset expansion in PBMCs collected from EBV-infected Donor D in response to CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with the indicated alternative anti-CD38 binding domains. A trispecific antibody lacking the CD38VH1 anti-CD38 binding domain was used as a negative control (Δ CD38VH1/ Δ CD28sup x Δ CD3mid IgG4 FALA). T cell populations were measured at indicated time points (D3 refers to day 3; D7 refers to day 7). The indicated trispecific antibodies were tested at the indicated concentrations of 0.2 nM and 1 nM. Flow cytometry was used to quantify EBV-specific CD8⁺ T cells (FIGS. 9A-9B), EBV-specific T_{cm} CD8⁺ cells (FIGS. 9C-9D), and EBV-specific T_{em} CD8⁺ cells (FIGS. 9E-9F). In addition, the percentages of EBV-specific T_{cm} (FIGS. 9G-10) and T_{em} (FIGS. 11-12) CD8⁺ cells were quantified at the indicated time points. All tested trispecific antibodies promoted the proliferation of EBV-specific memory CD8⁺ T cells with different potency and kinetics in dose response manner.

[0058] FIGS. 13A-13D show the change over time (days) in tumor volume (FIG. 13A) and body weight (FIG. 13B) in ZR-75-1 tumor bearing NSG mice engrafted with *in vitro* expanded human CD3⁺ T cells. Groups of 10 mice were either treated with vehicle or

Her2/CD28 x CD3 trispecific antibody at the indicated dosages. Arrow heads indicate days of administration. Tumor volume is depicted as mean $\pm$ SEM, mm³. Body weight change is depicted as % change, mean $\pm$ SEM. X-axis shows days after implantation with ZR-75-1 cells. Tumor volume (mm³) over time for individual mice in each treatment group are shown in **FIG. 13C**. Tumor weight (mg) for each treatment group is shown in **FIG. 13D**. ** = p<0.001; *** = p<0.0003 (two-way ANOVA, control vs. 100 & 10ug/kg).

[0059] **FIGS. 14A-14C** show the effect of Her2/CD28 x CD3 trispecific antibody treatment on T cells from whole blood. **FIG. 14A** shows the analysis of hCD45+, CD8+, CD4+, and mCD45+ cells by flow cytometry. **FIG. 14B** shows the effect of control or Her2/CD28 x CD3 trispecific antibody treatment (at the indicated doses) on hCD45+, CD8+, CD4+, and mCD45+ cell counts. **FIG. 14C** shows the effect of control or Her2/CD28 x CD3 trispecific antibody treatment (at the indicated doses) on human cell ratios (CD4+/CD45+ and CD8+/CD45+). For each x-axis parameter shown in **FIGS. 14B & 14C**, conditions are (left to right): control, 100ug/kg trispecific antibody, 10ug/kg trispecific antibody, 1ug/kg trispecific antibody, and 0.1ug/kg trispecific antibody. Percentages shown in **FIGS. 14B & 14C** are based on control sample vs. 100ug/kg.

[0060] **FIGS. 15A-15C** show the effect of Her2/CD28 x CD3 trispecific antibody treatment on tumor infiltrating lymphocytes (TILs), as examined by immunohistochemistry (IHC). Arrows indicate tumor infiltrating T cells identified in ZR-75-1 breast tumors. Upper images are at 1X magnification; lower images are at 20X magnification. In both sets of images, staining for human CD45, human CD4, and human CD8 are shown from left to right. Shown are tumors from mice treated with vehicle control (**FIG. 15A**), 100ug/kg trispecific antibody (**FIG. 15B**), or 0.1ug/kg trispecific antibody (**FIG. 15C**).

[0061] **FIGS. 16A-16C** show quantitation of the effect of Her2/CD28 x CD3 trispecific antibody treatment on TILs as measured by IHC. Each dot represents one tumor from an individual mouse; rectangles represent group means; and error bars indicate standard deviation. * = p<0.05 compared to vehicle control group (ANOVA). Numbers of CD45+ (**FIG. 16A**), CD4+ (**FIG. 16B**), or CD8+ (**FIG. 16C**) cells are shown. In **FIG. 16C**, a \$ area quantitation approach was used for CD8+ cells instead of cell counting algorithm due to excessive non-specific signal in the CD8 IHC slide.

[0062] **FIGS. 17A-17F** show *in vitro* cell lysis of HER2+ breast cancer target cells in the presence of human CD8+ T cells by Her2/CD28 x CD3 trispecific antibody with wild-type trastuzumab antigen binding domain and an anti-CD3 antigen binding domain without 32/35 QQ mutations in the VL domain ("ctl") as compared to a Her2/CD28 x CD3

trispecific antibodies having mutations in the anti-HER2 arm and the VL domain of the anti-CD3 arm (numbering as shown in Table 1). Cell killing activities against cell lines with varying expression of HER2 are depicted: HCC1954 for high HER2 expression (**FIG. 17A**), BT20 for intermediate HER2 expression (**FIG. 17C**), and MDA-MD-231 for low HER2 expression (**FIG. 17E**). Graphs depicting cell killing as a function of antibody concentration against target cells HCC1954 (**FIG. 17B**), BT20 (**FIG. 17D**), and MDA-MD-231 (**FIG. 17F**) are shown, comparing binding protein #2 vs. ctl or binding protein #1 and #5 vs. ctl.

[0063] **FIGS. 18A & 18B** summarize the mean EC₅₀ (pM) of *in vitro* cell killing by experimental or control Her2/CD28 x CD3 trispecific antibodies against the indicated breast cancer (**FIG. 18A**) or gastric cancer cell lines (**FIG. 18B**). Amino acid sequences of the indicated trispecific antibodies are provided in Table 1.

DETAILED DESCRIPTION

[0064] 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.

General Definitions

[0065] 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.

[0066] It is understood that aspects and embodiments of the disclosure described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0067] 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, phosphoraniladate and phosphoroamidate. The term "polynucleotide" specifically includes single-stranded and double-stranded forms of DNA.

[0068] 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.

[0069] 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).

[0070] 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.

[0071] 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.

[0072] 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.

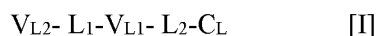
[0073] The term "Fc" as used herein refers to a molecule comprising the sequence of a non-antigen-binding fragment resulting from digestion of an antibody or produced by other means, whether in monomeric or multimeric form, and can contain the hinge region. The original immunoglobulin source of the native 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.

[0074] 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)

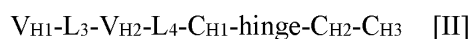
fragment can also include one light chain containing two variable domains separated by an amino acid linker and one heavy chain containing two variable domains separated by an amino acid linker and a C_{H1} domain.

[0075] 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.

[0076] 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. A trisppecific binding protein of the present disclosure, unless otherwise specified, typically comprises four polypeptide chains that form at least three antigen binding sites, wherein a first polypeptide chain has a structure represented by the formula:



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



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



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



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 the immunoglobulin C_{H1} heavy chain constant domain; and

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

L₁, L₂, L₃ and L₄ 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.

[0077] A "recombinant" molecule is one that has been prepared, expressed, created, or isolated by recombinant means.

[0078] 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).

[0079] 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."

[0080] 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.

[0081] The term "Her2" refers to human epidermal growth factor receptor 2 which is a member of the epidermal growth factor receptor family.

[0082] "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.

[0083] "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.

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

[0085] 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.

[0086] The term "monospecific binding protein" refers to a binding protein that specifically binds to one antigen target.

[0087] The term "monovalent binding protein" refers to a binding protein that has one antigen binding site.

[0088] The term "bispecific binding protein" refers to a binding protein that specifically binds to two different antigen targets.

[0089] The term "bivalent binding protein" refers to a binding protein that has two binding sites.

[0090] The term "trispecific binding protein" refers to a binding protein that specifically binds to three different antigen targets.

[0091] 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.

[0092] 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.

[0093] 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 macromolecular 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.

[0094] 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.

[0095] 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.

[0096] 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 a K_d 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.

[0097] In some embodiments, an antigen binding domain and/or binding protein of the present disclosure "cross reacts" with human and cynomolgus monkey CD38 polypeptides, *e.g.*, CD38 extracellular domains, human CD38 isoform A, human CD38 isoform E, and cynomolgus monkey CD38. A binding protein binding to antigen 1 (Ag1) is "cross-reactive" to antigen 2 (Ag2) when the EC₅₀s are in a similar range for both antigens. In the present application, a binding protein binding to Ag1 is cross-reactive to Ag2 when the ratio of affinity of Ag2 to affinity of Ag1 is equal or less than 20, affinities being measured with the same method for both antigens.

[0098] 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 L₁, 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 L₂, 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 L₃, which is located between the C-terminus of the V_{H1} and the N-terminus of the V_{H2} domain; and L₄, which is located between the C-terminus of the V_{H2} and the N-terminus of the C_{H1} domain.

[0099] 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.

[0100] 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.

[0101] 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.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] The term "patient" as used herein includes human and animal subjects.

[0108] 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 lymphoma 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] One embodiment of the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a binding protein.

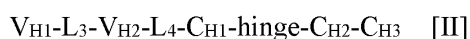
Trispecific and/or Trivalent Binding Proteins

[0113] Certain aspects of the present disclosure relate to 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. Any of the CDRs or variable domains of any of the antigen binding proteins described herein may find use in a trispecific binding protein of the present disclosure.

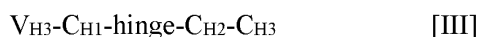
[0114] In some embodiments, each of the three antigen binding sites binds a different target (*e.g.*, polypeptide antigen). In some embodiments, the trispecific binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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

L₁, L₂, L₃ and L₄ 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.

[0115] It is contemplated that any of the antigen binding sites described herein may find use in a trispecific binding protein of the present disclosure, *e.g.*, comprising four polypeptide chains having the structures described *supra*. For example, in some embodiments, a trispecific binding protein of the present disclosure comprises a V_{H1} and V_{L1} domain pair that form a first antigen binding site, a V_{H2} and V_{L2} domain pair that form a second antigen binding site that binds a CD3 polypeptide, and a V_{H3} and V_{L3} domain pair that form a third antigen binding site. In some embodiments, a trispecific binding protein of the present disclosure comprises a V_{H1} and V_{L1} domain pair that form a first antigen binding site that binds a CD28 polypeptide, a V_{H2} and V_{L2} domain pair that form a second antigen binding site that binds a CD3 polypeptide, and a V_{H3} and V_{L3} domain pair that form a third antigen binding site. In some embodiments, a trispecific binding protein of the present disclosure comprises a V_{H1} and V_{L1} domain pair that form a first antigen binding site, a V_{H2} and V_{L2} domain pair that form a second antigen binding site that binds a CD3 polypeptide, and a V_{H3} and V_{L3} domain pair that form a third antigen binding site that binds a tumor target protein. In some embodiments, a trispecific binding protein of the present disclosure comprises a V_{H1} and V_{L1} domain pair that form a first antigen binding site that binds a CD28 polypeptide, a V_{H2} and V_{L2} domain pair that form a second antigen binding site that binds a CD3 polypeptide, and a V_{H3} and V_{L3} domain pair that form a third antigen binding site that binds a tumor target protein. In some embodiments, a trispecific binding protein of the present disclosure comprises a V_{H1} and V_{L1} domain pair that form a first antigen binding site that binds a CD28 polypeptide, a V_{H2} and V_{L2} domain pair that form a second antigen binding site that binds a CD3 polypeptide, and a V_{H3} and V_{L3} domain pair that form a third antigen binding site that binds a CD38 polypeptide. In some embodiments, a trispecific binding protein of the present disclosure comprises a V_{H1} and V_{L1} domain pair that form a first antigen binding site that binds a CD28 polypeptide, a V_{H2} and V_{L2} domain pair that

form a second antigen binding site that binds a CD3 polypeptide, and a V_{H3} and V_{L3} domain pair that form a third antigen binding site that binds a HER2 polypeptide.

[0116] 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 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 target protein is CD38 or HER2. Additional tumor target proteins are provided *infra*. In some embodiments, the one or more T cell target proteins are one or more of CD3 and CD28. Exemplary and non-limiting polypeptides that may find use in any of the trispecific binding proteins described herein are provided in Table 1.

[0117] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:156 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:156; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:157 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:157; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:158 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:158; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:159 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:159.

[0118] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:160 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:160; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:161 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:161; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:162 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:162; and the fourth

polypeptide chain comprises the amino acid sequence of SEQ ID NO:163 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:163.

[0119] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:164 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:164; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:165 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:165; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:166 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:166; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:167 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:167.

[0120] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:168 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:168; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:169 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:169; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:170 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:170; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:171 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:171.

[0121] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:172 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:172; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:173 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:173; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:174 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:174; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:175 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:175.

[0122] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain

comprises the amino acid sequence of SEQ ID NO:176 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:176; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:177 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:177; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:178 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:178; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:179 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:179.

[0123] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:181 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:181; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:182 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:182; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:183 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:183; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:184 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:184.

[0124] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:185 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:185; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:186 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:186; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:187 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:187; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:188 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:188.

[0125] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:100 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:100; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:101 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:101; the third polypeptide

chain comprises the amino acid sequence of SEQ ID NO:102 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:102; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:103 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:103.

[0126] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:104 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:104; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:105 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:105; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:106 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:106; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:107 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:107.

[0127] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:112 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:112; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:113 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:113; 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.

[0128] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:116 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:116; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:117 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:117; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:118 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:118; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:119 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:119.

[0129] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:120 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:120; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:121 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:121; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:122 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:122; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:123 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:123.

[0130] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:124 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:124; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:125 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:125; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:126 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:126; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:127 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:127.

[0131] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:128 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:128; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:129 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:129; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:130 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:130; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:131 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:131.

[0132] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:132 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:132; the second polypeptide

chain comprises the amino acid sequence of SEQ ID NO:133 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:133; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:134 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:134; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:135 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:135.

[0133] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:136 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:136; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:137 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:137; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:138 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:138; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:139 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:139.

[0134] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:140 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:140; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:141 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:141; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:142 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:142; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:143 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:143.

[0135] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:144 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:144; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:145 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:145; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:146 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:146; and the fourth

polypeptide chain comprises the amino acid sequence of SEQ ID NO:147 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:147.

[0136] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:148 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:148; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:149 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:149; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:150 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:150; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:151 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:151.

[0137] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:152 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:152; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:153 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:153; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:154 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:154; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:155 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:155.

[0138] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:286 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:286; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:287 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:287; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:288 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:288; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:289 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:289.

[0139] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain

comprises the amino acid sequence of SEQ ID NO:290 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:290; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:291 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:291; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:292 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:292; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:293 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:293.

[0140] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:294 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:294; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:295 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:295; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:296 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:296; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:297 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:297.

[0141] In some embodiments, a binding protein of the present disclosure comprises four polypeptide chains that form three antigen binding sites, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:298 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:298; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:299 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:299; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:300 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:300; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:301 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:301.

Anti-CD38 Binding Sites

[0142] Certain aspects of the present disclosure relate to binding proteins that comprise an antigen binding site that binds a CD38 polypeptide. In some embodiments, the CD38 polypeptide is a human CD38 polypeptide, also known as ADPRC1. Human CD38 polypeptides are known in the art and include, without limitation, the polypeptide represented

by NCBI Accession Number NP_001766.2, or a polypeptide produced from NCBI Gene ID Number 952. In some embodiments, the antigen binding site binds a human CD38 polypeptide, a non-human primate (*e.g.*, cynomolgus monkey) CD38 polypeptide, or a human CD38 polypeptide and a non-human primate (*e.g.*, cynomolgus monkey) CD38 polypeptide. In some embodiments, a binding protein comprising an antigen binding site that binds a CD38 polypeptide is monospecific and/or monovalent, bispecific and/or bivalent, trispecific and/or trivalent, or multispecific and/or multivalent.

[0143] In some embodiments, any of the CDRs and/or variable domains of the anti-CD38 binding sites described below can be used in a monospecific antibody.

[0144] In other embodiments, any of the CDRs and/or variable domains of the anti-CD38 binding sites described below can be used in any binding site of a trispecific binding protein comprising four polypeptides that form three antigen binding sites, *e.g.*, as described *supra*. In certain embodiments, a binding protein that comprises an antigen binding site that binds a CD38 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites as described *supra*, wherein the V_{H3} and V_{L3} domains pair and form a third antigen binding site that binds a CD38 polypeptide.

[0145] A variety of features of exemplary binding sites and binding proteins are described herein. For example, in some embodiments, an anti-CD38 binding site cross-reacts with human CD38 (*e.g.*, a human CD38 isoform A and/or isoform E polypeptide) and cynomolgus monkey CD38. In some embodiments, a binding protein comprising an anti-CD38 binding site induces apoptosis of a CD38⁺ cell. In some embodiments, a binding protein comprising an anti-CD38 binding site recruits a T cell to a CD38⁺ cell and optionally activates the T cell (*e.g.*, through TCR stimulation and/or costimulation).

[0146] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:13), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:14), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:15); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:16), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:17), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:18). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:13), a CDR-H2 sequence

comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:14), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:15); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:16), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:17), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:18).

[0147] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYTLTEFS (SEQ ID NO:19), a CDR-H2 sequence comprising the amino acid sequence of FDPEDGET (SEQ ID NO:20), and a CDR-H3 sequence comprising the amino acid sequence of TTGRFFDWF (SEQ ID NO:21); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSVISRF (SEQ ID NO:22), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:23), and a CDR-L3 sequence comprising the amino acid sequence of QQDSNLPIT (SEQ ID NO:24). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYTLTEFS (SEQ ID NO:19), a CDR-H2 sequence comprising the amino acid sequence of FDPEDGET (SEQ ID NO:20), and a CDR-H3 sequence comprising the amino acid sequence of TTGRFFDWF (SEQ ID NO:21); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSVISRF (SEQ ID NO:22), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:23), and a CDR-L3 sequence comprising the amino acid sequence of QQDSNLPIT (SEQ ID NO:24).

[0148] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYAFTTYL (SEQ ID NO:25), a CDR-H2 sequence comprising the amino acid sequence of INPGSGST (SEQ ID NO:26), and a CDR-H3 sequence comprising the amino acid sequence of ARYAYGY (SEQ ID NO:27); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QNVGTA (SEQ ID NO:28), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:29), and a CDR-L3 sequence comprising the amino acid sequence of QQYSTYPFT (SEQ ID NO:30). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYAFTTYL (SEQ ID NO:25), a CDR-H2 sequence comprising the amino acid

sequence of INPGSGST (SEQ ID NO:26), and a CDR-H3 sequence comprising the amino acid sequence of ARYAYGY (SEQ ID NO:27); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QNVGTA (SEQ ID NO:28), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:29), and a CDR-L3 sequence comprising the amino acid sequence of QQYSTYPFT (SEQ ID NO:30).

[0149] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYSFTNYA (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of ISPYYGDT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARRFEGFYYSMDY (SEQ ID NO:33); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHSNGNTY (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of SQSTHVPLT (SEQ ID NO:36). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYSFTNYA (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of ISPYYGDT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARRFEGFYYSMDY (SEQ ID NO:33); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHSNGNTY (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of SQSTHVPLT (SEQ ID NO:36).

[0150] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARDPGLRYFDGGMDV (SEQ ID NO:39); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QGISSY (SEQ ID NO:40), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:41), and a CDR-L3 sequence comprising the amino acid sequence of QQLNSFPYT (SEQ ID NO:42). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:37), a CDR-H2 sequence

comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARDPGLRYFDGGMDV (SEQ ID NO:39); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QGISSY (SEQ ID NO:40), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:41), and a CDR-L3 sequence comprising the amino acid sequence of QQLNSFPYT (SEQ ID NO:42).

[0151] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:43), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:44), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:45); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:46), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:47), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:48). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:43), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:44), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:45); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:46), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:47), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:48).

[0152] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYAMHWVKEAPGQRLEWIGYIYPGQGGTNYNQKFQGRATLTADTSASTAYMELSSLRSEDTAVYFCARTGGLRRAYFTYWGQGTLVTVSS (SEQ ID NO:79), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino

acid sequence of

DIVLTQSPATLSLSPGERATISCRASQSVSSYGQGMHWYQQKPGQPPRLLIYGASSR
ATGIPARFSGSGSGTDFTLTISPLEDFAVYYCQQNKEDPWTFGGGKLEIK (SEQ ID
NO:80). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:79, and/or
an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:80. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:79, and an
antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:80.

[0153] In some embodiments, a binding site that binds CD38 comprises: an antibody
heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
100% identical to the amino acid sequence of

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEFSIHWVRQAPGQGLEWMGGFDPED
GETIYAQKFQGRVIMTEDTSTDTAYMEMNSLRSEDTAIYYCTTGRFFDWFVGQGT
LVTSS (SEQ ID NO:81), and/or an antibody light chain variable (VL) domain comprising
an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least
89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least
96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence
of

EIILTQSPAILSLSPGERATLSRASQSVISRFLSWYQVKPGLAPRLLIYGASTRATGIPV
RFSGSGSGTDFTSLTISSLQPEDCAVYYCQQDSNLPITFGQGTRLEIK (SEQ ID NO:82).

In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain
variable (VH) domain comprising the amino acid sequence of SEQ ID NO:81, and/or an
antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:82. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:81, and an
antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:82.

[0154] In some embodiments, a binding site that binds CD38 comprises: an antibody
heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at

least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVQSGAEVKKPGASVKVSCKASGYAFTTYLVEWIRQRPQGQGLEWMGVINPGS
GSTNYAQKFQGRVTMTVDRSSTTAYMELSRSLRSDDTAVYYCARYAYGYWGQGT
LVTSS (SEQ ID NO:83), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRYTG
VPSRFSGSGSGTDFTLTISSLQPEDLATYYCQQYSTYPFTFGQGTKLEIK (SEQ ID NO:84). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:83, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:84. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:83, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:84.

[0155] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMWVRQAPGKGLEWVAVIWDYD
SNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDGGMD
VWGQGTITVSS (SEQ ID NO:87), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSGVP
SRFSGSGSGTEFTLTISLQPEDFATYYCQQLNSFPYTFGQGTKLEIK (SEQ ID NO:88).

In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:87, and/or an

antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:88. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:87, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:88.

[0156] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWDYGSNKYYADSVKGRFTISGDNSKNTLYLQMNSLRAEDTAVYYCARMFRGAFDYWGQGTLVTVSS (SEQ ID NO:89), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQSGVPSRFGSGSGTDFTLTISGLQPEDSATYYCLQDYIYYPTFGQGTKVEIK (SEQ ID

NO:90). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:89, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:90. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:89, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:90.

[0157] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVQSGAEVKKPGASVKVSCKASGYSFTNYAVHWVRQAPGQGLEWMGVISPY YGDTTYAQKFQGRVTMTVDKSSSTAYMELSRLRSDDTAVYYCARRFEGFYYSMDYWGQGTLVTVSS (SEQ ID NO:85), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DVVMTQSPLSLPVTLGQPASISCRPSQSLVHSNGNTYLNWYQQRPGQSPKLLIYKVS
KRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGTKVEIK

(SEQ ID NO:86). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:85, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:86. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:85, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:86.

[0158] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLQQSGPELVRPGTSVKVSCKASGYAFTTYLVEWIKQRPQGQLEWIGVINPGSGS
TNYNEKFKGKATLTVDRSSTTAYMHLSGLTSDDSAVYFCARYAYGYWGQGTTLTV

SS (SEQ ID NO:277), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIVMTQSQKFMSASVGDVRSITCKASQNVGTAVAWYQQQPGHSPKQLIYSASNRYT
GVPDRFTGSGAGTDFTLTISNIQSEDLADYFCQQYSTYPFTFGSGTKLEIK (SEQ ID

NO:278). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:277, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:278. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:277, and an antibody light chain variable (VL) domain comprising the amino acid

sequence of SEQ ID NO:278. In some embodiments, the VH and/or VL domains are humanized.

[0159] In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLLQSGAELVRPGVSVKISCTGSGYSFTNYAVHWVKQSHVKSLEWIGVISPPYGD
TTYNQKFTGKATMTVDKSSSTAYMELARLTSEDSAIYFCARRFEGFYYSMDYWGG
TSVTVSS (SEQ ID NO:279), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DVVMITPLSLPVSLGDQASISCRPSQSLVHSNGNTYLNWYLQRPQGSPKLLIYKVS
KRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYLCSQSTHVPLTFGSGTQLEIK (SEQ

ID NO:280). In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:279, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:280. In some embodiments, a binding site that binds CD38 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:279, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:280. In some embodiments, the VH and/or VL domains are humanized.

[0160] In some embodiments of any of the above embodiments, the binding protein is a trispecific binding protein. In some embodiments, the trispecific binding protein comprising an antigen binding site that binds a CD38 polypeptide, an antigen binding site that binds a CD28 polypeptide, and an antigen binding site that binds a CD3 polypeptide. In some embodiments, the binding protein is a trispecific binding protein comprising four polypeptides comprising three antigen binding sites, wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair (*e.g.*, as described herein). In some embodiments, the VH and VL domains of any of the anti-CD38 antigen binding sites described above represent V_{H3} and V_{L3} and form a third antigen binding site that binds a CD38 polypeptide. In some embodiments, V_{H1} and V_{L1} form a first antigen

binding site that binds a CD28 polypeptide, V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, and the V_H and V_L domains of any of the anti-CD38 antigen binding sites described above and/or in Table 2 represent V_{H3} and V_{L3} and form a third antigen binding site that binds a CD38 polypeptide.

[0161] Sequences of exemplary anti-CD38 antigen binding sites are provided in Table 2. In some embodiments, a binding protein comprising an anti-CD38 antigen binding site of the present disclosure comprises 1, 2, 3, 4, 5, or all 6 CDR sequences of an anti-CD38 antibody described in Table 2. In some embodiments, a binding protein comprising an anti-CD38 antigen binding site of the present disclosure comprises a V_H domain sequence and/or V_L domain sequence of an anti-CD38 antibody described in Table 2.

Table 2. Anti-CD38 binding protein sequences.

<i>Sequence Type</i>	<i>Molecule</i>	<i>Description</i>	<i>SEQ ID NO</i>	<i>Sequence</i>
CDR	Anti-CD38 (VH1)	CDR-H1	13	GYTFTSYA
		CDR-H2	14	IYPGQGGT
		CDR-H3	15	ARTGGLRRAYFTY
		CDR-L1	16	QSVSSYGQGF
		CDR-L2	17	GAS
		CDR-L3	18	QQNKEDPWT
	Anti-CD38 (hhy992)	CDR-H1	19	GYTLTEFS
		CDR-H2	20	FDPEDGET
		CDR-H3	21	TTGRFFDWF
		CDR-L1	22	QSVISRF
		CDR-L2	23	GAS
		CDR-L3	24	QQDSNLPIT
	Anti-CD38 (hyb5739)	CDR-H1	25	GYAFTTYL
		CDR-H2	26	INPGSGST
		CDR-H3	27	ARYAYGY
		CDR-L1	28	QNVGTA
		CDR-L2	29	SAS
		CDR-L3	30	QQYSTYPFT
	Anti-CD38 (hyb6284)	CDR-H1	31	GYSFTNYA
		CDR-H2	32	ISPYYGDT
		CDR-H3	33	ARRFEGFYYSMDY
		CDR-L1	34	QSLVHSNGNTY
		CDR-L2	35	KVS
		CDR-L3	36	SQSTHVPLT
	Anti-CD38 (hhy1195)	CDR-H1	37	GFTFSSYG
		CDR-H2	38	IWYDGSNK
		CDR-H3	39	ARDPGLRYFDGGMDV
		CDR-L1	40	QGISSY
		CDR-L2	41	AAS
		CDR-L3	42	QQLNSFPYT
	Anti-CD38 (hhy1370)	CDR-H1	43	GFTFSSYG
		CDR-H2	44	IWYDGSNK

		CDR-H3	45	ARMFRGAFDY
		CDR-L1	46	QGIRND
		CDR-L2	47	AAS
		CDR-L3	48	LQDYIYYPT
Variable domain	CD38 VH1	VH	79	QVQLVQSGAEVVKPGASVKVSCKASG YTFTSYAMHWVKEAPGQRLEWIGYIYP GQGGTNYNQKFQGRATLTADTSASTA YMELSSLRSEDNAVYFCARTGGLRRAY FTYWGGQTLVTVSS
		VL	80	DIVLTQSPATLSLSPGERATISCRASQSV SSYGQGFMHVYQKPGQPPRLIYGAS SRATGIPARFSGSGSGTDFTLTISPLEPED FAVYYCQQNKEDPWTFGGGKLEIK
	CD38 hhy992	VH	81	QVQLVQSGAEVVKPGASVKVSCKVS YTLTEFSIHWVRQAPGQGLEWMGGFDP EDGETIYAQKFQGRVIMTEDTSTDYAY MEMNSLRSEDNAIYYCTTGRFFDWFVG QGTTLVTVSS
		VL	82	EIILTQSPAILSLSPGERATLSCRASQSVI SRFLSWYQVKPGLAPRLIYGASTRATG IPVRFSGSGSGTDFSLTISSLQPEDCAVY YCQQDSNLPITFGQGTRLEIK
	CD38 hu5739	VH	83	QVQLVQSGAEVVKPGASVKVSCKASG YAFTTYLVEWIRQRPGQGLEWMGVINP GSGSTNYAQKFQGRVTMTVDRSSTAY MELSRLRSDDTAVYYCARYAYGYWGQ GTLVTVSS
		VL	84	DIQMTQSPSSLSASVGDRVTITCRASQN VGTAVAWYQKPGKSPKQLIYASNRY TGVPSTRFSGSGSGTDFSLTISSLQPEDLA TYYCQQYSTYPFTFGQGTKLEIK
	CD38 hu6284	VH	85	QVQLVQSGAEVVKPGASVKVSCKASG YSFTNYAVHWVRQAPGQGLEWMGVIS PYYGDTTYAQKFQGRVTMTVDKSSSTA YMELSRLRSDDTAVYYCARRFEGFYYS MDYWGQGTTLVTVSS
		VL	86	DVVMTQSPSLPVTLGQPASISCRPSQS LVHSNGNTYLNWYQQRPGQSPKLLIYK VSKRFSGVPDRFSGSGSGTDFTLKISR EAEDVGVIYCSQSTHVPLTFGGGKTKVE IK
	CD38 hhy1195	VH	87	QVQLVESGGGVVQGRSLRLSCAASGF TFSSYGMWVRQAPGKGLEWVAVIY DGSNKYYADSVKGRFTISRDNKNTLY LQMNSLRAEDTAVYHCARDPGLRYFD GGMDVWGQGTITVTVSS
		VL	88	DIQLTQSPSFLSASVGDRVTITCRASQGI SSYLAWYQKPGKAPKLLIFAASTLHS GVPSRFSGSGSGTEFTLTISLQPEDFAT YYCQQLNSFPYTFGQGTKLEIK
	CD38 hhy1370	VH	89	QVQLVESGGGVVQGRSLRLSCAASGF TFSSYGMWVRQAPGKGLEWVAVIY DGSNKYYADSVKGRFTISGDNSKNTLY

				LQMNSLRAEDTAVYYCARMFRGAFDY WGQGTLLVTVSS
		VL	90	AIQMTQSPSSLSASVGDRVITTCRASQGI RNDLGWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISGLQPEDSAT YYCLQDYIYYPTFGQGTKVEIK
	CD38 hyb5739	VH	277	QVQLQQSGPELVRPGTSVKVSKCASGY AFTTYLVEWIKQRPQGQLEWIGVINPGS GSTNYNEKFKGKATLTVDRSSTTAYMH LSGLTSDDSAVYFCARYAYGYWGQGT TLTVSS
		VL	278	DIVMTQSQKFMSASVGDRVSITCKASQ NVGTAVAWYQQPGHSPKQLIYSASNR YTGVPDRFTGSGAGTDFTLTISNIQSEDL ADYFCQQYSTYPFTFGSGTKLEIK
	CD38 hyb6284	VH	279	QVQLLQSGAELVRPGVSVKISCTGSGYS FTNYAVHWVKQSHVKSLEWIGVISPY GDTTYNQKFTGKATMTVDKSSSTAYM ELARLTSEDSAIYFCARRFEGFYYSMDY WGQGTSTVTVSS
		VL	280	DVVMITPLSLPVS LGDQASISCRPSQSL VHSNGNTYLNWYLQRPQSPKLLIYKV SKRFSGVPDRFSGSGSGTDFTLKISRVE AEDLGVYLCSTHVPLTFGSGTQLEIK

[0162] Further provided herein are antibodies (*e.g.*, monospecific antibodies) comprising any of the anti-CD38 CDRs and/or variable domains described *supra*.

[0163] In some embodiments, a binding protein of the present disclosure comprises an antigen binding site that binds an extracellular domain of a human CD38 polypeptide and an extracellular domain of a cynomolgus monkey CD38 polypeptide. Exemplary assays for determining whether an antigen binding site binds an antigen are described herein and known in the art, including (without limitation) ELISA, SPR, and flow cytometry assays.

Anti-HER2 Binding Sites

[0164] Certain aspects of the present disclosure relate to binding proteins that comprise an antigen binding site that binds a HER2 polypeptide. In some embodiments, the HER2 polypeptide is a human HER2 polypeptide, also known as NEU, NGL, ERBB2, TKR1, CD340, HER-2, MLN19, and HER-2/neu. Human HER2 polypeptides are known in the art and include, without limitation, the polypeptides represented by NCBI Accession Numbers XP_024306411.1, XP_024306410.1, XP_024306409.1, NP_001276867.1, NP_001276866.1, NP_001276865.1, NP_001005862.1, or NP_004439.2, or a polypeptide produced from NCBI Gene ID Number 2064. In some embodiments, a binding protein comprising an antigen binding site that binds a HER2 polypeptide is monospecific and/or monovalent, bispecific

and/or bivalent, trispecific and/or trivalent, or multispecific and/or multivalent. In some embodiments, a binding protein that comprises an antigen binding site that binds a HER2 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites as described *supra*, wherein V_{H3} and V_{L3} domain pair that form a third antigen binding site that binds a HER2 polypeptide.

[0165] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1) or GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), IYPTQGYT (SEQ ID NO:4), or IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), SRWGGEFGFYAMDY (SEQ ID NO:7), or SRWGGSGFYAMDY (SEQ ID NO:8); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9) or QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1) or GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), IYPTQGYT (SEQ ID NO:4), or IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), SRWGGEFGFYAMDY (SEQ ID NO:7), or SRWGGSGFYAMDY (SEQ ID NO:8); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9) or QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0166] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid

sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0167] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0168] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid

sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0169] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0170] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid

sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEFGFYAMDY (SEQ ID NO:7); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0171] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0172] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEFGFYAMDY (SEQ ID NO:7), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSFGFYAMDY (SEQ ID NO:8); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the

amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0173] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0174] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8); and/or an antibody light

chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGS GFYAMDY (SEQ ID NO:8); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0175] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEGFYAMDY (SEQ ID NO:7); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

[0176] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLLTVSS (SEQ ID NO:72),

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMDYW
GQGTLLTVSS (SEQ ID NO:73),

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSFGFYAMDYW
GQGTLLTVSS (SEQ ID NO:74),

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTNA
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSFGFYAMDYW
GQGTLLTVSS (SEQ ID NO:75), or

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTNA
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMDYW
GQGTLLTVSS (SEQ ID NO:76); and/or an antibody light chain variable (VL) domain
comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least
88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least
95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino
acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS
G VPSRFGSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77) or

DIQMTQSPSSLSASVGDRVTITCRASQDVQTAVAWYQQKPGKAPKLLIYSASFLYS
G VPSRFGSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:78). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:72, SEQ ID
NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76; and/or an antibody light chain
variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77 or SEQ ID
NO:78. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:72, SEQ ID
NO:73, SEQ ID NO:74, SEQ ID NO:75, or SEQ ID NO:76; and an antibody light chain
variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77 or SEQ ID
NO:78.

[0177] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLVTVSS (SEQ ID NO:72), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID

NO:77). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:72, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:72, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77.

[0178] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYW
GQGTLVTVSS (SEQ ID NO:73), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG

VPSRFSGSRSGTDFTLTISLQPEDFATYYCQGHYTPPTFGQGTKVEIK (SEQ ID NO:77). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:73, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:73, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77.

[0179] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWRQAPGKGLEWVARIYPTNAYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYWGQGTLLTVSS (SEQ ID NO:75), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISLQPEDFATYYCQGHYTPPTFGQGTKVEIK (SEQ ID

NO:77). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:75, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:75, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77.

[0180] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWRQAPGKGLEWVARIYPTQG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGSGGFYAMDYW
GQGTLLTVSS (SEQ ID NO:74), and/or an antibody light chain variable (VL) domain
comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least
88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least
95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino
acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFGSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:74, and/or
an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:77. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:74, and an
antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:77.

[0181] In some embodiments, a binding site that binds HER2 comprises: an antibody
heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWRQAPGKGLEWVARIYPTNA
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMDYW
GQGTLLTVSS (SEQ ID NO:76), and/or an antibody light chain variable (VL) domain
comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least
88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least
95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino
acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFGSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy
chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:76, and/or
an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID
NO:77. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy

chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:76, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:77.

[0182] In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLLTVSS (SEQ ID NO:72), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVQTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFSGSRSRGTDFLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID

NO:78). In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:72, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:78. In some embodiments, a binding site that binds HER2 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:72, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:78.

[0183] In some embodiments, an anti-HER2 antigen binding site of the present disclosure comprises 1, 2, 3, 4, 5, or all 6 CDR sequences of anti-HER2 antibody trastuzumab, 30R/55Q/102E, 30R/56A/102S, 30R/55Q/102S, 30R/56A/102E, or 30Q. In some embodiments, an anti-HER2 antigen binding site of the present disclosure comprises a VH domain sequence and/or VL domain sequence of anti-HER2 antibody trastuzumab, 30R/55Q/102E, 30R/56A/102S, 30R/55Q/102S, 30R/56A/102E, or 30Q.

[0184] Sequences of exemplary anti-HER2 antigen binding sites are provided in Table 3. In some embodiments, an anti-HER2 antigen binding site of the present disclosure comprises 1, 2, 3, 4, 5, or all 6 CDR sequences of an anti-HER2 antibody described in Table 3. In some embodiments, an anti-HER2 antigen binding site of the present disclosure comprises a VH

domain sequence and/or VL domain sequence of an anti-HER2 antibody described in Table 3.

Table 3. Anti-HER2 binding protein sequences.

<i>Sequence Type</i>	<i>Molecule</i>	<i>Description</i>	<i>SEQ ID NO</i>	<i>Sequence</i>
CDR	Anti-Her2 (trastuzumab) Heavy chain CDRs	CDR-H1 (original)	1	GFNIKDTY
		CDR-H1 30R	2	GFNIRDY
		CDR-H2 (original)	3	IYPTNGYT
		CDR-H2 55Q	4	IYPTQGYT
		CDR-H2 56A	5	IYPTNAYT
		CDR-H3 (original)	6	SRWGGDGFYAMDY
		CDR-H3 102E	7	SRWGGEFAYAMDY
		CDR-H3 102S	8	SRWGGSGFYAMDY
	Anti-Her2 (trastuzumab) Light chain CDRs	CDR-L1 (original)	9	QDVNTA
		CDR-L1 30Q	10	QDVQTA
		CDR-L2 (original)	11	SAS
		CDR-L3 (original)	12	QQHYTTP
Variable domain	Anti-Her2 Trastuzumab and variant VH	VH wt	72	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYP TNGYTRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDGFY AMDYWGQGTLLTVSS
		VH 30R/55Q/102E	73	EVQLVESGGGLVQPGGSLRLSCAASGF NIRDYIHWVRQAPGKGLEWVARIYPT QGYTRYADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCSRWGGEFAY MDYWGQGTLLTVSS
		VH 30R/55Q/102S	74	EVQLVESGGGLVQPGGSLRLSCAASGF NIRDYIHWVRQAPGKGLEWVARIYPT QGYTRYADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCSRWGGSGFYA MDYWGQGTLLTVSS
		VH 30R/56A/102S	75	EVQLVESGGGLVQPGGSLRLSCAASGF NIRDYIHWVRQAPGKGLEWVARIYPT NAYTRYADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCSRWGGSGFYA MDYWGQGTLLTVSS

		VH 30R/56A/102E	76	EVQLVESGGGLVQPGGSLRLSCAASGF NIRDITYIHWVRQAPGKGLEWVARIYPT NAYTRYADSVKGRFTISADTSKNTAYL QMNSLRAEDTAVYYCSRWGGEFYA MDYWGQGTLLTVSS
	Anti-Her2 Trastuzumab and variant VL	VL wt	77	DIQMTQSPSSLSASVGDRVTITCRASQ DVNTAVAWYQQKPGKAPKLLIYSASF LYSGVPSRFSGRSGTDFTLTISSLQPE DFATYYCQQHYTTPPTFGQGTKVEIK
		VL 30Q	78	DIQMTQSPSSLSASVGDRVTITCRASQ DVQTAVAWYQQKPGKAPKLLIYSASF LYSGVPSRFSGRSGTDFTLTISSLQPE DFATYYCQQHYTTPPTFGQGTKVEIK

Other Anti-Tumor Target Binding Sites

[0185] In some embodiments, a binding protein of the present disclosures comprises an antigen binding site that binds a tumor target protein. In some embodiments, the tumor target protein is a CD38 polypeptide (*e.g.*, a human CD38 polypeptide). In some embodiments, the tumor target protein is a HER2 polypeptide (*e.g.*, a human HER2 polypeptide). In some embodiments, a tumor target protein of the present disclosure includes, without limitation, 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, IFN α , 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, MUC-1, 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.

Anti-CD28 Binding Sites

[0186] Certain aspects of the present disclosure relate to binding proteins that comprise an antigen binding site that binds a CD28 polypeptide. In some embodiments, the CD28 polypeptide is a human CD28 polypeptide, also known as Tp44. Human CD28 polypeptides are known in the art and include, without limitation, the polypeptides represented by NCBI Accession Numbers XP_011510499.1, XP_011510497.1, XP_011510496.1, NP_001230007.1, NP_001230006.1, or NP_006130.1, or a polypeptide produced from NCBI Gene ID Number 940. In some embodiments, a binding protein comprising an antigen binding site that binds a CD28 polypeptide is monospecific and/or monovalent, bispecific and/or bivalent, trispecific and/or trivalent, or multispecific and/or multivalent. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD28 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD28 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, and one of which binds a CD3 polypeptide. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, one of which binds a CD3 polypeptide, and one of which binds a CD38 polypeptide. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, one of which binds a CD3 polypeptide, and one of which binds a HER2 polypeptide. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3

polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, one of which binds a CD3 polypeptide, and one of which binds a tumor target protein.

[0187] In some embodiments, a binding site that binds CD28 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYTFTSY (SEQ ID NO:49), a CDR-H2 sequence comprising the amino acid sequence of IYPGNVNT (SEQ ID NO:50), and a CDR-H3 sequence comprising the amino acid sequence of TRSHYGLDWNFDV (SEQ ID NO:51) and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QNIYVW (SEQ ID NO:52), a CDR-L2 sequence comprising the amino acid sequence of KAS (SEQ ID NO:53), and a CDR-L3 sequence comprising the amino acid sequence of QQGQTYPY (SEQ ID NO:54). In some embodiments, a binding site that binds CD28 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GYTFTSY (SEQ ID NO:49), a CDR-H2 sequence comprising the amino acid sequence of IYPGNVNT (SEQ ID NO:50), and a CDR-H3 sequence comprising the amino acid sequence of TRSHYGLDWNFDV (SEQ ID NO:51); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QNIYVW (SEQ ID NO:52), a CDR-L2 sequence comprising the amino acid sequence of KAS (SEQ ID NO:53), and a CDR-L3 sequence comprising the amino acid sequence of QQGQTYPY (SEQ ID NO:54).

[0188] In some embodiments, a binding site that binds CD28 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNV
NTNYAQKFQGRATLTVDTSISTAYMELSRLSDDTAVYYCTRSHYGLDWNFDVWG
KGTTVTVSS (SEQ ID NO:91), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of
DIQMTQSPSSLSASVGDRVTITCQASQNIYVWLNWYQQKPGKAPKLLIYKASNLHTG
VPSRFSGSGSGTDFTLTISSLQPEDIATYYCQQGQTYPYTFGQGTKLEIK (SEQ ID

NO:92). In some embodiments, a binding site that binds CD28 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:91, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:92. In some embodiments, a binding site that binds CD28 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:91, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:92.

[0189] In some embodiments of any of the above embodiments, the binding protein is a trispecific binding protein. In some embodiments, the trispecific binding protein comprising an antigen binding site that binds a tumor target protein (including, without limitation, CD38 or HER2), an antigen binding site that binds a CD28 polypeptide, and an antigen binding site that binds a CD3 polypeptide. In some embodiments, the binding protein is a trispecific binding protein comprising four polypeptides comprising three antigen binding sites, wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair (*e.g.*, as described herein). In some embodiments, the VH and VL domains of any of the anti-CD28 antigen binding sites described above represent V_{H1} and V_{L1} and form a first antigen binding site that binds a CD28 polypeptide. In some embodiments, the VH and VL domains of any of the anti-CD28 antigen binding sites described above and/or in Table 4 represent V_{H1} and V_{L1} and form a first antigen binding site that binds a CD28 polypeptide, V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, and V_{H3} and V_{L3} and form a third antigen binding site that binds a tumor target protein (including, without limitation, CD38 or HER2).

[0190] Sequences of exemplary anti-CD28 antigen binding sites are provided in Table 4. In some embodiments, an anti-CD28 antigen binding site of the present disclosure comprises 1, 2, 3, 4, 5, or all 6 CDR sequences of an anti-CD28 antibody described in Table 4. In some embodiments, an anti-CD28 antigen binding site of the present disclosure comprises a VH domain sequence and/or VL domain sequence of an anti-CD28 antibody described in Table 4.

Table 4. Anti-CD28 binding protein sequences.

<i>Sequence Type</i>	<i>Molecule</i>	<i>Description</i>	<i>SEQ ID NO</i>	<i>Sequence</i>
CDR	Anti-CD28 (sup)	CDR-H1	49	GYTFTSYY
		CDR-H2	50	IYPGNVNT

		CDR-H3	51	TRSHYGLDWNFDV
		CDR-L1	52	QNIYVW
		CDR-L2	53	KAS
		CDR-L3	54	QQGQTPY
Variable domain	Anti-CD28 (sup)	VH	91	QVQLVQSGAEVVKPGASVKVSCASGYT FTSYIHWVRQAPGQGLEWIGSIYPGNVN TNYAQKFQGRATLTVDTSISTAYMELSRL RSDDTAVYYCTRSHYGLDWNFDVWGKG TTVTVSS
		VL	92	DIQMTQSPSSLSASVGDRVTITCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLTGV PSRFGSGSGTDFTLTISSLQPEDIATYYCQ QQGQTPYTFGQGTKLEIK

Anti-CD3 Binding Sites

[0191] Certain aspects of the present disclosure relate to binding proteins that comprise an antigen binding site that binds a CD3 polypeptide. In some embodiments, the CD3 polypeptide is a human CD3 polypeptide, including CD3-delta (also known as T3D, IMD19, and CD3-DELTA), CD3-epsilon (also known as T3E, IMD18, and TCRE), and CD3-gamma (also known as T3G, IMD17, and CD3-GAMMA). Human CD3 polypeptides are known in the art and include, without limitation, the polypeptides represented by NCBI Accession Numbers XP_006510029.1 or NP_031674.1, or a polypeptide produced from NCBI Gene ID Numbers 915, 916, or 917. In some embodiments, a binding protein comprising an antigen binding site that binds a CD3 polypeptide is monospecific and/or monovalent, bispecific and/or bivalent, trispecific and/or trivalent, or multispecific and/or multivalent. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, and one of which binds a CD3 polypeptide. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, one of which binds a CD3 polypeptide, and one of which binds a CD38 polypeptide. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides

that form three antigen binding sites, one of which binds a CD28 polypeptide, one of which binds a CD3 polypeptide, and one of which binds a HER2 polypeptide. In some embodiments, a binding protein that comprises an antigen binding site that binds a CD3 polypeptide is a trispecific binding protein comprising four polypeptides that form three antigen binding sites, one of which binds a CD28 polypeptide, one of which binds a CD3 polypeptide, and one of which binds a tumor target protein.

[0192] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, the CDR-L1 sequence of the V_{L2} domain comprises an amino acid sequence selected from the group consisting of QSLVHQNAQTY (SEQ ID NO:59), QSLVHENLQTY (SEQ ID NO:60), QSLVHENLFTY (SEQ ID NO:61), and QSLVHENLRTY (SEQ ID NO:62).

[0193] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHQNAQTY (SEQ ID NO:59), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHQNAQTY (SEQ ID NO:59), a CDR-L2

sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65).

[0194] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLQTY (SEQ ID NO:60), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLQTY (SEQ ID NO:60), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65).

[0195] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLFTY (SEQ ID NO:61), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLFTY (SEQ ID NO:61), a CDR-L2

sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65).

[0196] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and/or an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLRTY (SEQ ID NO:62), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65). In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57); and an antibody light chain variable (VL) domain comprising a CDR-L1 sequence comprising the amino acid sequence of QSLVHENLRTY (SEQ ID NO:62), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65).

[0197] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY

WGQGTLLTVSS (SEQ ID NO:93), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGGTQYPFTFGSGTKVEIK (SEQ ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWY LQKPGQSPQSLIYKVS N
RFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWY LQKPGQSPQSLIYKVS NR
FSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWY LQKPGQSPQSLIYKVS N
RFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:98). In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and/or an antibody light chain variable (VL) domain comprising an amino acid sequence
selected from the group consisting of SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, and
SEQ ID NO:98. In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and an antibody light chain variable (VL) domain comprising an amino acid sequence
selected from the group consisting of SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, and
SEQ ID NO:98.

[0198] In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY
WGQGTLLTVSS (SEQ ID NO:93), and/or an antibody light chain variable (VL) domain
comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least
88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least
95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino
acid sequence of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWY LQKPGQSPQSLIYKVS N
RFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:95). In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of

SEQ ID NO:95. In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:95.

[0199] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY
WGQGTLVTVSS (SEQ ID NO:93), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ ID NO:96). In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:96. In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:96.

[0200] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY
WGQGTLVTVSS (SEQ ID NO:93), and/or an antibody light chain variable (VL) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least

88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVSNR
FSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:97). In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of
SEQ ID NO:97. In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and an antibody light chain variable (VL) domain comprising the amino acid sequence of
SEQ ID NO:97.

[0201] In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at
least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or
100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY
WGQGTLLTVSS (SEQ ID NO:93), and/or an antibody light chain variable (VL) domain
comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least
88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least
95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino
acid sequence of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWYLQKPGQSPQSLIYKVSN
RFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:98). In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of
SEQ ID NO:98. In some embodiments, a binding site that binds CD3 comprises: an antibody
heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:93,
and an antibody light chain variable (VL) domain comprising the amino acid sequence of
SEQ ID NO:98.

[0202] In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
NSYATYYASSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDYW
GQGTLTVTVSS (SEQ ID NO:302), and/or an antibody light chain variable (VL) domain

comprising an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ

ID NO:95). In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:302, and/or an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:95. In some embodiments, a binding site that binds CD3 comprises: an antibody heavy chain variable (VH) domain comprising the amino acid sequence of SEQ ID NO:302, and an antibody light chain variable (VL) domain comprising the amino acid sequence of SEQ ID NO:95.

[0203] In some embodiments of any of the above embodiments, the binding protein is a trispecific binding protein. In some embodiments, the trispecific binding protein comprising an antigen binding site that binds a tumor target protein (including, without limitation, CD38 or HER2), an antigen binding site that binds a CD28 polypeptide, and an antigen binding site that binds a CD3 polypeptide. In some embodiments, the binding protein is a trispecific binding protein comprising four polypeptides comprising three antigen binding sites, wherein the polypeptide of formula I and the polypeptide of formula II form a cross-over light chain-heavy chain pair (*e.g.*, as described herein). In some embodiments, the VH and VL domains of any of the anti-CD3 antigen binding sites described above represent V_{H2} and V_{L2} and form a second antigen binding site that binds a CD3 polypeptide. In some embodiments, V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide, the VH and VL domains of any of the anti-CD3 antigen binding sites described above and/or in Table 5 represent V_{H2} and V_{L2} and form a second antigen binding site that binds a CD3 polypeptide, and V_{H3} and

VL₃ form a third antigen binding site that binds a tumor target protein (including, without limitation, CD38 or HER2).

[0204] Sequences of exemplary anti-CD3 antigen binding sites are provided in Table 5. In some embodiments, an anti-CD3 antigen binding site of the present disclosure comprises 1, 2, 3, 4, 5, or all 6 CDR sequences of an anti-CD3 antibody described in Table 5. In some embodiments, an anti-CD3 antigen binding site of the present disclosure comprises a VH domain sequence and/or VL domain sequence of an anti-CD3 antibody described in Table 5.

Table 5. Anti-CD3 binding protein sequences.

<i>Sequence Type</i>	<i>Molecule</i>	<i>Description</i>	<i>SEQ ID NO</i>	<i>Sequence</i>
CDR	Anti-CD3 (mid)	CDR-H1 original	55	GFTFTKAW
		CDR-H2 original	56	IKDKSNSYAT
		CDR-H3 original	57	RGVYYALSPFDY
		CDR-L1 original	58	QSLVHNNANTY
		CDR-L1 QQ	59	QSLVHQNAQTY
		CDR-L1 ENLQ	60	QSLVHENLQTY
		CDR-L1 ENLF	61	QSLVHENLFTY
		CDR-L1 ENLR	62	QSLVHENLRTY
		CDR-L1 DNAQ	63	QSLVHDNAQTY
		CDR-L2 original	64	KVS
		CDR-L3 Original	65	GQGTQYPFT
		CD3mid consensus CDR-L1	180	QSLVHX ₁ NX ₂ X ₃ TY, wherein X ₁ is E or Q, X ₂ is A or L, and X ₃ is Q, R, or F
Variable Domain	Anti-CD3 (mid)	VH	93	QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDYWGQGTLLTVSS
		VL Original	94	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHNNANTYLSWYLQKPGQSPQSLIYKVS NRFGVPDRFSGSGSGTDFTLKISRVEAE DVGYYCGQGTQYPFTFGSGTKVEIK
		VL 32/35 QQ	95	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS

				NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCGQGTQYPFTFGSGTKVEIK
	VL ENLQ	96		DIVMTQTPLSLSVTPGQPASISCKSSQSL VHENLQTYLSWYLQKPGQSPQSLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCGQGTQYPFTFGSGTKVEIK
	VL ENLF	97		DIVMTQTPLSLSVTPGQPASISCKSSQSL VHENLFTYLSWYLQKPGQSPQSLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCGQGTQYPFTFGSGTKVEIK
	VL ENLR	98		DIVMTQTPLSLSVTPGQPASISCKSSQSL VHENLRITYLSWYLQKPGQSPQSLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCGQGTQYPFTFGSGTKVEIK
	VL DNAQ	99		DIVMTQTPLSLSVTPGQPASISCKSSQSL VHDNAQTYLSWYLQKPGQSPQSLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCGQGTQYPFTFGSGTKVEIK
	VH 185S	302		QVQLVESGGGVVQPGRSLRLSCAASGFT FTKAWMHWRQAPGKQLEWVAQIKDK SNSYATYYASSVKGRFTISRDDSKNTLY LQMNSLRAEDTAVYYCRGVYYALSPFD YWGQGTLLTVSS

Linkers

[0205] In some embodiments, the linkers L₁, L₂, L₃, and L₄ 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. L₁, L₂, L₃, and L₄ in one binding protein may all have the same amino acid sequence or may all have different amino acid sequences.

[0206] Examples of suitable linkers include, for example, GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO: 70), S, RT, TKGPS (SEQ ID NO: 68), GQPKAAP (SEQ ID NO: 67), GGS GSSSGG (SEQ ID NO: 71), and DKTHT (SEQ ID NO:66), as well as those disclosed in International Publication Nos. WO2017/074878 and WO2017/180913. 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.

[0207] 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.

[0208] In some embodiments, the length of L₁ is at least twice the length of L₃. In some embodiments, the length of L₂ is at least twice the length of L₄. In some embodiments, the length of L₁ is at least twice the length of L₃, and the length of L₂ is at least twice the length of L₄. In some embodiments, L₁ is 3 to 12 amino acid residues in length, L₂ is 3 to 14 amino acid residues in length, L₃ is 1 to 8 amino acid residues in length, and L₄ is 1 to 3 amino acid residues in length. In some embodiments, L₁ is 5 to 10 amino acid residues in length, L₂ is 5 to 8 amino acid residues in length, L₃ is 1 to 5 amino acid residues in length, and L₄ is 1 to 2 amino acid residues in length. In some embodiments, L₁ is 7 amino acid residues in length, L₂ is 5 amino acid residues in length, L₃ is 1 amino acid residue in length, and L₄ is 2 amino acid residues in length.

[0209] In some embodiments, L₁, L₂, L₃ and L₄ each independently are zero amino acids in length or comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO: 70), S, RT, TKGPS (SEQ ID NO: 68), GQPKAAP (SEQ ID NO: 67), and GSGSSGSGG (SEQ ID NO: 71). In some embodiments, L₁, L₂, L₃ and L₄ each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO: 70), S, RT, TKGPS (SEQ ID NO: 68), GQPKAAP (SEQ ID NO: 67), and GSGSSGSGG (SEQ ID NO: 71). In some embodiments, L₁ comprises the sequence GQPKAAP (SEQ ID NO: 67), L₂ comprises the sequence TKGPS (SEQ ID NO:68), L₃ comprises the sequence S, and L₄ comprises the sequence RT.

[0210] In some embodiments, at least one of L₁, L₂, L₃ or L₄ comprises the sequence DKTHT (SEQ ID NO:66). In some embodiments, L₁, L₂, L₃ and L₄ comprise the sequence DKTHT (SEQ ID NO:66).

Fc regions and constant domains

[0211] In some embodiments, a binding protein of the present disclosure comprises a second polypeptide chain further comprising 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, a binding protein of the present disclosure comprises a third polypeptide chain further comprising an Fc region linked to C_{H1}, 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.

[0212] In some embodiments, a binding protein of the present disclosure comprises a full-length antibody heavy chain or a polypeptide chain comprising an Fc region. In some embodiments, the Fc region is a human Fc region, *e.g.*, a human IgG1, IgG2, IgG3, or IgG4 Fc region. In some embodiments, the Fc region includes an antibody hinge, CH₁, CH₂, CH₃, and optionally CH₄ domains. In some embodiments, the Fc region is a human IgG1 Fc region. In some embodiments, the Fc region is a human IgG4 Fc region. In some embodiments, the Fc region includes one or more of the mutations described *infra*. In some embodiments, the Fc region is an Fc region of one of the heavy chain polypeptides (*e.g.*, polypeptide 2 or 3) of a binding protein shown in Table 4. In some embodiments, the heavy chain constant region is a constant region of one of the heavy chain polypeptides (*e.g.*, polypeptide 2 or 3) of a binding protein shown in Table 4. In some embodiments, the light chain constant region is a constant region of one of the light chain polypeptides (*e.g.*, polypeptide 1 or 4) of a binding protein shown in Table 4.

[0213] 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 been 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).

[0214] In some embodiments, a binding protein of the present disclosure (*e.g.*, a trispecific binding protein) 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.

[0215] 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.

[0216] 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.

[0217] 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.

[0218] 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.

[0219] 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.

[0220] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, wherein the first Fc region is a human IgG4 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 228, 354, 366, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, S354C, T366W, and R409K; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, wherein the second Fc region is a human IgG4 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 228, 349, 366, 368, 407, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, Y349C, T366S, L368A, Y407V, and R409K. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, wherein the first Fc region is a human IgG4 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 228, 349, 366, 368, 407, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, Y349C, T366S, L368A, Y407V, and R409K; and wherein the third polypeptide chain further comprises

a second Fc region linked to CH₁, wherein the second Fc region is a human IgG4 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 228, 354, 366, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, S354C, T366W, and R409K.

[0221] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH₁, wherein the first Fc region is a human IgG4 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 234, 235, 354, and 366 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A, L235A, S354C, and T366W; and wherein the third polypeptide chain further comprises a second Fc region linked to CH₁, wherein the second Fc region is a human IgG4 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 234, 235, 349, 366, 368, and 407 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A, L235A, Y349C, T366S, L368A, and Y407V. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH₁, wherein the first Fc region is a human IgG4 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 234, 235, 349, 366, 368, and 407 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A, L235A, Y349C, T366S, L368A, and Y407V; and wherein the third polypeptide chain further comprises a second Fc region linked to CH₁, wherein the second Fc region is a human IgG4 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 234, 235, 354, and 366 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A, L235A, S354C, and T366W.

[0222] 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 CH₁, the first Fc region comprising an immunoglobulin hinge region and CH₂ and CH₃ 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, and 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 Fc regions of the second and the third polypeptide chains are human IgG4 Fc regions, and the 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 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.

[0223] In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, wherein the first Fc region is a human IgG4 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 228, 234, 235, 354, 366, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, F234A, L235A, S354C, T366W, and R409K; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, wherein the second Fc region is a human IgG4 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 228, 234, 235, 349, 366, 368, 407, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, F234A, L235A, Y349C, T366S, L368A, Y407V, and R409K. In some embodiments, the second polypeptide chain further comprises a first Fc region linked to CH1, wherein the first Fc region is a human IgG4 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 228, 234, 235, 349, 366, 368, 407, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, F234A, L235A, Y349C, T366S, L368A, Y407V, and R409K; and wherein the third polypeptide chain further comprises a second Fc region linked to CH1, wherein the second Fc region is a human IgG4 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 228, 234, 235, 354, 366, and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P, F234A, L235A, S354C, T366W, and R409K.

[0224] In some embodiments, the Fc region is a human IgG4 Fc region comprising one or more mutations that reduce or eliminate FcγI and/or FcγII binding. In some embodiments, the Fc region is a human IgG4 Fc region comprising one or more mutations that reduce or eliminate FcγI and/or FcγII binding but do not affect FcRn binding. In some embodiments, the Fc region is a human IgG4 Fc region comprising amino acid substitutions at positions corresponding to positions 228 and/or 409 of human IgG4 according to EU Index. In some embodiments, the amino acid substitutions are S228P and /or R409K. In some embodiments, the Fc region is a human IgG4 Fc region comprising amino acid substitutions at positions

corresponding to positions 234 and/or 235 of human IgG4 according to EU Index. In some embodiments, the amino acid substitutions are F234A and/or L235A. In some embodiments, the Fc region is a human IgG4 Fc region comprising amino acid substitutions at positions corresponding to positions 228, 234, 235, and/or 409 of human IgG4 according to EU Index. In some embodiments, the amino acid substitutions are S228P, F234A, L235A, and/or R409K. In some embodiments, the Fc region is a human IgG4 Fc region comprising amino acid substitutions at positions corresponding to positions 233-236 of human IgG4 according to EU Index. In some embodiments, the amino acid substitutions are E233P, F234V, L235A, and a deletion at 236. In some embodiments, the Fc region is a human IgG4 Fc region comprising amino acid mutations at substitutions corresponding to positions 228, 233-236, and/or 409 of human IgG4 according to EU Index. In some embodiments, the amino acid mutations are S228P; E233P, F234V, L235A, and a deletion at 236; and/or R409K.

[0225] In some embodiments, the Fc region comprises one or more mutations that reduce or eliminate Fc receptor binding and/or effector function of the Fc region (*e.g.*, Fc receptor-mediated antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and/or antibody-dependent cellular cytotoxicity (ADCC)).

[0226] In some embodiments, the Fc region is a human IgG1 Fc region comprising one or more amino acid substitutions at positions corresponding to positions 234, 235, and/or 329 of human IgG1 according to EU Index. In some embodiments, the amino acid substitutions are L234A, L235A, and/or P329A. In some embodiments, the Fc region is a human IgG1 Fc region comprising amino acid substitutions at positions corresponding to positions 298, 299, and/or 300 of human IgG1 according to EU Index. In some embodiments, the amino acid substitutions are S298N, T299A, and/or Y300S.

[0227] 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.

[0228] In some embodiments, the Fc region is a human IgG1 Fc region comprising one or more amino acid substitutions at positions corresponding to positions 234, 235, and/or 329 of human IgG1 according to EU Index. In some embodiments, the amino acid substitutions are L234A, L235A, and/or P329A. In some embodiments, the Fc region is a human IgG1 Fc region comprising amino acid substitutions at positions corresponding to positions 298, 299, and/or 300 of human IgG1 according to EU Index. In some embodiments, the amino acid substitutions are S298N, T299A, and/or Y300S.

Nucleic acids

[0229] Other aspects of the present disclosure relate to isolated nucleic acid molecules comprising a nucleotide sequence encoding any of the binding proteins described herein. Exemplary and non-limiting nucleic acid sequences are provided in Table 5.

[0230] Other aspects of the present disclosure relate to kits of polynucleotides, *e.g.*, that encode one or more polypeptides of a binding protein as described herein. In some embodiments, a kit of polynucleotides of the present disclosure comprises one, two, three, or four polynucleotides of a kit of polynucleotides comprising: (a) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:189, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:190, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:191, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:192; (b) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:193, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:194, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:195, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:196; (c) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:197, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:198, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:199, and a fourth polynucleotide

comprising the polynucleotide sequence of SEQ ID NO:200; (d) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:201, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:202, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:203, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:204; (e) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:205, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:206, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:207, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:208; (f) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:209, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:210, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:211, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:212; (g) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:213, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:214, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:215, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:216; (h) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:217, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:218, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:219, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:220; (i) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:221, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:222, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:223, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:224; (j) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:225, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:226, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:227, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:228; (k) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:229, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:230, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:231, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:232; (l) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:233, a second polynucleotide

comprising the polynucleotide sequence of SEQ ID NO:234, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:235, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:236; (m) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:237, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:238, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:239, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:240; (n) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:241, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:242, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:243, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:244; (o) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:245, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:246, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:247, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:248; (p) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:249, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:250, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:251, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:252; (q) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:253, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:254, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:255, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:256; (r) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:257, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:258, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:259, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:260; (s) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:261, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:262, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:263, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:264; (t) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:265, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:266, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:267, and a fourth polynucleotide

comprising the polynucleotide sequence of SEQ ID NO:268; (u) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:269, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:270, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:271, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:272; or (v) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:273, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:274, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:275, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:276.

[0231] 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, *e.g.*, as shown in the polynucleotides of Table 6. 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. In some embodiments, the first, second, third, and fourth polynucleotides are present on one or more expression vectors, *e.g.*, one, two, three, or four expression vectors.

[0232] 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.

[0233] 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.

[0234] 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.

Host cells

[0235] Other aspects of the present disclosure relate to a host cell (e.g., an isolated host cell) comprising one or more isolated polynucleotides, vectors, and/or vector systems described herein. In some embodiments, an isolated host cell of the present disclosure is cultured *in vitro*. 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), Expi293[™] 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).

[0236] 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).

Pharmaceutical Compositions

[0237] 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.

[0238] Acceptable formulation materials are nontoxic to recipients at the dosages and concentrations employed.

[0239] 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 dextrans), 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 – *e.g.*, 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).

[0240] 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.

[0241] 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.

[0242] 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.

[0243] 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.

[0244] 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.

[0245] 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.

[0246] 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 where 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.

[0247] 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.

[0248] 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.

[0249] 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.

[0250] 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.

[0251] 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).

[0252] 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.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] The pharmaceutical compositions can be used to prevent and/or treat HIV infection. The pharmaceutical compositions can be used as a standalone therapy or in combination with standard anti-retroviral therapy.

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 (*e.g.*, HIV infection) 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.

Methods and Uses for Binding Proteins

Virus

[0257] Certain aspects of the present disclosure relate to methods for expanding virus-specific memory T cells. In some embodiments, the methods comprise contacting a virus-specific memory T cell with a binding protein of the present disclosure, *e.g.*, a trispecific binding protein that comprises a first antigen binding site that binds a CD28 polypeptide, a second antigen binding site that binds a CD3 polypeptide, and a third antigen binding site that binds a CD38 polypeptide.

[0258] In some embodiments, the virus-specific memory T cell is contacted with the binding protein *in vitro* or *ex vivo*.

[0259] In some embodiments, contacting the virus-specific memory T cell with the binding protein causes activation and/or proliferation of virus-specific memory T cells.

[0260] Other aspects of the present disclosure relate to methods for expanding T cells. In some embodiments, the methods comprise contacting a T cell with a binding protein of the present disclosure, *e.g.*, a trispecific binding protein that comprises a first antigen binding site that binds a CD28 polypeptide, a second antigen binding site that binds a CD3 polypeptide, and a third antigen binding site that binds a CD38 polypeptide.

[0261] In some embodiments, the T cell is a memory T cell or an effector T cell.

[0262] In some embodiments, the T cell expresses a chimeric antigen receptor (CAR) on its cell surface or comprises a polynucleotide encoding a CAR.

[0263] Other aspects of the present disclosure relate to methods for treating chronic viral infection, *e.g.*, in an individual in need thereof. In some embodiments, the methods comprise administering to an individual in need thereof an effective amount of a binding protein of the present disclosure, *e.g.*, a trispecific binding protein that comprises a first antigen binding site that binds a CD28 polypeptide, a second antigen binding site that binds a CD3 polypeptide, and a third antigen binding site that binds a CD38 polypeptide.

[0264] In some embodiments, the individual is a human.

[0265] In some embodiments, the binding protein is administered to the individual in pharmaceutical formulation comprising the binding protein and a pharmaceutically acceptable carrier.

[0266] In some embodiments, administration of the binding protein results in activation and/or proliferation of virus-specific memory T cells in the individual.

[0267] In any of the above methods, memory T cells can be CD8⁺ or CD4⁺ memory T cells. In any of the above methods, memory T cells can be central memory T cells (T_{CM}) or effector memory T cells (T_{EM}).

Cancer

[0268] Certain aspects of the present disclosure relate to methods for preventing and/or treating cancer in a patient. In some embodiments, the methods comprise administering to the patient a therapeutically effective amount of a binding protein or pharmaceutical composition of the present disclosure.

[0269] In some embodiments, a binding protein of the present disclosure is administered to a patient in need thereof for the treatment or prevention of cancer. 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, or pharmaceutical compositions related thereto, described herein. In some embodiments, the present disclosure relates to uses of at least one of the binding proteins, or pharmaceutical compositions related thereto, described herein for preventing and/or treating a proliferative disease or disorder (*e.g.*, cancer) in a patient in need thereof. In some embodiments, the present disclosure relates to at least one of the binding proteins, or pharmaceutical compositions related thereto, described herein for use in the manufacture of a medicament for preventing and/or treating a proliferative disease or disorder (*e.g.*, cancer) in a patient in need thereof. In some embodiments, the patient is a human.

[0270] In some embodiments, the at least one binding protein is administered (or is to be administered) in combination with one or more anti-cancer therapies (*e.g.*, any anti-cancer therapy known in the art, such as a chemotherapeutic agent or therapy). In some embodiments, the at least one binding protein is administered (or is to be administered) before the one or more anti-cancer therapies. In some embodiments, the at least one binding protein is administered (or is to be administered) concurrently with the one or more anti-

cancer therapies. In some embodiments, the at least one binding protein is administered (or is to be administered) after the one or more anti-cancer therapies.

[0271] In some embodiments, the binding protein comprises one or two antigen binding site(s) that binds a T-cell surface protein and another antigen binding site that binds the extracellular domain of a human HER2 polypeptide. In some embodiments, the binding protein comprises an antigen binding site that binds the extracellular domain of a human HER2 polypeptide, an antigen binding site that binds a human CD28 polypeptide, and an antigen binding site that binds a human CD3 polypeptide.

[0272] In some embodiments, cancer cells from the individual express HER2. In some embodiments, the patient is selected for treatment on the basis that the cells of the cancer express a human HER2 polypeptide. Assays known in the art suitable for detecting HER2 expression by cancer cells include, without limitation, immunohistochemical (IHC) and fluorescence *in situ* hybridization (FISH) assays.

[0273] In some embodiments, the cancer (*e.g.*, HER2-positive cancer) is breast cancer, colorectal cancer, gastric cancer, or non-small cell lung cancer (NSCLC).

[0274] In some embodiments, the binding protein comprises one or two antigen binding site(s) that binds a T-cell surface protein and another antigen binding site that binds the extracellular domain of a human CD38 polypeptide. In some embodiments, the binding protein comprises an antigen binding site that binds the extracellular domain of a human CD38 polypeptide, an antigen binding site that binds a human CD28 polypeptide, and an antigen binding site that binds a human CD3 polypeptide.

[0275] In some embodiments, cancer cells from the individual express CD38. In some embodiments, cells of the cancer express a human CD38 isoform A polypeptide on their cell surface. In some embodiments, cells of the cancer express a human CD38 isoform E polypeptide on their cell surface. In some embodiments, the patient is selected for treatment on the basis that the cells of the cancer express a human CD38 isoform E polypeptide on their cell surface. In some embodiments, the cancer cells express CD38 and CD28. In some embodiments, the cancer cells express CD38 and do not express CD28.

[0276] In some embodiments, the cancer (*e.g.*, CD38-positive cancer) is multiple myeloma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, lymphoma, breast cancer such as Her2+ breast cancer, prostate cancer, germinal center B-cell lymphoma or B-cell acute lymphoblastic leukemia. In certain embodiments, the cancer is multiple myeloma. In certain embodiments, the cancer is acute myeloid

leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or a B cell lymphoma.

[0277] In certain embodiments, the cancer is multiple myeloma. Anti-CD38 antibodies have been tested for the treatment of multiple myeloma, such as daratumumab. However, while multiple myeloma is considered treatable, relapse is inevitable in almost all patients, leading to the development of treatment-refractory disease. In some embodiments, the cancer is relapsed or refractory multiple myeloma. In some embodiments, the patient has been treated with a prior multiple myeloma treatment. In some embodiments, a binding protein of the present disclosure is administered to the patient as a 1st, 2nd, or 3rd line treatment for multiple myeloma. Without wishing to be bound to theory, it is thought that an anti-CD38xanti-CD28xanti-CD3 binding protein of the present disclosure may be useful in treating multiple myeloma, *e.g.*, by recruiting T cells to tumor cells via anti-CD38 (or anti-CD28/anti-CD38), activation of engaged T cells via anti-CD3/anti-CD28, and/or killing of tumor cells through perforin/granzyme-based mechanisms. CD28 has been reported as a novel cancer marker for multiple myeloma. *See Nair, J.R. et al. (2011) J. Immunol. 187:1243-1253.*

[0278] Any of the binding proteins described herein may find use in the methods of the present disclosure.

[0279] In some embodiments of any of the methods of the present disclosure, prior to administration of the binding protein, the patient has been treated with daratumumab. As described herein, the present disclosure provides anti-CD38 binding proteins and sites that do not compete for binding CD38 with daratumumab. Without wishing to be bound to theory, it is thought that this is advantageous because a patient previously treated with daratumumab can be treated with a binding protein of the present disclosure, *e.g.*, without a wash-out period prior to treatment.

[0280] 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.

[0281] 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 ³H, ¹⁴C, ³²P, ³⁵S, ¹²⁵I, ⁹⁹Tc, ¹¹¹In, or ⁶⁷Ga; a fluorescent

or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or an enzyme, such as alkaline phosphatase, β -galactosidase, or horseradish peroxidase.

[0282] 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.

[0283] For clinical or research applications, in certain embodiments, binding proteins can be conjugated to a cytotoxic agent. A variety of antibodies coupled to cytotoxic agents (*i.e.*, antibody-drug conjugates) have been used to target cytotoxic payloads to specific tumor cells. Cytotoxic agents and linkers that conjugate the agents to an antibody are known in the art; *see, e.g.*, Parslow, A.C. *et al.* (2016) *Biomedicines* 4:14 and Kalim, M. *et al.* (2017) *Drug Des. Devel. Ther.* 11:2265-2276.

Binding protein therapeutic compositions and administration thereof

[0284] 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. These pharmaceutical compositions may find use in any of the methods and uses described herein (*e.g.*, *ex vivo*, *in vitro*, and/or *in vivo*).

[0285] Acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

[0286] 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 dextrans), 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).

[0287] 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.

[0288] 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.

[0289] 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.

[0290] 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.

[0291] 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.

[0292] 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.

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] 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.

[0298] 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.

[0299] 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).

[0300] 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.

[0301] 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.

[0302] 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.

[0303] 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.

Table 1. Trispecific binding protein polypeptide sequences

<i>Molecule</i>	<i>Polypeptide Number (acc. to formula)</i>	<i>SEQ ID NO</i>	<i>Sequence</i>
HER2 (WT- trastuzumab) / CD28supxCD3 mid (32/35 QQ (LC); DKTHT linkers on HC/LC) IgG4 FALA BP # 1	1	100	DIVMTQTPLSLSVTPGQPASICKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCGGTQYPTFTSGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNI YVWLNWYQQKPGKAPKLLIYKASNLHTGVPSPRFSGSGSGTDFTLTISSLQPEDIAITYYCCGGQTYPYTFGGQ TKLEIKDKTHTRTVAAPSVFIPTSPDEQLKSGTASVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSLTSLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	101	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTAYMELSRISDDTA VYYCTRSHYGLDWNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQP RSLRSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDKNTLYLQM NSLRAEDTAVYYCRGVYYALSPFDYWGQGTLLTVSSDKTHTASTKGPVFPPLAPCSRSTSESTAALGCLVK DYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKY GPPCPAPEAAAGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLG
	3	102	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLTVSSASTKGPSVFPPLAPCSRSTSES TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPKPSNTK VDKRVESKYGPPCPAPEAAAGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYVTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSV MEALHNHYTQKSLSLSLG
	4	103	DIQMTQSPSSLASVGDRTVITTCRASQDVNTAVAWYQQKPGKAPKLLIYSASFYSGVPSRFSGSGTDFTL TISSLQPEDFATYYCQQHYTTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNFFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYLSLTSLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

HER2 (30R/55Q/102E +LC-WT- trastuzumab) / CD28supxCD3 mid (32/35 QQ (LC); DKTH linkers on HC/LC) IgG4 FALA BP # 2	1	104	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIKVSNRFSGVPDFRFSGSGG TDFTLKISRVEAEDVGYYCGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNI YVWLNWYQQKPGKAPKLLIKASNLHTGVPSRFSGSGGTDFTLTISLQPEDIAITYYCCQGGQTYPTFTGQ TKLEIKDKTHRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	105	QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSRISDDTAIVYYCTRSHYGLDWNFDVWVGKGTIVTVSSDKTHTVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKSNYSATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGGQTLTVSSDKTHASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	106	EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHWVVRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYWGQGTIVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLG
	4	107	DIQMTQSPSSLSASVGDRTVITTCRASQDVNTAVAWYQQKPGKAPKLLIYASFLYSGVPSRFSGSGRSGTDFTL TISLQPEDFAITYYCCQHYTTPPTFGQGTQVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2 (30R/55Q/102E +LC-WT-	1	108	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHDNAQTYLSWYLQKPGQSPQSLIKVSNRFSGVPDFRFSGSGG TDFTLKISRVEAEDVGYYCGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNI YVWLNWYQQKPGKAPKLLIKASNLHTGVPSRFSGSGGTDFTLTISLQPEDIAITYYCCQGGQTYPTFTGQ

trastuzumab) / CD28 ^{sup} xCD3 _{mid} (DNAQ (LC); DKTHT linkers on HC/LC) IgG4 FALA				TKLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
BP # 8	2	109		QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGGLWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSRISDDTAIVYYCTRSYGLDWNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTITVTVSSDKTHTASTKGPSVFLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKITYTCNVVHDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSVFLPPKPKDTLMISRTPETCVVVDVVSQEDPEVQFNWYVDGVEVHNAKTKPREE QENSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	110		EVQLVESGGGLVQPGGSLRLSCAASGFTNIRDTYIHWVVRQAPGKGLWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYWGQGTITVTVSSASTKGPSVFLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKITYTCNVVHDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGPSVFLPPKPKDTLMISRTPETCVVVDVVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGYFPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLG
	4	111		DIQMTQSPSSLSASVGDRTVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2 (30R/56A/102S +LC-WT- trastuzumab) / CD28 ^{sup} xCD3 mid	1	286		DIVMTQTPLSLSTPQGPASISCKSSQSLVHQNAQTYLSWYLOKPGQSPQSLIYKVSNRFSGVDPDRFSGSGG TDFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVTITCQASQNI YVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGGTDFTLTISLQPEDIATYYCQQGQTYPTFTFGQ TKLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(32/35QQ185E) IgG4 FALA BP # 3					QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATLTVDTSTAYMELSRRLSDDTAVYYCTRSHYGLDNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGLTVTVSSDKTHTASTKPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPCCPPCAPEAAAGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVTHQDVLNGKEYCKKVSNGKGLPSSIEKTISKAKGQPREPQVCTLPSPSQEEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELVSKLTVTDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	2	287			EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHWVRQAPGKGLEWVARIYPTNAYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPCCPPCAPEFLGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVTHQDVLNGKEYCKKVSNGKGLPSSIEKTISKAKGQPREPQVYTLPPCQEE MTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSKLTVTDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLG
HER2 (30R/55Q/102 E +LC-WT- trastuzumab) / CD28supxCD3 mid (32/35QQ185E) IgG4 FALA BP # 4					DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGRSGTDFTL TISSLPEDFAITYYCCQHYTTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	1	290			DIVMTQTPLSLVTPGPASISCKSSQSLVHQAQTYLSWYLQKPGQSPQSLYKVSINRFSGVPPDRFSGSGSG TDFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKGPKAAPDIQMTQSPSSLSASVGDRTVITTCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLQPEDIATYYCCQQGQTYPYTFG QGTGLEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	291			QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATLTVDTSTAYMELSRRLSDDTAVYYCTRSHYGLDNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQPG

			<p> RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKNSYATYYAESVKGRFTISRDDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGLTVTVSSDKTHTASTKGPVFPPLAPCSRSTSESTAAAGCLVK DYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKY GPPCPAPEAAGGSPVFLPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWYVDGVEVHNATKPRPEE QENSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG </p>
3	292		<p> EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHVVVRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYWGQGLTVTVSSASTKGPVFPPLAPCSRSTSES TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTK VDKRVESKYGPPCPAPEAAGGSPVFLPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWYVDGVEV HNAKTPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLG </p>
4	293		<p> DIQMTQSPSSLSASVGDRTVITTCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQHHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC </p>
HER2 (30R/55Q/102 E +LC-WT- trastuzumab) / CD28supxCD3 mid (32/35QQ185S) IgG4 FALA BP # 5	1	294	<p> DIVMTQTPLSLVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLYKVSINRFSGVPDFRFSGSG TDFTLKISRVEAEDVGYVYCGQGTQYPTFGSGTKVEIKGQPKAAPIDIQTQSPSSLSASVGDRTVITTCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLQPEDIATYYCQQGQTYPYTFG QGTKLEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC </p>
2	295		<p> QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSISTAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTITVTVSSSQVQLVESGGGVVQPGRSRLR LSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKNSYATYYASSVKGRFTISRDDSKNTLYLQMNSLR AEDTAVYYCRGVYALSPFDYWGQGLTVTVSSRTASTKGPVFPPLAPCSRSTSESTAAAGCLVKDYFPEPT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCP APEAAGGSPVFLPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWYVDGVEVHNATKPRPEEQFNSTYR VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGF </p>

			YPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFLLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLG
	3	296	EVQLVESGGGLVQPGGSLRLSCAASGFTNIRDTYIHVVRRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRRAEDTAVVYCSRWGGEGFYAMDYWGQGTLLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVVDHKPSNTK VDKRVESKYGPPCPPEAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYVTLPPCQEE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFLLVSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGL
	4	297	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQGHYTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEHKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2 (30R/55Q/102 E +LC-WT- trastuzumab) / CD28supxCD3 mid (32/33/35QSQ 185S) IgG4 FALA BP # 6	1	298	DIVMTQPLSLSVTPGGQASISCKSSQSLVHQSQAQTYLSWYLOKPGQSPQSLIYKVSNRFSGVPDFRFSGSGGT DFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKGQPKAAPDIQMTQSPSSLSASVGDRVTITTCQASQN IYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIAITYYCCQQGTQYPTFTGQ GTKLEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWVVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEHKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	299	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTITVTVSSQVQLVESGGGVVQPGRSRLR LSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKNSYATYYASSVKGRFTISRDDSKNTLYLQMNSLR AEDTAVYYCRGVYALSPFDYWGQGTLLVTVSSRTASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVVDHKPSNTKVDKRVESKYGPPCPPEP APEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPEQEEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFLLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLG
	3	300	EVQLVESGGGLVQPGGSLRLSCAASGFTNIRDTYIHVVRRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRRAEDTAVVYCSRWGGEGFYAMDYWGQGTLLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVVDHKPSNTK

				<p>VDKRVESKYGPPCPPCAPEAAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG</p>
	4	301		<p>DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGRSGTDFTL TISLQPEDFAITYYCQHHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</p>
HER2 (30R/55Q/102E +LC-WT- trastuzumab) / CD28 _{sup} xCD3 _{mid} (32/35QQ (LC); L1 linker) IgG4 FALA BP # 9	1	112		<p>DIVMTQTPLSLSVTPGPASISCKSSQSLVHQNATYLSWYLKQPGSPQSLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDGVIYCGQGTQYPTFGSGTKVEIKGQPKAAPIDIQTQSPSSLSASVGDRTVITTCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGTDFTLTISLQPEDIAITYYCQGGQTYPTFG QGTKEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSITYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</p>
	2	113		<p>QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTITVTVSSSQVQLVESGGGVVQPGRSRLR LSCAASGFTFTKAWMHVWRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLR AEDTAVYYCRGVVYALSPFDYWGQGTITVTVSSRTASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKITYTCNVVDHKPSNTKVDKRVESKYGPPCPPCP APEAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPQEEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLG</p>
	3	114		<p>EVQLVESGGGLVQPGGSLRLSCAASGFINRDITYIHWVVRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRADDTAVYYCSRWGGEGFYAMDYWGQGTITVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKITYTCNVVDHKPSNTK VDKRVESKYGPPCPPCAPEAAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG</p>

4	115	DIQMTQSPSSLSASVGDRTVITTCRASQDVNTAVAWYQQKPGKAPKLLIYSASFYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQHHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2-30R/ 55Q/102S+LC- WT- trastuzumab/ CD28supxCD 3mid L1 linker IgG4 FALA BP # 10	116	DIVMTQTPLSLSVTPGPASISCKSSQSLVHNNANTYLSWYLQKPGQSPQSLIYKVSNRFSGVDPDRFSGSGG TDFTLKISRVEAEDVGVYYCGQGTQYPTFGSGTKVEIKGQPKAAPDIQMTPSPSSLSASVGDRTVITTCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFLTITSLQPEDIATYYCQQGGQTYPTFG QGTKEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
2	117	QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSLRSDDTAVYYCTRSHYGLDNFDVWGKGTITVTVSSSQVQLVESGGGVVQPGRSRLR LSCAASGFTTKAWMHWRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQMNSLR AEDTAVYYCRGVYALSPFDYWGQGTITVTVSSRTASTKGPSVFPLAPCSSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVNDHKPSNTKVDKRVESKYGPPCPPCP APEAAGGPSVFLPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTTISKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSL SLG
3	118	EVQLVESGGGLVQPGGSLRLSCAASGFINRDITYIHWVVRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYWGQGTITVTVSSASTKGPSVFPLAPCSSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVNDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLPPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTTISKAKGQPREPQVYTLPPCQEE MTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV MEALHNHYTQKSLSLGLG
4	119	DIQMTQSPSSLSASVGDRTVITTCRASQDVNTAVAWYQQKPGKAPKLLIYSASFYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQHHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2-30R/ 56A/102S+LC- WT-	120	DIVMTQTPLSLSVTPGPASISCKSSQSLVHNNANTYLSWYLQKPGQSPQSLIYKVSNRFSGVDPDRFSGSGG TDFTLKISRVEAEDVGVYYCGQGTQYPTFGSGTKVEIKGQPKAAPDIQMTPSPSSLSASVGDRTVITTCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFLTITSLQPEDIATYYCQQGGQTYPTFG

trastuzumab/ CD28 ^{sup} CD3 mid L1 linker IgG4 FALA BP # 11			QGTKLEIKTKGPSRTVAAPSVFIFFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKSDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	121	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGGLWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSRRLSDDTAVYYCTRSYGLDWNFDVWGKGTITVTVSSQVQLVESGGGVVQPGRSRLR LSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQMNSLR AEDTAVYYCRGVVYALSPFDYWGGGLVTVSSRTASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVVDHKPSNTKVDKRVESKYGPPCPPCP APEAAGGSPVFLFPPKPKDITLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVVHNATKPREEQFNSTYR VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSL SLG
	3	122	EVQLVESGGGLVQPGGSLRLSCAASGFRNIRDYIHWVVRQAPGKGLWVARIYPTNAYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDITLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVVHN NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQEE MTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV MEALHNHYTQKSLSL
	4	123	DIQMTQSPSSLSASVGDRTVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2-30R/ 56A/102E/ CD28 ^{sup} CD3 mid L1 linker IgG4 FALA BP # 12	1	124	DIVMTQTPLSVTPGQPASISCKSSQSLVHNNANTYLSWYLOKPGQSPQSLYKVSNRFSGVDPDRFSGSGSG TDFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKGQPKAAPDIQTQSPSSLSASVGDRTVTITCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIATYYCQQGQTYPTFTG QGTKLEIKTKGPSRTVAAPSVFIFFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKSDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	125	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGGLWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSRRLSDDTAVYYCTRSYGLDWNFDVWGKGTITVTVSSQVQLVESGGGVVQPGRSRLR

			<p>LSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLR AEDTAVYYCRGVYALSPFDYWGQGLTVTVSSRTASTKGPSVFLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSL SLG</p>
	3	126	<p>EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHVVVRQAPGKGLEWVARIYPTNAYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYWGQGLTVTVSSASTKGPSVFLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPCQEE MTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV MEALHNHYTQKSLSLGL</p>
	4	127	<p>DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQGHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</p>
HER2- WT+trastuzum ab/ CD28supxCD3 mid (32/35QQ) L1 linker IgG4 FALA BP # 15	1	128	<p>DIVMTQTPLSLVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIKVSNRFSGVDPDRFSGSGS GTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIKGQPKAAPIDIQTQSPSSLSASVGDRVTITCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIATYYCQQGQTYPYTFG QGTKEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</p>
	2	129	<p>QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSRISDDTAVYYCTRSHYGLDWNFDVWGKGTIVTVSSSQVQLVESGGGVVQPGRSRLR LSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLR AEDTAVYYCRGVYALSPFDYWGQGLTVTVSSRTASTKGPSVFLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGF</p>

			YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFLLVSKLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSL SLG
	3	130	EVQLVESGGGLVQPGGSLRLSCAASGFRNIKDTYIHVVVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVVDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYVTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFLLVSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGL
	4	131	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQGHYTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEHKHYACEVTHQGLSSPVTKSFNRGEC
HER2/ CD28 _{sup} xCD3 _{mid} DKTHT linkers on HC/LC IgG4 FALA BP # 25	1	132	DIVMTQPLSLSVTPGPASISCKSSQSLVHNANNTYLSWYLQKPGQSPQSLIYKVSINRFSGVPPDRFSGSGSG TDFTLKISRVEAEDVGVYYCGGQTQYPTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNI YVWLNWYQQKPGKAPKLLIYKASNLHTGVPSPRFSGSGSGTDFTLTISLQPEDIATYYCQGGQTYPTFTFGQ TKLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEHKHYACEVTHQGLSSPVTKSFNRGEC
	2	133	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISATYMELSRLRSDDTAVYYCTRSHYGLDWNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKSNYSATYYADSVKGRFTISRDDSKNTLYLQM NSLRAEDTAVYYCRGVYYALSPFDYWGQGLTVTVSSDKTHTASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFLLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLGL
	3	134	EVQLVESGGGLVQPGGSLRLSCAASGFRNIKDTYIHVVVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTTKTYTCNVVDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYVTLPPCQE

			EMTKNQVSLWCLVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSLKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG
	4	135	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQGHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2/ CD28 _{sup} xCD3 _{mid} (32/33/3435 ENLR (LC); DKTHT linkers on HC/LC) IgG4 FALA BP # 26	1	136	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRITYLSWYLQKPGQSPQSLIYKVSNRFSGVPDFSGSGSGT DFTLKISRVEAEDVGVYYCGGQGTQYPFTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGTDFTLTISSLQPEDIATYYCQGGQTYPTFTGGGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	137	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQP RSLRSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKNSYATYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGLTVTVSSDKTHTASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTKYTCNVVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPETCVVVDVVSQEDPEVQFNWYVDGVVHNAAKTKPREE QFNSTYRVVSVLTVHLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV/MHEALHNHYT QKSLSLGLG
	3	138	EVQLVESGGGLVQPGGSLRLSCAASGFTNIKDTYIHWVVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTKYTCNVVDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPETCVVVDVVSQEDPEVQFNWYVDGVV HNAAKTKPREEQFNSTYRVVSVLTVHLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYVTLPPCQE EMTKNQVSLWCLVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSLKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG
	4	139	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQGHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

HER2/ CD28 ^{sup} xCD3 ^{mid} (32/33/3435 ENLQ (LC); DKTHT linkers on HC/LC) IgG4 FALA BP # 27	1	140	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPPDRFSGSGSGT DFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLPEDIAITYYCCQQGTQYPTFTGQGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWVKVDNALQSGNSQESVTEQDSK DSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	141	QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSLRSDDTAVYYCTRSHYGLDNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQPQ RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTITVTVSSDKTHTASTKGPSPVPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKITYTCNVVDHKPSNTKVDKRVESKY GPPCPPEAAAGGSPVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QENSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	142	EVQLVESGGGLVQPGGSLRLSCAASGFKNIKDTYIHWVVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTITVTVSSASTKGPSPVPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKITYTCNVVDHKPSNTK VDKRVESKYGPPCPPEAAAGGSPVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYITLPPCQE EMTKNQVSLVCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLG
	4	143	DIQMTQSPSSLSASVGDRTVITTCRASQDVNTAVAWYQQKPGKAPKLLIYASFLYSGVPSRFSGSGSGTDFTL TISSLPEDIAITYYCCQHYTTPFTGQGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
HER2/ CD28 ^{sup} xCD3 ^{mid} (32/33/3435 ENLF (LC); DKTHT linkers	1	144	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVSNRFSGVPPDRFSGSGSGT DFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLPEDIAITYYCCQQGTQYPTFTGQGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWVKVDNALQSGNSQESVTEQDSK DSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

on HC/LC IgG4 FALA BP # 28	2	145	<p>QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSLRSDDTAVYYCTRSHYGLDNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQP RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGLTVTVSSDKTHTASTKGPVPLAPCSRSTSESTAAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKITYTCNVDHKPSNTKVDKRVESKY GPPCPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLG</p>
	3	146	<p>EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSASTKGPVPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKITYTCNVDHKPSNTK VDKRVESKYGPPCPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPPSQE EMTKNQVSLVCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV MEALHNHYTQKSLSLSLG</p>
	4	147	<p>DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFYSGLVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQHHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</p>
anti- Her2/CD3/3CD 28 IgG4 FALA BP # 29	1	148	<p>DIVMTQTPLSLSTPQPASISCKSSQSLVHNNANTYLSWYLQKPGQSPQSLIYKVSNRFSGVDPDRFSGSGG TDFTLKISRVEAEDVGYVYCGQGTQYPTFGSGTKVEIKGQPKAAPDIQMTQSPSSLSASVGDRVTITCQASQ NIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIATYYCQQGQTYPTFG QGTGLEIKTKGPSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKIDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</p>
	2	149	<p>QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTISITAYMELSLRSDDTAVYYCTRSHYGLDNFDVWGKGTITVTVSSQVQLVESGGGVVQPGRSRL LSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQMNSLR AEDTAVYYCRGVYALSPFDYWGQGLTVTVSSRTASTKGPVPLAPCSRSTSESTAAALGCLVKDYFPEPV VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKITYTCNVDHKPSNTKVDKRVESKYGPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR</p>

			VVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPQSEEMTKNQVSLSCAVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLG
	3	150	EVQLVESGGGLVQPGGSLRLSCAASGFFNIKDTYIHVVVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSPVFLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKITYTCNVVDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGSPVFLPPKPKDITLMISRTEPVTCVVVDVSDQEDPEVFQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLGLG
	4	151	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQGHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEHKHYVACEVTHQGLSSPVTKSFNRGEC
HER230R/55Q/ 102E/ CD28 _{sup} xCD3 _{mid} (32/33/3435 ENLR (LC); DKTHT linkers on HC/LC) IgG4 FALA BP # 31	1	152	DIVMTQTPLSLSTVTPGQPASISCKSSQSLVHENLRITYLSWYLVQKPGQSPQSLIYKVSNRFSGVPDFSGSGSGT DFTLKISRVEAEDVGVYYCGGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIATYYCQGGQTYPTFTGQGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYLSLSTLTLSKADYEHKHYVACEVTHQGLSSPVTKSFNRGEC
	2	153	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTITVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQM NSLRAEDTAVYYCRGVYYALSPFDYWGQGTLVTVSSDKTHTASTKGPSPVFLAPCSRSTSESTAAAGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKITYTCNVVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGSPVFLPPKPKDITLMISRTEPVTCVVVDVSDQEDPEVFQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPQSEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLGLG
	3	154	EVQLVESGGGLVQPGGSLRLSCAASGFFNIKDTYIHVVVRQAPGKGLEWVARIYPTQGYTRYADSVKGRFTIS ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYWGQGTLVTVSSASTKGPSPVFLAPCSRSTSES

			TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVEV HNAKTKPREEQFNSTYRVVSVLTVHLQDVLWNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG
	4	155	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTL TISSLQPEDFATYYCQCHYTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
CD38VH1 CD28 ^{sup} _x CD3mid_ENL Q DKTHT IgG4 FALA	/ 1	156	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPDFRSGSGSGT DFTLKISRVEAEDVGVYYCGQGTQYPTFTGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIATYYCQGGQTYPYTFGGGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
BP # 1	2	157	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHVWRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISATYMELSRLSDDTAVYYCTRSHYGLDWNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQP RSLRLSCAASGFTTKAWMHWVRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYVALSPFDYWGQGTLLTVSSDKTHTASTKGPVFPPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVEVHNATKPREE QENSTYRVVSVLTVHLQDVLWNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPQSEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG
	3	158	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYAMHWVKEAPGQRLEWIGYIYYPGQGGTNYNQKFQGRAT LTADTSAATYMELSRLSDEDTAVYFCARTGLRRAYFTYWGQGTLLTVSSASTKGPVFPPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVEV HNAKTKPREEQFNSTYRVVSVLTVHLQDVLWNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQE EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGGSFFLYSKLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLG
	4	159	DIVLTQSPAATLSLSPGERATISCRASQSVSSYQGQFMHWYQQKPGQPPRLIYGASSRATGIPARFSGSGSGTD FTLTISPLEPEDEAVYYCQQNKEDPWTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

CD38hy992 / CD28sup x CD3mid_ENL Q DK'THT IgG4 FALA	1	160	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPRFSGSGSGT DFTLKISRVEAEDVGVYYCGQGTQYPTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VVLNWWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLPEDIAITYYCCQGGQTYPTFGQGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
BP # 5'	2	161	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTTLTVSSDKTHTASTKGPSVFLAPCSRSTSESTAAALGCLVK DYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVNVDHKPSNTKVDKRVESKY GPPCPCPAPEAAGGPSVFLPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QENSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	162	QVQLVQSGAEVVKPGASVKVSCKVSGYTLTEFSIHWVVRQAPGQGLEWVGDFDPEDGETTYAQKFQGRVIM TEDTSTDTAYMEMNSLRSEDTAIYYCTGRFFDWFVGQGTTLTVSSASTKGPSVFLAPCSRSTSESTAAALG CLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVNVDHKPSNTKVDKRV ESKYGPPCPCPAPEAAGGPSVFLPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEEMTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCVMHEALH NHYTQKSLSLSLG
	4	163	EIILTQSPAILSLSPGERATLSCRASQSVISRFLSWYQVKPGLAPRLLIYGASTRATGIPVRFSGSGSGTDFSLTIS SLQPEDCAVYYCQQDSNLPITFGQGTGRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
CD38hyb5739 / CD28sup x CD3mid_ENL Q DK'THT IgG4 FALA	1	164	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPRFSGSGSGT DFTLKISRVEAEDVGVYYCGQGTQYPTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITTCQASQNIY VVLNWWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLPEDIAITYYCCQGGQTYPTFGQGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
BP # 6'	2	165	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQPG

			<p> RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQMN NSLRAEDTAVYYCRGVYYALSPFDYWGQGTTLTVSSDKTHTASTKGPVFPPLAPCSRSTSESTAALGCLVK DYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTCTCNVDHDKPSNTKVDKRVESKY GPPCPCPAPEAAGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QENSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG </p>
	3	166	<p> QVQLQQSGPELVRPGTSVKVSCKASGYAFTTYLVEWIKRPGQGLEWIGVINPGSGSTNYNEKFKGKATLT VDRSSTTAYMHLISGLTSDDSAVYFCARYAYGYWGQGTTLTVSSASTKGPVFPPLAPCSRSTSESTAALGCLV KDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTCTCNVDHDKPSNTKVDKRVESK YGPPCPCPAPEAAGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVYTLPPCQEEEMTKNQVS LWCLVKGFPYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHN HYTQKSLSLSLG </p>
	4	167	<p> DIVMTQSQKFMSASVGDVRSITCKASQNVGTA VAWYQQQGHSPKQLIYSASNRYTGVPPDRFTGSGAGTDF TLTISNIQSEDLADYFCQQYSTYPTFTGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC </p>
CD38hyb6284 / CD28sup x CD3mid_ENL Q DKTHT IgG4 FALA BP # 7	1	168	<p> DIVMTQTPLSLSVTPGPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPPDRFSGSGSGT DFTLKISVEAEDVGYYCGQGTQYPTFTGSGTKVEIKDKTHTDITQMTQSPSSLSASVGDVYTLTTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISLQPEDIATYYCQQGQTYPTFTGQGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC </p>
	2	169	<p> QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSISTAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHVVRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDDSKNTLYLQMN NSLRAEDTAVYYCRGVYYALSPFDYWGQGTTLTVSSDKTHTASTKGPVFPPLAPCSRSTSESTAALGCLVK DYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTCTCNVDHDKPSNTKVDKRVESKY GPPCPCPAPEAAGGPSVFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QENSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG </p>
	3	170	<p> QVQLLQSGAEELVRPGVSVKISCTGSGYSFTNYAVHWVKQSHVKSLEWIGVISPYPGDTTNYNQKFTGKATMT VDKSSSTAYMELARLTSEDSAIYFCARRFEGFYMDYWGQGTSTVTVSSASTKGPVFPPLAPCSRSTSESTA </p>

			ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNVDPHKPSNTKVD KRVESKYGPPCPPCAPEAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEM TKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQEGNVFSCSVMIH EALHNHYTQKSLSLGLG
	4	171	DVVMIQTPLSLPVSLGDQASISCRPSQSLVHSNGNTYLNWYLQRPQGQSPKLLIYKVSKRFSGVPDRFSGSGSG TDFTLKISRVEAEDLGVYLCSQSTHVPPLTFGSGTQLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEEKHVYACEVTHQGLSSPVTKSFNRGEC C
CD38 ^{hh} 1195 / CD28 ^{sup} x CD3 ^{mid} ENL Q DKTHT IgG4 FALA BP # 8	1	172	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPDRFSGSGSGT DFTLKISRVEAEDVGYVYCGQGTQYPTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVTITCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDTLTITSSLPQEDIAITYYCCQGGQTYPYTFGGGT KLEIKDKTHTRITVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSTLTLSKADYEEKHVYACEVTHQGLSSPVTKSFNRGEC
	2	173	QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHVVRRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSRISDDTAVYYCTRSHYGLDNFDFVWGKTTVTSSDKTHTQVQLVESGGGVVQPQ RSRLSCAASGFTFTKAWMHWVRRQAPGKQLEWVAQIKDKNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTLLVTVSSDKTHTASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNVDPHKPSNTKVDKRVESKY GPPCPPCAPEAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREE QENSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVCTLPSPQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLGLG
	3	174	QVQLVESGGGVVQPGRSRLSCAASGFTFSYGMVWVRRQAPGKGLEWVAIVWYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDGGMDFVWGQTTVTSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNVDPHKPS NTKVDKRVESKYGPPCPPCAPEAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP CQEEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLGLG
	4	175	DIQLTQSPSFLSASVGDRTVTITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSGVPSRFSGSGSGTEFTLT SSLQPEDFATYYCQQLNSFPYTFGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEEKHVYACEVTHQGLSSPVTKSFNRGEC

CD38hy1370 / CD28sup x CD3mid_ENL Q DK'THT IgG4 FALA	1	176	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPDRFSGSGSGT DFTLKISRVEAEDVGYVYCGQGTQYPTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLPEDIAITYYCCQGGQTYPYTFGGGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
BP # 9	2	177	QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTTLTVSSDKTHTASTKGPSVFLAPCSRSTSESTAAALGCLVK DYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVNVDHKPSNTKVDKRVESKY GPPCPAPEAAGGPSVFLPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNATKPREE QENSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSIEKTSKAKGQPREPQVCTLPPSQEEMTKNQVSL CAVKGYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	178	QVQLVESGGGVVQPGRLRLSCAASGFTFSYGMHWVRQAPGKGLEWVAWIYDGSNKYYADSVKGRFTI SGDNSKNTLYLQMNLSRAEDTAVYYCARMFRGAFDYWGQGTTLTVSSASTKGPSVFLAPCSRSTSESTAA LGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVNVDHKPSNTKVDK RVESKYGPPCPAPEAAGGPSVFLPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAT KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSIEKTSKAKGQPREPQVCTLPPSQEEMT KNQVSLWCLVKGYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCVMHE ALHNHYTQKSLSLSLG
	4	179	AIQMTQSPSSLSASVGDRTVITTCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTL TISGLQPEDSATYYCLQDIYIYPTFGGTQVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
CD38hu5739 / CD28sup x CD3mid_ENL Q DK'THT IgG4 FALA	1	181	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPDRFSGSGSGT DFTLKISRVEAEDVGYVYCGQGTQYPTFGSGTKVEIKDKTHTDIQMTQSPSSLSASVGDRTVITCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLPEDIAITYYCCQGGQTYPYTFGGGT KLEIKDKTHTRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	182	QVQLVQSGAEVVKPGASVKVCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTISAYMELSLRSDDTAVYYCTRSHYGLDWNFDVWGKGTTVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKSNSYATYYADSVKGRFTISRDSDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTTLTVSSDKTHTASTKGPSVFLAPCSRSTSESTAAALGCLVK

				DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTCTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSTFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	183		QVQLVQSGAEVKKPGASVKVCKASGYAFTTYLVEWIRQRPQGQGLEWGMVINPGSGSTNYAQKFQGRVT MTVDRSSTTAYMELSLRSDDTAVYCYARYAYGYWQGTLTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTCTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEAAGGPSTFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPCQEEMTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELVSKLTVDKSRWQEGNVFSCVMHEALH NHYTQKLSLSLG
	4	184		DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRYTGVPSRFSGSGGTDF LTISLQPEDLATYCYCQYSTYPTFTGGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
CD38 ^{hu} 6284 / CD28 ^{sup} x CD3 ^{mid} ENL Q DKTHT IgG4 FALA	1	185		DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVSNRFSGVPDFRSGSGGT DFTLKISRVEAEDVGYVYCGQGTQYPTFTGGQGTKEIKDKTHTDIQTMTQSPSSLSASVGDRTVITTCQASQNIY VWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGGTDFTLTISLQPEDLATYCYCQYSTYPTFTGGQGT KLEIKDKTHTRITVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSTLTLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	2	186		QVQLVQSGAEVKKPGASVKVCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNVNTNYAQKFQGRATL TVDTSTAYMELSLRSDDTAVYCYCTRSHYGLDWNFDVWGKGTITVTVSSDKTHTQVQLVESGGGVVQPG RSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKSNYSATYYADSVKGRFTISRDDSKNTLYLQM NSLRAEDTAVYYCRGVYALSPFDYWGQGTITVSSDKTHTASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTCTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEAAGGPSTFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVCTLPSPSQEEMTKNQVSL CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELVSKLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLG
	3	187		QVQLVQSGAEVKKPGASVKVCKASGYSTFTNYAVHWVRQAPGQGLEWGMVISPYGDTTYAQKFQGRVT MTVDKSSSTAYMELSLRSDDTAVYCYARRFEGFYVSMGYWGQGTITVTVSSASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTCTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEAAGGPSTFLFPKPKDITLMISRTPEVTCVVVDVSDQEDPEVFQFNWVVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPC

			QEEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLGLG
	4	188	DVVMQTQSPSLPVTLGQPASISCRPSQSLVHSNGNTYLNWYQQRPGQSPKLLIYKVKSRFSGV/PDRFSGSGG TDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

Table 6. Trispecific binding protein polynucleotide sequences

<i>Molecule</i>	<i>Polypeptide Number (acc. to formula)</i>	<i>SEQ ID NO</i>	<i>Sequence</i>
HER2 (WT- trastuzumab) / CD28supxCD3m id (32/35 QQ (LC); DKTHT linkers on IgG4 FALA BP # 1	1	189	GACATCGTGATGACCCAGACCCCTTGAGCCTGAGCGTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCAACCAGAACGCCAGACCTACCTGAGCTGGTATCTGCAGAACCCCGGCCAGAGCCCCAG TCCTGATCTACAAAGGTGTCCAAACAGATTCAGCGGTGTCGCCAGACAGATTCTCCGGCAGCGGTCTTGGCACCAGCT TCACCTGAAGATCAGCCGGGTGGAAAGCCAGGACGTGGCGGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCACCAAGGTGGAAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTCAAGGCCAGCCAGAACATCTACGTGTGGCTGA ACTGATATCAGAGAAAGCCCGGCAAGGCCCTCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCGCGTGC CCAGCAGATTTTCTGGCAGCGGTCCGGCACCGACTTACCTGACATCAGCTCCCTGCAGCCCCGAGGACATTGC CACCTACTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTTGGCCAGGCCACCAAGCTGGAAATCAAGGATAA GACCCACACCGGTAGCGTGGCGCTCCAGCGGTGTTCTATCTCCCACTAGCGACGAGCAGCTGAAATCCGGCACA GCCTCTGTGCTGCTGCTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAAGTGGAGAGGTGGACAACGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACGCTTGCAGAAAGTGACCCACAGGGCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGGAGTGT
	2	190	CAGGTGCAGCTGGTGCACTTGGCGCGAGGTCTGTGAAACCTGGCGCCTCTGTGAAAGGTGTCTTGCAGGCCAGC GGCTACACCTTTACAGCTACTACATCCACTGGGTGCGCCAGGCCCTTGGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTACGCCAGAAAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCCAGC ATCAGCACCGCTTACATGGAATGAGCCGGGTGAGAAAGCAGCAGCCCGGTGTACTACTGCAACCCGTCCAC TACGGCCTGGAATTGGAATTCGACCTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGACAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGAGTGTGTCAGCTGCGAGAAAGCTGAGACTGAGCTGTGCGGCCAGC GGCTTCACTTACCAAGGCCTGGATGCACTGGGTGCGCCAGGCCCTTGGAAAGCAGCTGGAATGGGTGGGCCAG

			<p>ATCAAGGACAAAGAGCAACAGCTACGCCACCTACTACGCCGACAGCGTGAAAGGGCCGGTTTACCATCAGCCGGGAC GACAGAAAGAACACCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCGTGTACTGTGCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCGTGACCGGTGTCTAGTATAAGACCCACA CCGCAGCAAAAGGGCCCATCGGTGTTCCCTGCGCCCTTGACGAGAAACACAGCAATCTACAGCCGCCCT GGGTGCTCGTGAAAGGACTACTTCCGAGCCCGTACCGTGTCTGGAACCTGGCGCTCTGACAAAGGGCGGTG CACACCTTTCAGCCGTGCTCCAGAGCAGCGGCTGTACTCTGTGACGACGTGTGAGCAACAGCGGTGGAATCTA TGGGCACCAAGACCTACACCTGTAACTGTGACCAACAGCCCAACACCAAGGTGGAACAGCGGTGGAATCTA AGTACGGCCCTCCCTCCCTTGGCCAGCCCTGAAGTCCGGGGAACCTCCGTGTCTCTGTTCCCTCCCAAG CCCAAGACACCTGATGATCAGCCGACCCCGAAGTGACTGCTGCTGTGGTGTGTCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGTGGACGGCGTGGAAAGTGCAACACGCCAAGACCAAGCCAGAGGAACAGTTT AACAGCACCTACCGGGTGGTCCGTGCTGACCGTGTGACACAGACTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCACAAAGGGCCTGCCAGCTCCTCAGAAACCATCAGAAAGGCCAAGGCCAGCCCGCGAGGCT CAAGTGTGTAACCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACACAGGTGCTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCAGCGACATTGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACACCCCCCT GTGTGACAGCGACGGCTCAITCTTCTTGGTGTCCAAGTGTGACCGTGGACAAGACCGGTGGCAAGGAGCAAC GTGTTAGTGTCTCGTGATGACAGAGCCCTGCACAACTACACCCAGAAAGTCTCTGTCTCCCTGGGC</p>
3	191		<p>GAGTGCAGCTGGTGAATCTGGCGGGGACTGGTGCAGCCTGGCGGATCTTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCAAGGACACCTACATCCACTGGGTGCGCAGGCCCTGCGCAAGGACTGGAATGGGTGGCCAGA ATTACCCCAACACCGGTACACAGATAACCGCAGCTGAGGGCCGGTTTACCATTAGCCCGCACACCGAGC AAGAACACCGCTACCTGCAGATGAACACCTGCGGGCCAGGACACCGCGTGTACTACTGTAGTAGATGGGA GGCAGCGCTTCTACGCCATGACTATTGGGGCCAGGGCACCTCTGACCGGTGTCTAGTGTGCGTACCAAGGGCC CATCGGTGTCTCTGGCCCTTGCAGAGAACACAGCAAGTGTGACCGCCCTGGGCTGCTCGTGAAGGA CTACTTTCAGAGCCCGTGAACGTGTCTGGAACTCTGGCGCTCTGACAAAGCGGCGTGCAACCTTTCCAGCCGTG CTCAGAGCAGCGGCTGTACTCTGTGACAGCTGTGACAGTCCAGCAGCGCTGGGCACCAAGACCTAC ACCTGTAACTGGAGCAACAGCCCAAGCAACCAAGGTGGACAGCGGTGGAATCTAAGTACGGCCCTCCCTGC CCTCTTGCCAGCCCTGAAGCTGCGGCGGACCCCTCGTGTCTCTGTTCCCTCCCAAGCCCAAGGACACCTGA TGATCAGCCGGACCCCGAAGTGACCTGCGGTGGTGGATGTCTCCAGGAAGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGAAGTGACACAGCCCAAGACCAAGCCAGAGAAACAGTTCACAGCACCTACCCG GTGGTTCCTGCTGACCTGCTGCACCCAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGGTGTCCAACAAAG GGCTGCCCATCTCAGAAACCATCAGCAAGGCCAAGGCCAGCCCGCAGCCTCAAGTGTATACCTGT CCCCCTTGCCAGGAAGATGACCAAGAACAGGTGTCTGTTGTTCTGTGAAAGGCTTCTACCCAGCGACA TTGCCGTGGAATGGGAGAACCGCCAGCCCGAGAACAACTACAAGACACCCCTGTGCTGTGACAGCGACG GCTCATTTCTCTGTACTCCAAGCTGACCGGTGGAACAGAGCCGTGGCAGGAAGGCAACGTGTTCAGTGTCTCCGT GATGCACGAGGCCCTGCACAACTACACCCAGAAAGTCTCTGTCTCCCTGGGC</p>
4	192		<p>GACATCCAGATGACCCAGAGCCCAAGCCTGTCTGCCAGCTGGGCGACAGATGACCATCACCTGTAGAGCC AGCCAGGACGTGAACACCGCCGTGGCTGGTATCAGCAGAAAGCCTGGCAAGGCCCCCAAGCTGTGTATACAGC GCCAGTTCTGTACAGCGGCGTGCACAGATTCAGCGGAAGCAGAAAGCGGACCGCACTTCAACCTGACCATC AGTCCCTGACGCCGAGGACTTCGCCACCTACTACTGCCAGCAGCACTACCAACCCCTCCCATTTGGCCAGG GCACCAAGGTGGAATCAAGCGTACGGTGGCCGCTCCAGCGTGTCTATCTTCCCACTAGCGACGAGCGTGA</p>

HER2 (30R/55Q/102E +LC-WT- trastuzumab) / CD28supxCD3mi d (32/35 QQ (LC); DKHT linkers on HC/LC) IgG4 FALA BP # 2	1	193	<p>AGTCCGGCACAGCCTCTGTGCTGCTGCTGAACAACTTCTACCCCCCGGAGGCCAAAGTGCAAGTGAAGGTGG AACAGCCCTGACAGGGCAACAGCCAGGAAAGCTGACCGAGACAGACAGGACTCCACCTACAGCCTG AGCAGCACCTTGACACTGAGCAAGGCCGACTACGAGAAACAGCAAGGCTGACGCTGCGAAAGTGACCCACAGGG CCTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p> <p>GACATCTGTGATGACCAAGCCCTCTGAGCCTGAGCGTGACACCTGGACAGCCTGCCAGCATCAGCTGAAGAGC AGCCAGGCTGTGTCACCAAGAACGCCAGCACTCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCCAG TCCCTGATCTACAAGGTGTCCACAGATTACGCGGCTGCCGACAGATTCTCCGGCAGCGGCTCTGGCACCGACT TCACCTGAAGATCAGCCGGTGAAGCCGAGGACGTGGGCTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGCAACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGGCGACAGAGTGACCATCACCTGTACGGCCAGGCCAGAACATCTACGTGTGGCTGA ACTGGTATCAGCAAGAGCCCGGCAAGGCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCGGCGTGC CCAGCAGATTCTTGGCAGCGGCTCCGGCACCGACTTACCTTGACAAATCAGCTCCCTGCAGCCCGAGGACATTGC CAGCTACTACTGCCAGCAGGGCCAGACCTACCCCTACAGCTTTGGCCAGGGCACCAAGCTGGAAATCAAGGATAA GACCCACACCGTACGGTGGCGCTCCAGCGTGTCTATCTTCCCACTAGCGACGAGCAGCTGAAGTCCGGCACAA GCCCTGTGCTGCTGTGAACAACTTCTACCCCGGAGGCCAAAGTGCAGTGGAAAGGTGGAACAAAGCCCTGC AGAGGGCAACAGCCAGGAAAGCTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAAGCAAGGCTGACGCTGCGAAAGTGACCCACAGGGCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
	2	194	<p>CAGGTGACAGCTGGTGCAGTCTGGCGCGAGCTGTGAAAACCTGGCGCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGTGGCGCCAGGCCCTTGACAGGAGCTGGAATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCAACTACGCCACAGTTCCAGGGCAGGCCACCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAGAAAGCAGCAGCCCGTGTACTACTGCACCCGGTCCAC TACGGCTGGAATTGGAATTTCGACGTGTGGGCAAGGGCACCAACCGTGACAGTGTACGCGACAAACCCATACC CAGGTGACAGTGGTGAATCTGGCGGGAGTGGTGCAGCCTGGCAGAAAGCCTGAGACTGAGCTGTGCCCGCAGC GGCTTACCTTACCAAGGCTTGATGCACTGGTGCAGGCGCTGAAAGCAGCTGGAATGGTGGGCGCCAG ATCAAGGACAAGACAAGCTACGCCACCTACTACGCCGACAGCGTGAAGGGCCGGTTACCATCAGCCGGGAC GACAGCAAGAACACCTGTACCTGCAGATGAACAGCTGGGGCCGAGGACACCCCGTGTACTACTGTGGGGC GTGTACTATGCTTACGCTTCCGATTCGATTACTGGGGCCAGGAAACCTCTGACCGTGTCTAGTATAGACCCACA CCGCCAGCAAAAGGGCCATCGGTGTTCCTCTGGCCCTTGCAGCAGAAAGCACAGCAATCTACAGCGCCCT GGGTGCTGTGAAGGACTACTTTCCGAGCCCGTGAACCTGTGGAACCTTGGCGCTCTGCAAGCGGCGTG CACACCTTTCAGCGGTGCTCCAGAGCAGCGCTGTACTCTGAGCAGCGTGTGACAGTGGCCAGCAGCAGCC TGGGCAACCAAGACCTACACCTGAACGTGGACCAACAGCCAGCAACCAAGGTGGACAAAGCGGTGGAAATCTA AGTACGGCCCTGCTGCTTTCCTTGGCCAGCCCTGAAGCTGCCGGCGGACCTCCCTGCTTCTTCCCCCAAG CCCCAGGACACCTGTATCAGCCGACCCCGAAGTACCTGCTGGTGGTGGTGTGTGTCTCCAGGAAGATCCC GAGGTGCAGTTCAATTGTGACGTGGACGGCTGGAAGTGCAACGCCAAGACCAAGCCAGAGAGGAAACAGTTT AACAGCACCTACCGGGTGTGTCCGTGTGACCGTGTGACAGGACTGGCTGAACGGCAAGAGATCAAGTGC AAGGTGTCCAAAGGGGCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGGAGCCT CAAGTGTGTAACCTTCCCCCTAGCCAGGAAGATGACCAAGAACCGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCCGAGCGACATTGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAAACACTACAAGAGCACCCCT</p>

			GTGCTGGACAGCGACGGCTCATTTCTTCTGGTGTCCAAGTGAACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAAC GTGTTACAGCTGCTCCGTGATGCACGAGGCGCTGCACAAACCACTACACCCAGAAAGTCCCTGTCTGTCTGCTGGC
3	195		GAAGTGCAGCTGTGGTGAATCTGGCGGGGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCAGCCCTGGCAAGGGAAGTGGTGGCCAGA ATCTACCCACCCAGGGTACACAGATACGCGTGAAGGCGCGTTCCACATAGCGCCGACACCCAGC AAGAACCCGCTACCTGCAGATGAACAGCTGCGGGCGAGGACACCGCTGTACTACTGTAGTAGATGGGA GGCGAAGGCTTCTACGCCATGGACTATTGGGGCCAGGCCCTGTGACCCGTGTACTGTGCTGACCAAGGC CCATGGGTTCCTCTGGCCCCCTTGCAGCAGAACACAGCAATCTACAGCCGCTGGGTGCTCGTGAAGG ACTACTTTCGAGCCCGTGAACCGTGTCTGTGAACCTGTGGCGCTGTGACAGCGCGTGCACACCTTTCAGCCGT GCTCCAGAGCAGCGGCTGTACTCTGTGACAGGCTGTGACAGTGCACAGCAGCCTGGGCAACCAAGACCTA CACTGTAACTGTGACCAAGCCACGACCAACCAAGGTGGACAAAGCGGTGGAATCTAAGTACGGCTTCCCTG CCCTCTTGGCCAGCCCTGAAGCTGCCGGCGGACCTCCGTGTTCCTGTTCCTCCCAAGCCCAAGGACACCTG ATGATCAGCCGACCCCGAAGTGAACCTGCGTGGTGGTGGTGTGCTCCAGGAAGATCCCGAGGTGCAGTTCAAT TGGTACGTGACCGGCTGGAAGTGCACAAACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTACCG GGTGGTTCCTGCTGACCTGCTGACACAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGTCAAGGTGTCCAACAA GGCTGCCCCAGCTCCATCGAAGAAACCATCAGCAAGGCCAAGGCCAGCCCCGAGCCTCAAGTGTATACCT GCCCCCTTGGCAGGAAGAGATGACCAAGAACCAAGGTGTCCCTGTGGTGTCTGTGAAAGGCTTACCCAGCGAC ATTGCCGTGGAATGGAGAGCAACGGCCAGCCGAGAACCACTACAAGACCAACCCCTGTGCTGGACAGCGAC GGTCAATTCTTCTGTACTCCAAGCTGACCGTGCAGCAAGCGCGTGGCAGGAAGCAACGTTCCTGCTCCCTGGG TGATCAGCAGGCGCTGCACACCACTACACCCAGAAAGTCCCTGTCTGTCCCTGGG
4	196		CAGGTGCAGCTGTGGTGTGGCGCGAGGTCTGTAACCTGGCGCTCTGTGAAGGTGTCTGTGCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGACGC ATCTACCCCGGCAACGTGAACACCAACTACGCCCAAGAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAAGAGCAGCAGACCCCGTGTACTACTGCACCCGTTCCAC TACGGCTGGAATGGAACTTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGACAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGCGGAGTGTGCAAGCTGGCAGAACCTGAGACTGAGCTGTGCCGCCAGC GGCTTACCTTCAACCAAGGCTGGATGCACTGGGTGGCCAGGCCCTGGAAAGCAGCTGGGAATGGGTGGCCAG ATCAAGGACAAGAGCAACAGTACGCCACTACTACGCCGACAGCTGAAGGCCGCTTCACTACCAAGCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCTTGGCGCCGAGGACACCCGCTGTACTACTGTCCGGGC GTGTATATGCCCTGAGCCCCCTTCGATTACTGGGGCCAGGGAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCCAGCACAAAGGGCCCATCGGTGTTCCTCTGGCCCTTGCAGCAGAAAGCAGCGAATCTACAGCCGCT GGCTGCTCGTGAAGGACTACTTCCGAGCCCTGACCTGTCTTGGAACTCTGGCGCTCTGACAAAGCGCGTG CAGACTTTCAGCGCTGCCAGACAGCGCTGTACTCTGTGACGACGCTGTGAGCAGCTGCCCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGTAACGTGGACCAACAGCCAGCAACCAAGGTGGAACAGCGGTGGAACTTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGGCGGAGCCCTCCGTGTCTGTTCTGTTCCCTCCCAAG CCCAAGGACACCTGATGATCAGCCGACCCCGAAGTGAACCTGCGTGGTGGTGTGTCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGTGGACGGCGTGGAAAGTGCACAAACGCCAAGCAAGCCAGAGAGGAACAGTTT AACAGCACCTACCGGGTGGTTCCTGCTGACCGTGTGACCAAGGACTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCTGCCCCAGCTCCATCGAAGAAACCATCAAGCAAGGCCAAGGGCCAGCCCCGCGAGCT

HER2 (30R/55Q/102E+ LC-WT- trastuzumab) / CD28 ^{sup} xCD3 ^{mid} (DNAQ (LC); DKHT linkers on HC/LC) IgG4 FALA BP # 8	1	197	CAAGTGTGTACCCCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACACAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCAGCGACATTCGCGTGAATGGAGAGCAACGGCCAGCCGAGAACCACTACAAGACCAACCCCCCT GTGCTGGACAGCGACGGCTCATTTCTGCTGTCCAAAGTGAACCGTGGACAAGAGCCGGTGGCAGGAAGCAAC GTGTTCAAGCTGCTCCGTGATGACAGAGGCCCTGCACAAACCACTACACCAAGAGTCCCTGCTCTGTCCCTGGGC GACATCGTGATGACCAAGCCCTGAGCTGAGCTGACACCTGGACAGCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCTGTGTGACGACCAACGCCAGACCTACCTAGCTGATCTGCGAGAACGCCGGCCAAGCCCCCAG TCCCTGATCTACAAAGGTGCCAACAGATTACGGGCTGCCGACGATTTCTCCGGCAGCGGCTCTGGCACCGACT TCACCTGAAGATCAGCCGGGTGAAGCCAGGACGTGGGCTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCAACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTGTGCCAGCGTGGGCGACAGAGTGACCATCACCTGTGAGGCCAGCCAGAACATCTACGTGTGGCTGA ACTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCGGCTGC CCAGCAGATTTCCTGGCAGCGGCTCCGGCACCCGACTTACCTTGACAAATCAGCTCCCTGCAGCCCGAGGACATTGC CAGCTACTACTGCCAGCAGGGCCAGACCTACCCCTACAGCTTTGGCCAGGCAACCAAGCTGGAAATCAAGGATAA GACCCACACCCGTACGGTGGCGCTCCAGCGTGTCTATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCACA GCCCTGTGCTGCTGTGAACAATCTTACCCCGGAGGCCAAAGTGCAGTGAAGGTGGAACAAAGCCCTGC AGAGGGCAACAGCCAGGAAGCGTGAACCGAGCAGGACAGCAAGGACTCCACCTACAGCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACAGGGCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT
	2	198	CAGGTGACAGCTGGTGCAGTCTGGCGCGAGCTGTGAAAACCTGGCGCTCTGTGAAAGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGTGGCGCCAGGCCCTGGACAGGAGTGGATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCAACTACGCCACAGTTCCAGGGCAGAGCACCCCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAGAAAGCAGCAGCACCGCGTGTACTACTGCACCCGGTCCAC TAGCGCTGGAATTGGAATTCGACGTGTGGGCAAGGGCAACCCGTGACAGTGTACGCGACAAACCCATACC CAGGTGACAGCTGGTGAATCTGGCGGGAGTGGTGCAGCCTGGCAGAAAGCCTGAGCTGAGCTGTGCCCGCAGC GGCTTCACTTCAACAGGCCTGGATGCACTGGTGCAGGCCCTGGAAGCCAGCTGGAATGGTGGCCAG ATCAAGGACAAGACAAGCTACGCCACCTACTACGCCGACAGCGTGAAGGGCCGTTACCATCAGCCGGGAC GACAGCAAGAACACCTGTACCTGCAGATGAACAGCCTGGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGACCGTGTCTAGTATAGACCCACA CCGCCAGCAAAAGGGCCATCGGTGTTCCCTCTGGCCCTTGCAGCAGAAAGCACAGCAATCAAGCCGCTT GGGTGCCCTGTGAAGGACTACTTTCCGAGCCCGTGAACCGTGTCTGGAACCTTGGCGCTCTGACAAGCGCGTG CACACCTTCCAGCCGTCTCCAGAGCAGCGCTGTACTCTGAGCAGCGTGTGACAGTGGCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGAACGTGGACCAACAGCCAGCAACACCAAGGTGGACAAGCGGTGGAAATCTTA AGTACGGCCCTGCCCTCTTGGCCAGCCCTGAAGCTGCCGGCGGACCCCTCCGTCTCTGTTCCCCCAAG CCCCAGGACACCCCTGATCAGCCGACCCCGAAGTACCTGGTGGTGGTGGTGTGTGTCTCCAGGAAGATCCC GAGGTGCAGTTCAATTGTGACGTGACGGCGTGAAGTGACACCGCAAGACCAAGCCAGAGAGGAGAACAGTTC AACAGCACCTACCGGGTGTGTCCGTGTGACCGTGTGACAGGACTGGCTGAACGGCAAGAGATCAAGTGC AAGGTGTCCAAACAAGGGCCCTGCCAGCTCCATCGAGAAAACCATCAGCAAGGCCAAGGCCAGCCCGGAGCCT CAAGTGTGTACCCCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACCCAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCAGCGACATTTCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACCACTACAAGACCAACCCCCCT

			<p>GTGCTGGACAGCGACGGCTCATTTCTTCTGGTGTTCCAAAGTGAACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAAC GTGTTACAGCTGCTCCGTGATGACAGAGGCCCTGCAACAACTACATACCCAGAAAGTCCCTGTCTGTCTGCTGGC</p> <p>199</p>
3			<p>GAA GTG CAG CTG GTG GA ATCTG GCG GGG GGA CTG GTG CAG CCTG GCG GATCTCTG AGACTG AGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCGCCAGGCCCTTGCAAGGGA CTGGAATGGGTGGCCAGA ATCTACCCACCCAGGGTACACAGATACGCGTGAAGGCGCGTTCCACATAGCGCCGACACCCAGC AAGAACCCGCTACCTGCAGATGAACAGCTGCGGGCGAGGACACCGCTGTACTACTGTAGTAGATGGGA GGCGAAGGCTTCTACGCCATGGACTATTGGGGCCAGGCCCTGTGACCCGTGTACTAGTGCCTGACCAAGGC CCATGGGTTCCTCTGGCCCCCTTGACAGCAAGACACAGCAATCTACAGCCGCCCTGGGTGCTCGTGAAGG ACTACTTTCGAGCCCGTGAACCGTGTCTGTGAACTCTGGCGCTGTGACAAGCGCGTGCACACCTTTCCAGCCGT GCTCCAGAGCAGCGGCCCTGTACTCTGTAGCAGGCTGTGACAGTGCCCAAGCAGCAGCCTGGGCAACCAAGACCTA CACTGTAACTGTGACCAAGCCCAAGCAACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCCCTCCCTG CCCTCTTGGCCAGCCCTGAAGCTGCCGGCGGACCTCCGTGTCTGTTCCTGTTCCCCAAAGCCCAAGGACACCTG ATGATCAGCCGACCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCAGGAAGATCCCGAGGTGCAGTTCAAT TGGTACGTGACGGCGTGAAGTGCACAACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTACCG GGTGTGTCCTGCTGACCTGCTGACACAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGTCAAGGTGTCCAACAA GGCTGCCCAGCTCCATCGAAGAAACCATCAGCAAGGCCAAGGCCAGCCCCGAGCCTCAAGTGTATACCT GCCCCTTGCCAGGAAGAGATGACCAAGAACCAAGGTGTCCCTGTGTGTCTGTGAAAGGCTTACCCAGCGAC ATTGCCGTGGAATGGAGAGCAACGGCCAGCCGAGAACCACTACAAGACACCCCTCTGTCTGTGACAGCGAC GGTCAATTCTTCTGTACTCCAAGCTACCGTGAACAGCGCGTGGCAGGAAGCAACGTTCCTGCTCCCTGGGC TGATCAGCAGGCCCTGCACACCACTACACCCAGAAAGTCCCTGTCTGTCCCTGGGC</p> <p>200</p>
4			<p>CAGGTGCAGCTGGTGCAGTGTGGCGCGAGGTCTGTAACCTGGCGCTCTGTGAAGGTGTCTGTGCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTACGCCCAAGAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAAGAGCAGCAGACCCCGTGTACTACTGCACCCGGTCCAC TACGGCTGGAATTGAACTTCGACGTGTGGGCAAGGGCACCCGTGACAGTGTCTAGCGACAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGCGGAGTGTGCAAGCTGGCAGAAAGCTGAGACTGAGCTGTGCCGCCAGC GGCTTACCTTCAACCAAGGCTGGATGCATGGGTGCGCCAGGCCCTTGAAAGCAGCTGGGAATGGGTGGCCCCAG ATCAAGGACAAGACAAGTACGCCACTACTACGCCGACAGCTGAAGGCCCGTTTCACTACAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCTTGGGCGCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTATATGCCCTGAGCCCCCTTCGATTA CTGGGGCCAGGGAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCCAGCACAAAGGGCCCATCGGTGTTCCTCTGGCCCTTGACGAGAAAGCAAGCTGGAATCTACAGCCGCCCT GGGTGCTCGTGAAGGACTACTTCCGAGCCCTGACCTGTCTTGGAACTCTGGCGCTCTGACAAAGCGCGGTG CAGACTTTCAGCGCTGCCAGACAGCGCTGTACTCTGTGACGACGCTGTGAGCTGCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGTAACGTGGACCAAGCCCCAGCAACCAAGGTGGAACAAGGGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGGCGGAGCCCTCCGTGTCTCTGTTCCCTCCCAAG CCCAAGGACACCTGATGATCAGCCGACCCCGAAGTGAACCTGCGTGGTGGTGTGTCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGTGGACGGCGTGAAGTGCACAACGCCAAGCAAGCCAGAGAGGAACAGTTTC AACAGCACCTACCGGGTGGTTCCTGCTGACCGTGTGACCAAGGACTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCCTGCCAGCTCCATCGAAGAAACCATCAAGCAAGGCCAAGGGCCAGCCCCGCGAGCT</p>

HER2 (30R/55Q/102E +LC-WT- trastuzumab) / CD28 ^{sup} xCD3 ^{mid} (32/35QQ (LC); L1 linker) IgG4 FALA BP # 9	1	201	CAAGTGTGTACCCCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACACAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCACGCGACATTCGCGTGAATGGAGAGAACGCGCCAGCCGAGAACATCAAGACCAACCCCT GTGCTGGACAGCGACGGCTCATTTCTGCTGTCCAAAGTGAACCGTGGACAAAGACCGGTGGCAGGAAGCAAC GTGTTCACTGCTCCGTGATGACAGAGGCCCTGCACAAACCACTACACCAAGATCCCTGCTCTGTCCCTGGC GACATCTGTGATGACCAAGACCCCTGAGCCCTGAGCTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCTGTGTACCAAGACGCCAGCACTACTAGCTGTGTATCTGAGAAAGCCGGCCAGAGCCCTCCAG TCCCTGATCTCAAGGTGTCCAAACAGATTACGGGGTGTCCCGACAGATTTCTCCGGACGGCTCTGGCACCGACT TCACCTGAAGATCAGCGGGTGAAGCCAGGACGTGGGGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCAACAAAGGTGGAATCAAGGGCCAGCCCAAGGCCGCCCGCCGACATCCAGATGACCCAGA GCCCAAGCAGCTGTGTCCAGGTTGGGACAGAGTGAACCTGATCAGGCCAGGCCAGAAATCATCTACGTGT GGCTGAACCTGGTATCAGCAAGAGCCCGGCAAGGCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCG GCGTGCCACAGCAATTTCTGGCAGCGGCTCCGGACCCGACTTACCTTGACAACTAGCTCCCTGCAGCCCGAGGA CATTGCCACCTACTACTGCCAGAGGGCCAGACTACCTTACCTTTGGCCAGGGCAACAAAGCTGGAAATCAAG ACCAAGGGCCCCAGCGTACGGTGGCCGCTCCAGCGTGTACTTTCCCACTAGCCAGCAGCAGCTGAAGTCCG GCACAGCTCTGTGCTGCTGCTGTAACAACTTCTACCCCGGAGGCCAAAGTGAAGTGAAGGAAAGTGAAGC CCCTGCAAGCGGCAACAGCCAGGAAGCGTGAACGAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGC ACCTGACACTGACCAAGGCCGACTACGAGAAGCAAGGTTAGCCTGCGAAGTGAAGCAAGCAAGCAAGCAAGC AGCCCGGTGACCAAGAGCTTCAACCGGGCGAGTGT
	2	202	CAGGTGACAGCTGTGCGCTGCGCGAGGTGCTGTAACCTGGCGCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACAGCTACTACATCCACTGGTGGCGCCAGGCCCTGGACAGGAGTGGATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCAACTACGCCACAGTTCCAGGGCAGGCCACCTGACCGTGGACACCCAGC ATCAGCACCGCTACATGGAACCTGAGCCGGTGAAGAGCAGCAGCCGCTGTACTAGCAGCCCGTCCAC TACGGCTGGAATTGGAATTCGACGTGTGGGCAAGGGCAACCCGTGACAGTGTCTAGCAGCCAGGTGCAAGTG GTGGAATCTGGCGGAGTGTGACGCTGGCAGAAAGCCTGAGACTGAGCTGTCCGCCAGCGGCTTCACTTC ACCAAGGCCTGGATGCACTGGTGGCCAGGCCCTGGAAGCAGCTGGAATGGGTGGCCAGATCAAGGACAA GAGCAACAGTACGCCACCTACTACGCCGACAGCTGAAGGGCCGCTTACCATCAGCCGGGACGACAGCAAGAA CACCTGTACTGCAGATGAACAGCTGCGGGCGAGGACACCCCGCTGTACTACTGTGGGGCTGTACTATGCC CTGAGCCCTTCGATTACTGGGGCCAGGAACCTCTGTAACCTGTCTAGTCGGACCGCCAGCAACAAAGGCCAT CGGTGTCCCTCTGGCCCTTGACGCAAGAACCAAGCAATCTACAGCCGCTGGCTGCTGTGAAGGACTA CTTCCGAGCCGTGACCGTCTCTGGAATCTGGCGCTCTGACAGCGGCTGACACCTTTCCAGCCGTGCTC CAGAGCAGCGGCTGTACTCTGACAGCGCTGTGACGTGCCAGCAGCCTGGGCAACCAAGACCTACACC TGTAACGTGGAACCAAGCCAGCAACCAAGGTGGACAGCGGTGGAATCTAAGTACGGCTCCCTGCTGCTGCT CCTTGGCCAGCCCTGAAGTGGCGGAGACCTCCGCTGCTTCCCTCCCAAGCCCAAGGACACCTGATGA TCAGCCGACCCCGAAGTGAACCTGGTGGTGGTGTGTCCTCCAGGAAGATCCCGAGGTGCAATTCATTTGGT ACGTGAGCGGCTGGAAGTGCACAAACGCCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAG GTGTCCGTGTGACCGTGTGACCAAGACTGGCTGAACGGCAAGAGTACAAGTGAAGGTGTCCAAACAGGGC CTGCCAGCTCCATCGAATAACCATCAGCAAGGCCAAGGGCCAGCCCGGAGCTCAAGTGTACCTGCTGCC CCTAGCCAGGAAGATGACCAAGAACAGGTGTCCCTGAGCTGTGCGGTGAAGGCTTCTACCCAGCGCAT GCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCCCTGCTGTGCTGGACAGCGAGCGG

			CTCATCTTCCTGGTGTCACAGCTGACCCGTGGACAAAGAGCCGGTGGCAGGAAGGCAACGTTTCAGCTGCTCCGTG ATGCAAGAGGCCCTGCACAACTACACCCAGAACTCCCTGTCTCTGTCCTGGGC
3	203		GAAGTGCAGCTGGTGGAACTCTGGCGGGGACTGGTGACGCTGGGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCGCCAGGCCCTGGCAAGGACTGGAATGGGTGGCCAGA ATCTACCCACCCAGGGTACACAGATACAGCGACAGCGTAAGGGCCGGTTCCACATAGCGCCGACACCCAGC AAGAACCCGCTACCTGCAGATGAACAGCCTGCGGGCCAGGACACCGCCGTGTACTGTAGTAGATGGGA GGCGAAGGCTTCTACGCCATGGACTATTGGGGCCAGGCCACCTCTGACCCGTGTCTAGTGCCTGACCAAGGC CCATCGGTGTTCCCTCTGGCCCTTGCAGCAGAACACAGCAATCTACAGCCGCCCTGGGTGCTCGTGAAGG ACTACTTTCGAGCCCGTACCGGTCTCTGGAATCTGGCGCTCTGACAGCGCGTGCACACCTTTCAGCCGT GCTCAGAGCAGCGGCTGTACTCTGTAGCAGGCTGTGACAGTGCACAGCAGCCCTGGGCAACCAAGACCTA CACCTGTAACTGTGACCAAGCCACGACACCAAGGTGGACAAAGGGGTGGAATCTAAGTACGGCCCTCCCTG CCCTCTTGGCCAGCCCTGAAGCTGCCGGCGGACCTCCGTGTCTGTTCCCTCCCAAGCCAAAGGACACCTG ATGATCAGCCGACCCCGAAGTGAAGTGCACACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTAACG TGGTACGTGACCGGCTGGAAGTGCACACGCCAAGACCAAGCCAGAGAGAGGAACAGTTCAACAGCACCTAACG GGTGGTGCCTGCTGACCTGCTGACACAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGGTGCAAGGTGTCCAACA GGCTGCCCAGCTCATCGAAGAACCATCAGCAAGGCCAAGGCCAGCCCGGAGCTCAAGTGTATACCT GCCCCCTTGGCAGGAAGAGATGACCAAGAACAGGTGTCCCTGTGTGTCTGTGAAAGGCTTCTACCCAGCGAC ATTGCCGTGGAATGGAGAGCAACGGCCAGCCGAGAACAACTACAAGACACCCCTCTGTCTGTGACAGCGAC GGTCAATCTTCTGTACTCCAAGCTGACCGTGCAGCAAGAGCCGTGGCAGGAAGCAACGTTTCAAGCTGCTCCG TGATGACAGAGGCCCTGCACACCACTACACCCAGAACTCCCTGTCTGTCCCTGGGC
4	204		CAGTGTGAGCTGGTGGAGTCTGGCGCGAGGTCTGTGAACCTGGCGCTCTGTGAAGGTGTCTGTCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTACGCCCAAGAGTTTCAAGGCAAGAGCCACCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAAGAGCAGACACCGCCGTGTACTACTGCACCCCGTCCAC TACGGCTGGATTGGAATTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGACAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGCGGAGTGTGCAAGCCTGGCAGAACCTGAGACTGAGCTGTGCCGCCAGC GGCTTACCTTCAACCAAGCCCTGGATGCACTGGGTGCGCCAGGCCCTTGGAAGCAAGCAGCTGGAATGGGTGGCCAG ATCAAGGACAAGAGCAACAGTACGCCACTACTACGCCAGACAGCTGAAGGCCCGGTTCAACATCAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTATATGCCCTGAGCCCTTCGATTAATGGGGCCAGGGAACCTCTGTGACCCGTGTCTAGTATAAGACCCACA CCGCCAGCAAAAGGGCCCATCGGTGTTCCCTTGGCCCTTGACGAGAAAGCAAGCTGGAATCTACAGCCGCCCT GGCTGCTCGTGAAAGGACTACTTCCGAGCCCTGACCTGTCTTGGAACTCTGGCGCTCTGACAAAGCGGCGTG CAGACTTTCAGCCGTGCTCAGAGCAGCGCTGTACTCTGTGACAGCTGTGAGCTGCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGTAACTGTGGACCAAGCCCAAGCAACCAAGGTGGAACAGGGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGGCGGAGCCCTCCGTGTCTGTCTGTTCCCTCCCAAG CCCAAGGACACCCCTGATCAGCCGACCCCGAAGTGAAGTGTGGTGGTGTGTCTCCAGGAAGATCCC GAGGTGCACTTCAATTGGTACGTGGACGGCGTGAAGTGCACAAAGCCCAAGCAAGCCAGAGAGGACAGTTTC AACAGCACCTACCGGGTGGTCCGTGCTGACCGGTGCAACGAGTGGCTGAACGGCAAGAGGTACAAGTGC AAGGTGTCCAACAAGGGCCCTGCCAGCTCCATCGAGAAAACCATCAAGCAAGGCCAAGGGCCAGCCCCGCGAGCT

HER2-30R/ 55Q/1025+LC- WT- trastuzumab/ CD28supxCD3 mid L1 linker IgG4 FALA BP # 10	1	205	<p>CAAGTGTGTACCCCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACACAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCAGCGACATTCGCGTGGAATGGGAGAGAACGCGCCAGCCGAGAACCACTACAAGACCAACCCCT GTGCTGGACAGCGACGGCTCATTTCTCTGGTGTCAAAGTGAACCGTGGACAAGAGCCGGTGGCAGGAAGGCAAC GTGTTCAAGCTGCTCCGTGATGACAGAGGCCCTGCACAACTACACCAAGAGTCCCTGTCTGTCCCTGGGC GACATCGTGATGACCAAGACCCCTGAGCCCTGAGCTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCTGTGTGCAACAACAGCCCACTACCTAGCTGGTATCTGCAAGAACCCGGCCAGAGCCCTCCAG TCCCTGATCTCAAGGTGTCCAAACAGATTACGGGGTGTCCCGACAGATTCTCCGGACAGCGCTCTGGCACCGACT TCACCTGAAGATCAGCGGGTGAAGCCAGGACGTGGCGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCAACAAAGGTGGAATCAAGGGCCAGCCCAAGGCCGCCCCGACATCCAGATGACCCAGA GCCCAAGCAGCTGTGTGCAAGAGCGTGGGACAGAGTGAACCTACCTGTCAAGGCCAGGCCAGAACATCTACGTGT GGCTGAACCTGGTATCAGCAAGAGCCCGGCAAGGCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCG GCGTGCCACAGCAATTTCTGGCAGCGGCTCCGGCAACCGACTTACCTTGACAACTACCTCCCTGCAGCCCGAGGA CATTGCCACCTACTACTGCCAGAGGGCAGAGCTACCTTACCTTTGGCCAGGGCAACCAAGCTGGAAATCAAG ACCAAGGGCCCCAGCGTACGGTGGCCGCTCCAGCGTGTACTTCCCCACTAGCGACGAGCAGCTGAAGTCCG GCACAGCTCTGTGTGCTGCTGTGAACAACTTACCCCGGAGGCCAAAGTCAAGTGAAGGAGGAGGAGGACAAACG CCCTGCAAGAGCGGCAACAGCCAGGAAGCGTGAACGAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGC ACCTGACACTGACCAAGGCCGACTACGAGAAGCAAGGTTACGCTGCGAAGTGAACCAAGCAAGCAAGCAAGCAAGC AGCCCGGTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
	2	206	<p>CAGGTGACAGCTGTGCGCTGCGCGAGGTGCTGAAAACCTGGCGCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGGTGCGCCAGGCCCTGGACAGGAGTGGATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCACTACGCCCAAGTTCCAGGGCAGGCAACCTGACCGTGGACACCCAGC ATCAGCACCGCTACATGGAACCTGAGCCGGTGAGAGCGACACCGCGTGTACTAGCACCCCGTCCAC TACGGCTGGAATTGGAATTTCGACGTGTGGGCAAGGGCAACCCGTGACAGTGTCTAGCAGCCAGGTGCAAGTG GTGGAATCTGGCGGAGTGTGACGCTGGCAGAAAGCTGAGACTGAGCTGTCCGCCAGCGGCTTCACTTC ACCAAGGCTGATGCACTGGTGGCCAGGCCCTGGAAGCAGCTGGAATGGGTGGCCAGATCAAGGACAA GAGCAACAGTACGCCACCTACTACGCCGACAGCTGAAGGGCCGCTTACCATCAGCCGGGACGACAGCAAGAA CACCTGTACTGCAGATGAACAGCTGCGGGCGAGGACACCGCCGTGTACTACTGTGGGGCTGTACTATGCC CTGAGCCCTTCGATTACTGGGGCAGGGAACCTCTGTGACCTGTCTAGTCGGACCGCCAGCAAAAGGGCCAT CGGTGTCCCTCTGGCCCTTGACGAGAAACCAAGCAATCTACAGCCGCTTGGCTGCTGTAAGGACTA CTTCCGAGCCGTGACCGTGTCTGGAATCTGGCGCTGTGACAAGCGGCTGACACCTTTCAGCCGTGCTC CAGAGCAGCGGCTGTACTCTGACAGCGCTGTGACGTGCCAGCAGCGCTGGGCAACCAAGACCTACACC TGTAACGTGGAACCAAGCCAGCAACCAAGGTGGACAGCGGTGGAATCTAAGTACGGCTTCCCTGCCCT CCTTGGCCAGCCCTGAAGCTGCGGCGGACCTCCCTGCTGTCTTCCCTCCCAAGCCCAAGGACACCTGTATGA TCAGCCGACCCCGAGTGAAGTGCACAAACGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAG ACGTGACGCGGTGGAAGTGCACAAACGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAG GTGTCCGTGTGACCGTGTGACCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAG CTGCCAGCTCCATCGAAGAAACCATCAGCAAGGCCAAGGGCCAGCCCGGAGCTCAAGTGTACCTGCCCC CCTAGCCAGGAAGATGACCAAGAACAGGTGTCCCTGAGCTGTGCGGTGAAGGCTTCTACCCAGCGCAT GCCGTGGAATGGGAGAGCAACGGCCAGCCCGGAGCAACTACAAGACCCCTGCTGTGTGGACAGCGAGCGG</p>

			CTCATCTTCCTGGTGTCCTCAAGCTGACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAACGTTGTCAGCTGCTCCGTG ATGCAAGAGGCCCTGCACAACTACACCCAGAACTGCTCTGTCCTCCCTGGGC
3	207		GAAGTGCAGCTGGTGGAACTCTGGCGGGGGAATGGTGCAGCCTGGGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCACCGCCCTGGCAAGGGAAGTGGTGGCCAGA ATCTACCCACCCAGGGTACACAGATACAGCGACAGCGTGAAGGCGCGTTCCACCTAGCGCCGACACACAGC AAGAACCCGCTACCTGCAGATGAACAGCCTGGCGGCGAGGACACCGCCGTGTACTACTGTAGTATGGGA GGCTCCGGCTTCTACCCATGGACTATTGGGGCCAGGGACCTCGTGCACCGTGTCTAGTGCAGTGCACCAAGGCC CATCGGTGTCCCTCTGGCCCTTGCAGCAGAACACAGCAATCTACAGCCGCTGGGTGCTCGTGAAGGA CTACTTCCGAGCCCGTGAACCTGCTGGAACCTGGCGCTCTGACAAAGCGGCTGCACACCTTTCAGCCGTG CTCAGAGCAGCGGCTGTACTCTGTGACAGGCTGTGACAGTGCACAGCAGCCTGGGCACCAAGACCTAC ACCTGTAACTGTGACCAAGCCAGCAACACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCCCTCCCTGC CTCCTTCCAGCCCTGAATTTCTGGCGGACCTCCGTCTGTTCCCTCCCAAGCCCAAGGACACCTGTAT GATACGCCGACCCCGAAGTGAACCTGCTGGTGGTGGATGTGTCCAGGAAGATCCCGAGGTGCAGTTCAATTG GTACGTGACGGCGTGAAGTGCACACGCCAAGACCAAGCCAGAGAGAACTTCAACAGCACCTACCGGG TGGTGTCCGTGCTGACCGTGTGACACAGGACTGGCTGAACGGCAAGAGTACAAGTGAAGTGAAGTGAAGG GCCTGCCAGCTCCATCGAAGAACCAATCAAGCAAGGCCAAGGCCAGCCCGGAGCCTCAAGTGTATACCTTC CCCCTTGCCAGGAAGATGACCAAGAACAGGTGTCCCTGTGTGTCTGTGTAAGGCTTCTACCCAGGACAT TGCGTGAATGGGAGAGCAACGGCCAGCCGAGAACAACTACAAGACCAACCCCTGTGCTGGACAGGACGG CTCATTTCTCTGTACTCAAGCTGACCTGACCAAGAGCCGCTGGCAGGAAGCAACGTTTCAAGCTGCTCCGTG ATGACGAGGCCCTGCACAACTACACCCAGAACTGCTCTGTCCTCCCTGGGC
4	208		CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGCTGAACCTGGCGCTCTGTGAAGGTGCTCTGCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTGGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTACGCCAGAAAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAAGCGACGACACCGCGTGTACTACTGCACCCCGTCCAC TACGGCTGGATTGGAATTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGACAAAACCCATACC CAGGTGCAGCTGGTGGAACTCTGGCGGCGAGTGTGCAAGCCTGGCAGAAAGCTGAGACTGAGCTGTGCCGCCAGC GGCTTACCTTCAACCAAGGCTGGATGCACTGGGTGGCCAGGCCCTGGAAAGCAGCTGGGAATGGGTGGCCAG ATCAAGGACAAGAGCAACAGTACGCCACTACTACGCCAGACAGCTGAAGGCCGCTTCACTACAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTCCGGGC GTGTATATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCAGCACAAAGGGCCCATCGGTGTTCCCTTGCCCTTGACGAGAAAGCAGCAAGTGTGTAAGACCCCT GGCTGCTCGTGAAGGACTACTTCCGAGCCCTGACCTGTCTTGGAACTCTGGCGCTCTGACAAAGCGGCGTG CAGACTTTCAGCCGTGTCAGAGCAGCGCTGTACTCTGTGACGAGCTGTGAGCAGCAGCAGCAGCAGCAGC TGGGCACCAAGACCTACACCTGTAACTGTGGACCAAGCCCAAGCAACCAAGTGAACAGGGGTGGAACTTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGGCGGAGCCCTCCGTGTCTGTTCCCTCCCAAG CCCAAGGACACCTGATCAAGCCGACCCCGAAGTGAACCTGCTGGTGGTGTGTCTCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGTGGACGGCGTGAAGTGCACACGCCAAGCAAGCCAGAGAGGACAGTTTC AACAGCACCTACCGGGTGGTCCGTGCTGACCGTGTGACCAAGACTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCCAAACAAAGGGCCTGCCAGCTCCATCGAGAAACCATCAAGCAAGGCCAAGGGCCAGCCCCGCGAGCT

HER2-30R/ 56A/102S+LC- WT- trastuzumab/ CD28supxCD3mi d L1 linker IgG4 FALA BP # 11	1	209	CAAGTGTGTAACCTGCCCTAGCCAGGAAGAGATGACCAAGAACACAGGTGTCTCTGAGCTGTGCCGTGAAAGGC TTCTACCCACGACATTTGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCAACCCCTCT GTCTGGACAGCAGCGCTCATTTCTCTGTGTCCAAGCTGACCGTGGACAAGAGCCGTGGCAGGAAGGCAAC GTGTACGCTGCTCGTACAGAGGCCCTGCACAACCACTACACCCAGAAATCCCTGTCTCTGTCTCTGCTGCGC GACATCTGTGATGACCCAGACCCCTGAGCTGAGCGTGACCTGGACAGCTGACAGCTGACAGCTGACAGCTGACAGC AGCCAGAGCTGTGTGCACAACAACGCCACAACCTACCTGACGTGTGATCTGCAAGAGCCCGGCCAGACGCCCCAG TCCCTGATCTACAAGGTGTCCAACAGATTCAGCGGCTGCCGACAGATTCCTCCGACGCGCTCTGGCACCCGACT TCACCTGAAGATCAAGCCGGTGGAAAGCCGAGACGTGGGCGTGTACTATTGTGGCCAGGGCAACCAAGTACCCCT TCACCTTTGGCAGCGGCCAACAGGTGGAATCAAGGCCAGCCCAAGCCCGCCCCCGACATCCAGATGACCCAGAGA GCCCCAGCAGCTGTCTGCCAGCGTGGCGACAGAGTGACATCACTGTCAAGCCAGCCAGCAACATCTACGTGT GGTGAACCTGGTATCAGCAAGAGCCGGCAAGGCCCAAGCTGTGATCTACAAGGCCCAACCTGCACACCG GCGTCCCCAGCAGATTTCTGGCAGCCGCTCCGGCACCGCACTTCAACCTGACATACAGTCTCCCTGCAGCCCGAGGA CATTGCCACCTACTCTGCCAGAGGCCAGACCTACCCCTACACCTTTGGCCAGGGCAACCAAGCTGGAAATCAAG ACCAAGGCCCCAGCGTACGGTGGCCCTCCCAAGCGTGTTCATCTTCCCACTAGCAGCAGCAAGCTGAAGTCCCG GCACAGCTCTGTCTGTGCTGTGCTGAACAACTTCTACCCCGGAGGCCAAAGTGCAAGTGAAGTGACAAACG CCCTGCAGAGCGGCAACAGCCAGGAAGCGTGAACGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGC ACCTGACACTGAGCAAGGCCGACTACGAGAAGCAAGGTGTACGCTCGCAAGTGTACCCACCAAGGCGCTGTCT AGCCCGTGACCAAGACTTCAACCGGCGCAGTGT
	2	210	CAGGTGCAGCTGTGTCAGTCTGGCGCCGAGGTGTGAAACCTTGGCGCTCTGTGAAAGTGTCTGCAAGGCCAGC GGCTACACCTTTACAGCTACTACATCCACTGGGTGGCCAGGCCCTGGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCAACTACGCCACAGATTCAGGGCAGAGCCAACCTGACCCGTGGACACCAAGC ATCAGCACCCGCTACATGGAATGAGCCGGCTGAGAACGACGACACCCCGCTGTACTACTGCACCCCGTCCCAC TACGGCTGGAATTGGAATTCGACGTGTGGGCAAGGCCACACCGTGACAGTGTCTAGCAGCCAGGTGCAGCTG GTGGAATCTGGCGCGGAGTGTGTGCAAGCTGGCAAGGCTGAGCTGTGCGGCCAGCGGCTTCACTCTC ACCAAGGCTGTGATGCACTGGGTGCGCCAGGCCCTGGAAAGCAGCTGGAATGGGTGGCCACAGATCAAGACAA GAGCAACAGCTACGCCACCTACTACGCCGACAGCGTGAAGGCCGCTTCAACCTAGCCGGGACGACAGCAAGAA CACCTGTACCTGCAGATGAACAGCTGCGGGCCGAGGACACCGCGTGTACTCTGTCGGGCGTGTACTATGCG CTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGTGACCGTGTCTAGTCGGACCGCCAGCAAAAGGCCCAT CGGTGTCCCTTGCGCCCTTGACGACAGAACCCAGCAATCTACAGCCGCTTGGCTGCCCTGTGTAAGGACTA CTTTCGAGCCGTCGACCGTCTCGGAACCTGTGGCTCTGACAAAGCGGCGTGCACACCTTTCAGCCGCTGCTC CAGACAGCGGCTGTACTCTGTGACAGCGTGTGACGTGCCAGCAGCGCTGGGCCACCAAGACCTACAC TGTAACGTGGACCAAGCCAGCAACCAAGGTGGACAAGCGGTGGAATCTAAGTCAGGCCCTCCCTGCCCT CCTTGCCAGCCCTGAAGCTGCCGGGACCTCCGCTTCTCTTCCCCCAAGGCCAAGGACACCCCTGATGA TCAGCCGACCCCGAAGTGAACCTGCTGGTGGTGGATGTGTCCAGGAAGATCCCGAGGTGCAATTGCT ACGTGGACGGCTGGAAGTGCAACAAGCCAAAGCAAGCCACAGAGGAACAGTTCAACAGCACCTACCCGGTG GTGTCGTGCTGACCGTGTGACACAGGACTGGCTGAACGGCAAGAGTACAAAGTGAAGGTGTCCAACAGGGC CTGCCAGCTCCATCGAGAAACCATACGAAGGCCAGGCCAGCCCGGACGCTCAAGTGTACCTGCC CTTAGCCAGGAAGATGACCAAGAACCAAGGTGTCCCTGAGCTGTGCCGTGAAAGGCTTCTACCCACGCGACAT GCCGTGGAATGGGAGCAACGGCCAGCCCGAGACACTACAGCAACCCCTCTGTCTGTCTGTCAGCGG

			CTCATCTTCCTGGTGTCCAAAGCTGACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAACGTTTCAGCTGCTCCGTG ATGCAAGAGGCCCTGCACAACTACACCCAGAACTCCCTGTCTCTGTCCTGGGC
3	211		GAAGTGCAGCTGGTGGAACTCTGGCGGGGACTGGTGACGCTGGGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCGCCAGGCCCTGGCAAGGACTGGAATGGGTGGCCAGA ATCTACCCACCAACGCTACACAGATACCGGACAGCGTGAAGGCGCGTTCCACATAGCGCCGACACACAGC AAGAACCAGCCTACCTGAGATGAACAGCTCGGGCCAGGACACCGCCGTGTACTGTAGTGTAGATGGGA GGCTCCGGCTTCTACGCCATGGAATATTGGGGCCAGGACCTCGTGTCTAGTGTGACCAAGGGCC CATCGGTGTCCCTCTGGCCCTTTCAGAGAACAGCAGCAATCTACAGCCGCTGGGTGCTCGTGAAGGA CTACTTCCGAGCCCGTGAACCGTGTCTGGAACCTCTGGCGCTCTGACAAAGCGGCTGCACACCTTTCAGCCGTG CTCAGAGCAGCGGCTGTACTCTGTGACAGGCTGTGACAGTGCACAGCAAGCGGCTGGGCACCAAGACCTAC ACCTGTAACTGTGACCAAGCCAGCAACACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCTTCCCTGC CTCCTTGCCAGCCCTGAATTTCTGGCGGACCTCCGTCTGTTCCCAAGCCCAAGGACACCTTGAT GATACGCCGACCCCGAAGTGAACCTGCTGGTGGTGGATGTGTCACAGGAAGTCCCGAGGTGCAATTCATTTG GTACGTGACGGCGTGAAGTGCACACGCCAAGACCAAGCCAGAGAGGAACAGTTTCAACAGCACCTACCGGG TGGTGTCCGTGCTGACCGTGTGCACACGACTGGCTGAACGGCAAGAGTACAAGTCAAGTGAAGGTGTCCAACAAGG GCTGCCAGCTCATCGAATAACATCAGCAAGGCCAAGGCCAGCCCGGAGCCTCAAGTGTATACCTTGC CCCCTTGCCAGGAAGATGACCAAGAACAGGTGTCCCTGTGGTGTCTCGTGAAGGCTTCTACCCAGGACAT TGCGTGAATGGGAGACACGGCCAGCCGAGAACAACTACAAGACCAACCCCTGTGCTGGACAGGACGG CTCATTTCTCTGTACTCCTCAAGCTGACCGTGGACAAAGCCGCTGGCAGGAAGCAACGTTTACGCTGCTCCGTG ATGACGAGGCCCTGCACAACTACACCCAGAACTGTCCTGTCTGTCCTGGGC
4	212		CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGCTGAACCTGGCGCTCTGTGAAGGTGCTCTGCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGACGC ATCTACCCCGGCAACGTGAACACCACTACGCCAGAAAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACACG ATCAGCACCGCTACATGGAACTGAGCCGGTGAAGCGACGACACCGCGTGTACTACTGCACCCGTTCCAC TACGGCTGGATTGGAATTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGACAAAACCCATACC CAGGTGCAGCTGGTGGAACTCTGGCGGAGTGTGCAAGCCTGGCAGAACCTGAGACTGAGCTGTGCCGCCAGC GGCTTACCTTCAACCAAGGCTGGATGCACTGGGTGCGCCAGGCCCTTGAAAGCAGCTGGGAATGGGTGGCCAG ATCAAGGACAAGACAAGTACGCCACTACTACGCCAGACGCTGAAGGCCGCTTACCATCAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCGCTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCAGCAACAAGGGCCCATCGGTGTCCCTTGGCCCTTGACGAGAAAGCAGCAATCTACAGCCGCCCT GGCTGCTCGTGAAGGACTACTTCCGAGCCCTGACCGTGTCTTGGAACTCTGGCGCTCTGACAAAGCGGCGTG CAGACTTTCAGCCGTGTCAGAGCAGCGCTGTACTCTGTGACGACGCTGTGAGCAGCAGCAGCAGCAGCAGC TGGGCACCAAGACCTACACCTGTAACTGGGACCAAGCCCAAGCAACCAAGGTGGAACAAGGGTGGAACTTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGGCGGAGCCCTCCGTGTCTGTTCCCTCCCAAG CCCAAGGACACCTGATCAGCCGACCCCGAAGTGAACCTGCTGGTGGTGTGTCTCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGTGGACGGCGTGAAGTGCACAACGCCAAGCAAGCCAGAGGAGCAAGTTTC AACAGCACCTACCGGGTGGTCCGTGCTGACCGTGTGACCAAGACTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCCAAACAAGGGCCTGCCAGCTCCATCGAGAAAACCATCAAGCAAGGCCAAGGGCCAGCCCCGCGAGCT

HER2-30R/ 56A/102E/ CD28supxCD3mi d L1 linker IgG4 FALA BP # 12	1	213	<p>CAAGTGTGTACCCCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACACAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCACGCGACATTCCTGTGGAATGGAGAGACACGCGCACCCGAGAACAACTACAAGACCAACCCCCCT GTGCTGGACACGCGACGGCTCATTTCTCTGTGTCCAAAGTGAACCGTGGACAAGAGCCGGTGGCAGGAAGGCAAC GTGTTCACTGCTCCGTGATGACAGAGGCCCTGCACAACTACACCCAGAACTCCTGTCTGTCCCTGGGC GACATCTGTGATGACCAAGACCCCTGAGCCCTGAGCTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCTGTGTGCAACAACAACGCCAACACTACTCTGAGCTGGTATCTGCAAGAACCCGGCCAGAGCCCCCAG TCCCCTGATCTACAAAGGTGTCCAAACAGATTACGCGGCTGCCCCAGAGATTCTCCGGACAGCGCTCTGGCACCCGAT TCACCCCTGAAGATACGCGGGTGAAGCCAGGACGTGGGCTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCAACAAAGGTGGAATCAAGGGCCAGCCCAAGGCCGCCCGCCGACATCCAGATGACCCAGA GCCCCAGCAGCTGTGTGCCAGGTTGGGCGACAGAGTGAACCTGTCAGGCCAGGCCAGAAATCATCTACGTGT GGCTGAACCTGGTATCAGCAGAAGCCCCGGCAAGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCG GCGTGCCACAGCATTTCTGGCAGCGGCTCCGGCAACCGACTTCAACCTTGACAATCAGCTCCCTGCAGCCCGGAGGA CATTGCCACCTACTACTGCCAGAGGGCCAGACTACCTTACACCTTTGGCCAGGGCAACCAAGCTGGAAATCAAG ACCAAGGGCCCCAGCCGTACGGTGGCCGCTCCAGCGTGTACTTCCCCACTAGCGACGAGCAGCTGAAGTCCG GCACAGCCTCTGTGTGTGCTGCTGTAACAATTTACCCCCGGAGGCCAAAGTCAAGTGGAAAGTGGACAAACG CCCTGCAGAGCGGCAACAGCCAGGAAGCGTGAACCGAGCAGAGCAAGCAAGCACTCCACCTACAGCCTGAGCAGC ACCTGACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACAGGGCCTGTCT AGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	2	214	<p>CAGGTGACGCTGGTGTGCTGGCGCGAGGTCTGTAACCTGGCGCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGCTACTACATCCACTGGTGGCGCCAGGCCCTGGACAGGAGTGGAAATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCAACTACGCCCAAGTTCCAGGGCAGAGCACCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGGAATGAGCCGGTGAAGAGCGACACCGCGTGTACTACTGACCCCGTCCAC TACGGCTGGAATTGGAATTCGACGTGTGGGCAAGGGCAACCCGTGACAGTGTCTAGCAGCCAGGTGCAAGTGTG GTGGAATCTGGCGGAGTGTGACGCTGGCAGAAAGCCTGAGACTGAGCTGTCCGCCAGCGGCTTCACTTC ACCAAGGCCCTGGATGCACTGGTGCAGCCAGGCCCTGGAAGCAGCTGGAATGGTGGCCAGATCAAGGACAA GAGCAACAGCTACGCCACCTACTACGCCGACAGCTGAAGGGCCCGTTACCATCAGCCGGGACGACAGCAAGAA CACCTGTACTGCAGATGAACAGCTGCGGGCGAGGACACCCCGCTGTACTACTGTGGGGCTGTACTATGCTG CTGAGCCCTTCGATTACTGGGGCCAGGAACCTCTGTGACCTGTCTAGTCGGACCGCCAGCACAAGGGCCCAT CGGTGTCCCTCTGGCCCTTGACGCAAGAACCAAGCAATCAGCCGCTGGGCTGGCTCGTGAAGGACTA CTTCCGAGCCGTGACCGTGTCTGGAATCTGGCGCTCTGACAAGCGGCTGACACCTTTCCAGCCGTGCTC CAGAGCAGCGGCTGTACTCTGTGACAGCGCTGTGACGTGCCAGCAGCCTGGGACCAAGACCTACACC TGTAACGTGGACCAAGCCAGCAACCAAGGTGGACAGCGGTGGAACTAAAGTACGGCTCCCTGCTGCTG CCTTGCCAGCCCTGAAAGTGCAGCGGCAACCTCCGTGTCTGTTCCCTCCCAAGCCCAAGGACACCTGATGA TCAGCCGACCCCGAAGTGAACCTGCGTGGTGTGTTCCAGGAAGATCCCGAGGTGCAAGTCAATTGGT ACGTGACGGGTGGAAGTGCACAACGCCAAGACCAAGCAAGAGAGAGTCAACAGCACTACCGGGTG GTGTCCGTGTGACCGTGTGACCAAGACTGGTGAACGGCAAGAGTCAAGTGAAGGTGTCCAAAGGGC CTGCCAGCTCCATCGAAGAAACCATCAGCAAGGCCAAGGGCCAGCCCGGAGCTCAAGTGTACCCCTGCCC CCTAGCCAGGAAGAGATGACCAAGAACAGGTGTCCCTGAGCTGTGCGGTGAAGGCTTCTACCCAGCGCAT GCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCCCTGCTGTGCTGGACAGCGAGCGG</p>

			CTCATCTTCCTGGTGTCACAGCTGACCCGTGGACAAAGAGCCGGTGGCAGGAAGGCAACGTTGTCAGCTGCTCCGTG ATGCAAGAGGCCCTGCACAACTACACCCAGAACTCCCTGCTCTGTCCTCCCTGGGC
3	215		GAAGTGCAGCTGGTGGAACTCTGGCGGGGGAATGGTGACGCTGGGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCGCCAGGCCCTGGCAAGGGAAGTGGTGGCCAGA ATCTACCCACCAACGCTACACAGATACCGGACAGCGTGAAGGGCCGGTTCACCATAGCGCCGACACACAGC AAGAACCCGCTACCTGCAGATGAACAGCTCGGGGCGAGGACACCGCCGTGTACTGTAGTAGATGGGA GGCGAAGGCTTCTACGCAATGGACTATTGGGGCCAGGGCACCCCTGTGACCCGTGTACTGTGCTGACCAAGGC CCATCGGTGTTCCCTCTGGCCCTTGCAGCAAGAACACAGCAATCTACAGCCGCCCTGGGTGCTCGTGAAGG ACTACTTTCGAGCCCGTGACCGGTCTCTGGAATCTGGCGCTCTGACAAAGCGCGTGCACACCTTTCAGCCGT GCTCAGAGCAGCGGCTGTACTCTGTAGCAGGCTGTGACAGTGCACAGAGCCAGCAGCCCTGGGCAACCAAGACCTA CACCTGTAACTGTGACCAAGCCAGCAACACCAAGGTGGACAAAGCGGTGGAATCTAAGTACGGCCCTCCCTG CCCTCTTGGCCAGCCCTGAATTTCTGGCGGACCCCTCCGTGTTCTGTTCCTCCCAAGCCCAAGGACACCCCTGA TGATCAGCCGGAACCCCGAAGTGCACACGCAAGACCAAGCCAGCAAGTGCCTCAGAGGAATCCCGAGGTGCAATTT GGTACGTGGACGGGTGGAAGTGCACACGCAAGACCAAGCCAGCAAGTGCCTGAGTGCCTGAGTGCCTGAGTGCCTG GTGGTCCGTGCTGACCTGCTGACACAGGACTGGCTGAACGGCAAGAGTACAAGTGCCTGAGTGCCTGAGTGCCTG GGCTGCCAGCTCCATCGAAGAAACCAATCAGCAAGGCCAAGGGCCAGCCCGAGCCCTCAAGTGTATACCTG CCCCCTTGCAGGAAGATGACCAAGAACAGGTGTCCCTGTGTTGCTGCTGTAAGAGGCTTCTACCCAGCGACA TTGCGTGAATGGAGAGCAACGGCCAGCCGAGAACCACTACAAGACCAACCCCTGTGCTGAGCAGCGACG GTCAATCTCTCTGTAAGTACCTGACCTGACCAAGAGCCGTGGCAGGAAGCAACGTTGTTCAAGCTGCTCCGT GATGCAGAGGCCCTGCACAACTACACCCAGAAAGTCCCTGCTCTGTCCTCCCTGGGC
4	216		CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGCTGAAACCTGGCGCTCTGTGAAGGTGCTCTGCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGGTGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAAGC ATCTACCCCGGCAACGTGAACACCAACTACGCCCAAGAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCAAGC ATCAGCACCGCTACATGGAACTGAGCCGGTGAAGAGCAGCAGCACCCCGTGTACTACTGCACCCCGTCCAC TACGGCTGGAATGGAACTTCGACGTGTGGGCAAGGGCACCCGTGACAGTGTCTAGCGACAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGCGGAGTGTGCAAGCCTGGCAGAAAGCTGAGACTGAGCTGTGCCGCCAGC GGCTTACCTTCAACCAAGGCTGGATGCACTGGGTGCCAGGCCCTTGAAAGCAGCTGGAAATGGTGGGCCAG ATCAAGGACAAGAGCAACAGTACGCCACTACTACGCCGACAGCTGAAGGCCCGTTCAACCATAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTGTCCGGGC GTGTATATGCCCTGAGCCCTTCGATTAATGGGGCCAGGAAACCTCTGTGACCCGTGTCTAGTATAAGACCCACA CCGCGACACAAGGGCCCATCGGTGTTCCCTCTGGCCCTTGACAGCAAGACCAAGCTGGAATCTACAGCCGCCCT GGCTGCTCGTGAAGGACTACTTCCGAGCCCTGACCTGTCTTGGAACTCTGGCGCTCTGACAAAGCGGCGTG CAGACTTTCAGCCGTGTCAGAGCAGCGCTGTACTCTGTGAGCAGCCTGTGAGCTGCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGTAACGTGGACCAACAGCCCAAGCAACCAAGGTGGAACAGGGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTCCGGGAGCCCTCCGTGTTCTGTTCTGTTCCCTCCCAAG CCCAAGGACACCTGATGATCAGCCGACCCCGAAGTGAACCTGCGTGGTGGTGTGTCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGTGGACGGCGTGAAGTGCACACGCCAAGCAAGCCAGAGAGGAACAGTTTC AACAGCACCTACCGGGTGGTCCGTGCTGACCGGTGCAACGAGTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCCAAACAAGGGCCTGCCAGCTCCATCGAGAAAACCATCAAGCAAGGCCAAGGGCCAGCCCCGCGAGCT

HER2- WT+trastuzumab / CD28supxCD3mi d (32/35QQ) L1 linker IgG4 FALA BP # 15	1	217	<p>CAAGTGTGTACCCCTGCCCCCTAGCCAGGAAGAGATGACCAAGAACACGAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCCAAGCGACATTCGCGTGGAATGGAGAGAACGCGCCAGCCGAGAACCTCAAGACACACCCCT GTGCTGGACAGCGACGGCTCATTTCTCTGGTGTCAAAGTGAACCGTGGACAAAGACCGGTGGCAGGAAGGCAAC GTGTTCAAGCTGCTCCGTGATGACAGAGGCCCTGCACAACTACACCCAGAACTGCTCTCTGTCCTGCTGGC GACATCTGTGATGACCAAGACCCCTGAGCCCTGAGCTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCTGTGTGACACCAAGCCAGACCTCTCTGAGCTGTGTCTGAGAAAGCCGGCCAGAGCCCTCCAG TCCCTGATCTCAAGGTGTCCAAAGATTACGGGGCTGCCCCAGAGATTCTCCGGACGGCTCTTGGACCCGACT TCACCTGAAGATACGCGGTGGAGCCAGGACGTGGGGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGCACCAAGGTGGAAATCAAGGGCCAGCCCAAGGCCCTCCGACATCCAGATGACCCAGA GCCCAAGCAGCTGTGTGCAAGGTGGGACAGAGTAGACCTACCTGTCAAGGCCAGCCAGAACATCTACCTGT GGCTGAACCTGGTATCAGCAAGAGCCCGGCAAGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCG GGTGGCCAGCAGATTCTTGGCAGCGGCTCCGGCACCCGACTTACCTTGACAAATCAGCTCCCTGCAGCCCGAGGA CATTGCCACCTACTACTGCCAGAGGGCCAGACTACCTTACCTTTGGCCAGGGCAACAGCTGGAAATCAAG ACCAAGGGCCCCAGCCGTACGGTGGCCCTCCAGCGTGTCTATCTTCCCACTAGCCAGCAGCAGCTGAAGTCCG GCACAGCTCTGTGTGCTGCTGTGAACAACTTCTACCCCGGAGGCCAAAGTCAAGTGAAGGTTGGAAGGTTGACAAACG CCCTGCAAGAGCGGCAACAGCCAGGAAGCGTGAACGAGCAAGCAAGGACTCCACCTACAGCTGAGCAGC ACCTGACACTGACCAAGGCCGACTACGAGAAGCAAGGTTACGCTGCGAAGTGACCCACACAGGCGCTGTCT AGCCCGGTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	2	218	<p>CAGGTGACGTGTGAGCTGTGGCGCGAGGTGCTGTAACCTGGCGCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGGTGGCCAGGCCCTGGACAGGAGTGGATGGATCGGCAGC ATCTACCCCGCAACGTGAACACCAACTACGCCACAGTTCCAGGGCAGAGCACCTGACCGTGGACACCCAGC ATCAGCACCGCTACATGGAACTGAGCCGCTGAGAAAGCGACACCGCGTGTACTACTGACCCCGTCCAC TACGGCTGGAATTGGAATTTCGACGTGTGGGCAAGGGCACACCGTGAAGTGTCTAGCAGCCAGGTGCAAGTG GTGGAATCTGGCGGAGTGTGACGCTGGCAGAAAGCTGAGCTGAGCTGTCCGCCAGCGGCTTCACTTC ACCAAGGCTGGATGCACTGGGTGCGCCAGGCCCTGGAAGCAGCTGGAATGGGTGGCCAGATCAAGGACAA GAGCAACAGTACGCCACCTACTACGCCGACAGCTGAAGGGCCGCTTACCATCAGCCGGGACGACAGCAAGAA CACCTGTACTGCAGATGAACAGCTGCGGGCGAGGACACCGCCGTGTACTACTGTGGGGCTGTACTATGCC CTGAGCCCTTCGATTACTGGGGCCAGGAACCTCTGTGACCTGTCTAGTCGGACCGCCAGCAAAAGGGCCAT CGGTGTCCCTCTGGCCCTTGACGCAAGAACCAAGCAATCTACAGCCGCTGGCTGCTGTAAGGACTA CTTCCGAGCCGTGACCGTGTCTGAACTCTGGCGCTGTGACAGCGGCTGACACCTTTCCAGCCGTGCTC CAGAGCAGCGGCTGTACTCTGTGACAGCGTGTGACAGTGGCCAGCAGCCTGGGACCAAGACCTACACC TGTAACGTGGACCAAGCCAGCAACCAAGGTGGACAGCGGTGGAACTAAAGTACGGCTTCCCTGCTGCT CCTTGGCCAGCCCTGAAGTGGCGGAGACCTCTGCTGTCTTCCCTCCCAAGCCCAAGGACACCTGTATGA TCAGCCGACCCCGAGTGAACCTGCGGTGGTGTGTCCTCCAGGAAGATCCCGAGGTGCAATTCATTTGGT ACGTGACGGGTGGAAGTGCACAAACGCCAAGCAAGCCAGAGAGAGTTCACAGCAGCTACCGGGTG GTGTCCGTGTGACCGTGTGACCAAGACTGGTGAACGGCAAGAGTACAAGTGAAGGTGTCCAAACAGGGC CTGCCAGCTCCATCGAAGAAACCATCAGCAAGGCCAAGGGCCAGCCCGGAGCTCAAGTGTACCTGCCCC CCTAGCCAGGAAGAGATGACCAAGAACAGGTGTCTGCTGCTGAGTGTGCGGTGAAGGCTTCTACCCAGCGCAT GCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACTACAAGACACCCCTGCTGTGCTGGACAGCGAGCGG</p>

			CTCATCTTCCTGGTGTCACAGCTGACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAACGCTGTTCAAGCTGCTCCGTG ATGCAAGAGCCCTGCACAACTACACCCAGAACTCCCTGCTCTGTCCTGGGC
3	219		GAAGTGCAGCTGTGGAACTGTGGCGGGGACTGGTGACGCTGGGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCAAGGACACCTACATCCACTGGGTGGCCAGGCCCTGGCAAGGACTGGAATGGGTGGCCAGA ATCTACCCACCAACGGGTACACAGATAGCGCGACAGCGTAAGGGCCGGTTCCACCTAGCGCCGACACCCAGC AAGAACCCGCTACCTGCAGATGAACAGCTCGCGGCCGAGGACACCGCTGTACTACTGTAGTAGATGGGA GGCGACGGCTTACGCCATGGACTATTGGGGCCAGGGCACCCCTGTGACCCGTGTCTAGTGGCTGACCAAGGGCC CATCGGTGTTCCCTCTGGCCCTTTCAGAGAACACAGCAAGTCTACAGCCGCTGGGTGCTCGTCTGTAAGGA CTACTTCCCGAGCCCGTGAACCGTGTCTGGAACCTCTGGCGCTCTGACAAAGCGGCTGCACACCTTTCAGCCGTG CTCAGAGCAGCGGCTGTACTCTGTGACAGGCTGTGACAGTGCACAGCAGCCCTGGGCAACCAAGACCTAC ACCTGTAACTGTGACCAAGCCCAAGCAACCAAGGTGGACAAGCGGGTGAATCTAAGTACGGCTTCCCTGC CTCCTTCCCGAGCCCTGAAGCTGCCGGGACCTCCGTGTCTCTGTTCCCTCCCAAGCCCAAGGACACCCCTGA TGATCAGCCGGAACCCGGAAGTGAACCTGTGGTGGTGTGATGTGTCAGGAAGATCCCGAGGTGCAAGTTCAATT GGTACGTGGACGGCGTGAAGTGCACAACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTACCCG GTGGTGTCCGTGCTGACCTGTCTGACACAGGACTGGCTGAACGGCAAGAGTCAAGTCAAGGTGTCCAACAAG GGCTGGCCAGCTCCATCGAATAAACATCAGCAAGGCCAAGGCCAGGCCGAGCCGAGCCCTAAAGTGTATACCTG CCCCCTTGGCAGGAAGATGACCAAGAACAGGTGTCCCTGTGGTGTCTGTGAAAGGCTTCTACCCAGGACA TTGCGGTGAATGGAGAGCAACGGCCAGCCGAGAACAACTAAGACCAACCCCTGTGCTGGACAGGACG GTCACTTCTCTGTACTCCAAGTGAACCTGACCGTGGACAAGAGCCGGTGGCAGGAAGGCAACGTTTCAAGCTGCTCCGT GATGCACGAGGCCCTGCACAACTACACCCAGAAAGTCCCTGTCTGTCCCTGGGC
4	220		GACATCCAGATGACCCAGCCCCAGCAGCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTAGAGCC AGCCAGGACGTGAACACCCCGTGGCTGTATACGAGAAGCTGGCAAGGCCCAAGCTGTGATCTACAGC GCCAGCTTCTGTACAGCGGCTGCCAGAGATTCAGCGGAAGCAGAGAGCGGCAACCGACTTCAACCTGACCATC AGTCCCTGCAGCCGAGGACTTCCCACTACTACTGCCAGCAGCTACACACCCCTCCACATTTGGCCAGG GCACCAAGGTGGAATCAAGCGTACGGTGGCGCTCCAGCGTGTCTATCTTCCCACTAGCAGCAGCAGCTGA AGTCCGGCACAGCCTCTGTCTGTGCTGTGAACAACTTCTACCCCGCAGGCCAAAGTGCAAGTGAAGTGG ACAACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTG AGCAGCACCTGACACTGAGCAAGGCCGACTACGAGAAGCAAGGTGTACGCTGCGAAAGTGACCCACCAAGG CCTGTCTAGCCCCGTGACCAAGAGCTTCAACCCGGCGAGTGT
HER2/ CD28 ^{sup} ×CD3 ^{mild} DKTHT linkers on HC(LC) IgG4 FALA BP # 25	1	221	GACATGATGACCCAGACCCCTGTAGCCTGAGCGTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGTGACAAACACGCCAACCTACCTAGCTGGTATCTGCAGAAGCCCGGCCAGAGCCCCCAG TCCCTGATCTACAAGGTGTCAACAGATTCAGCGGCTGCCGACAGATTCCTCGGACGGCTCTGGCACCGACT TCACCTGAAGATCAGCGGCTGGAAGCCGAGGACCTGGCGGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTGGCAGCGGCAACAAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCTGGGAGACAGAGTACCCTACCTGTCAAGGCCAGCCAGAACATCTACGTGTGGCTGA ACTGGTATCAGCAAGAGCCCGCAAGGCCCTCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCCGGCTGC CCAGCAGATTTTCTGGCAGCGGCTCCGGCAGCGACTTCAACCTGACAACTCAAGCTCCCTGCAGCCCGAGGACATTGC CACCTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTGGCCAGGGCAACCAAGCTGGAAATCAAGGATAA

			<p>GACCCACACCCGTACGGTGGCCGCTCCACAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCACA GCCTCTGCTGTCCTGCTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGAAGGTGGAACAAAGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCAGCACCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACAGGCCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	222		<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGCTGAAACCTGGCGCCCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGGTGGCCAGGCCCTTGACAGGGACTGGAAATGGATCGGCAGC ATCTACCCCGCAACCGTGAACACCAACTACGCCAGAACTTCCAGGGCAGAGCCACCTGACCCGTGGACACCAGC ATCAGCACCGCTACATGGAATGAGCCGCTGAGAGCGACGACACCGCCGTGTACTACTGACCCCGTCCAC TAGGGCTGGATTGGAACCTTCGACGTGTGGGGCAAGGGCACCAACCGTGACAGTGTCTAGCGACAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGGAGTGGTGACGCTGGCAGAAAGCCTGAGCTGAGCTGTGCCGCCAGC GGCTTCACTTACCAAGGCCTGGATGCACTGGGTGCGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGCCAG ATCAAGGACAAGACAAGTACGCCACTACTACGCCGACAGCGTGAAGGGCCGGTTACCATCAAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCGTGACCGTGTCTAGTGATAAGACCCACA CCGCCAGCAAAAGGGCCCATCGGTGTTCCCTTGCCCTTGACGACAGAACACAGCAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTTCGAGCCCGTACCGTGTCTTGAACTCTGGCGCTCTGACAAAGCGCGTG CACACCTTTCAGCGGTCTCCAGAGACGCGCTGTACTCTGAGCAGCGTGTGACAGTGCCAGCAGCAGCAGC TGGCACCAAGACCTACACCTGTAACGTGGACACAAAGCCCAAGCAACCAAGGTGGACAAAGGTGGAAATCTA AGTAGGGCCCTCCCTGCCCTTGGCCAGCCCTGAAGTGGCGGCGGACCCCTCGGTGTTCTTCCCTCCCAAG CCCAAGGACACCTGTATGATCAGCCGACCCCGAAGTACCTGCGTGGTGGTGTGTCTCCAGGAATCCC GAGTGCAGTTCAATTGTGACGTGGACGCGGTGGAAGTGCAACCGCAAGACCAAGCCAGAGAGAACAGTTC AACAGCACCTACCGGGTGGTGTCCGTGTGACCGTGTGACCAAGGACTGGCTGAAACGGCAAGAGTACAAGTGC AAGGTGTCCAAACAAGGGCCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGCAGCCT CAAGTGTGTACCCCTGCCCTAGCCAGGAAGATGACCAAGAACCCAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCCAAGCAGATTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCAACCCCT GTGCTGGACAGCGACGGCTCATTTCTGTTGTTCCAAAGTGAACCGTGGACAAGAGCCGTGGCAGGAAGGCAAC GTGTTCAAGCTGCTCCGTGATGCACGAGGCCCTGCACCAACCACTACACCAAGATCCCTGTCTCTGCCCTGGC GAAGTGCAGCTGGTGAATCTGGCGCGGACTGTGTGACGCTGGCGGATCTGTAGACTGAGCTGTGCCCGCCAGC GGCTTCAACATCAAGGACACCTACATCCACTGGGTGGCGCCAGGCCCTTGGCAAGGGAATGGGTGGCCAGA ATCTACCCCAACCAACGGCTACACAGATACCGCGACAGCGTGAAGGCCCGGTTCAACCATCAGCCCGCACACAGC AAGAACACCCGCTACCTGCAGATGAACAGCTGCGCGGAGGACACCGCGTGTACTGTAGTAGATGGGGA GGCAGCGCTTCTACGCCATGGACTATTGGGGCCAGGGCACCCCTGTGACCGGTGTCTAGTGTCTGACCAAGGGC CATCGGTGTCCCTCTGGCCCTTGACGACAAGAACCCAGCAATCTACAGCCCGCTGGGTGCCTCGTGAAGGA CTACTTCCCGAGCCCGTGAACGTGTCTTGAACTCTGGCGCTCTGACAAAGCGGTGTGACACCTTTCCAGCCGTG CTCCAGAGCAGCGGCTGTACTCTGTGACAGCGTCTGACAGTGGCCAGCAGCAGCCTGGGCAACCAAGACCTAC ACCTGTAACTGTGGAACCAAGCCAGCAACCAAGGTGGACAAGCGGGTGGAAATCTAAGTAGCGCCCTCCCTGC CCTCTTGGCCAGCCCTGAAGCTGCCGGCGGACCCCTCGTGTCTTCTTCCCGCAAGGCCAAGGACACCCCTGA TGATCAGCCGGACCCCGAAGTACCTGCGTGGTGGTGTGTCTCCAGGAAGATCCCGAGGTGCGAGTTCAATT</p>
3	223		

			GGTACGTGGACGGCGTGAAGTGCACAACGCCAAGACCAAGCCACAGAGAGGAACAGTTCAACAGCACCTACCGG GTGGTTCCTGCTGACCGTGTGCAACAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGGTGTCCAACAAG GGCTGCCACAGTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGGAGCCTCAAGTGTATACCTG CCCCCTGCCAGGAAGATGACCAAGAACAGGTGTCCCTGTGGTGTCTGTGAAGGCTTCTACCCAGCGACA TTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTACAAGACACCCCTGTGTGGACAGCGACG GTCAATTCTTCTGTACTCCAAGCTGACCGGTGGAACAGAGCCGGTGGCAGGAAGGCAACGTGTTCAGCTGCTCCGT GATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCTGTCCCTGGGC GACATCCAGATGACCCAGAGCCCCAGCAGCTGTGCGCAGCGTGGCGACAGATGACCATCACCTGTAGAGCC AGCCAGGACGTGAACACCGCGTGGCTGGTATCAGCAGAAAGCTGGCAAGGCCCAAGCTGTGATCTACAGC GCCAGCTTCTGTACAGCGGGTGGCCAGAGATTACGGGAAGCAGAAAGCGGACCGGACTTCAACCTGACCATC AGTCCCTGACGCCGAGGACTTCGCCACTACTGCCAGCAGCTACACACCCCTCCACATTTGGCCAGG GCACCAAGGTGGAATCAAGCGTACGGTGGCCGCTCCAGCGTGTCTTCCACCTAGCGACGAGCAGCTGA AGTCCGGCACAGCTCTGTGTGCTGTGTGAACAACTTCTACCCCGGAGGCCAAAGTGCAGTGGAAAGGTGG ACAACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTG AGCAGCACCTGACACTGAGCAAGGCCGACTACGAGAAGCAAAAGGTGTACGCTGCGAAAGTGACCCACCAAGG CCTGTACGCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT
HER2/ CD28 _{sup} xCD3 _{mid} (32/33/3435 ENLR (LC); DK1HT linkers on HC/LC) IgG4 FALA BP # 26	1	225	GACATCGTATGACCCAGACCCCTGTAGCCTGAGCGTGAACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCACGAGAACCTGCGTACCTACCTAGCTGGTATCTGCAAGAACCCCGGCCAGAGCCCCAG TCCTGATCTACAAGGTGTCCAACAGATTACGGCGTGGCCGACAGATTCTCCGGCAGCGGCTCTGGCACCCGACT TCACCTGAAGATCAGCGGGTGAAGCCGAGGACGCTGGCGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTACGGCCAGCCAGCAATCATCTAGTGGTGA ACTGGTATCAGCAGAAAGCCCGGCAAGGCCCAAGCTGCTGATCTACAAGGCCAGCAACCTGCAACCCGGCTGC CCAGCAGATTTCTGGCAGCGGCTCCGGCACCGACTTACCTGACATCAGCTCCCTGCAGCCCGAGGACATTGC CACCTACTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTTGGCCAGGCAACCAAGCTGGAAATCAAGGATAA GACCAACCCGTAGCGTGGCGCTCCAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAAGTCCGGCACAC GCCTGTGTGTGCTGCTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGGAGGACAAACCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGCAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAAGTGACCCACCAAGGCGCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT
	2	226	CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTCTGTGAACCTGGCGCTCTGTGAAGGTGTCTTGCAAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTAGCCCAAGAGTTCCAGGGCAGAGCCCTGACCCGTGGACACCAAGC ATCAGCACCCGCTACATGGAACTGAGCCGGTGAAGCGACACCGCGGTGTAATACTGCAACCCCGTCCAC TACGGCTGGAATTGGAATTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTAGCGCAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGAGTGGTGCAGCTGAGAGAGCTGAGAGTGTGCTGCCCGCAGC GGCTTCACTTCAACCAAGGCTGGATGCATGGGTGGCCAGGCCCTTGAAAGCAGCTGGGAATGGGTGGCCCCAG ATCAAGGACAAGAGCAACAGCTACGCCACCTACTACGCCGACAGCGTGAAGGGCCGGTTACCATCAGCCGGGAC

[illegible]

HER2/ CD28 ^{sup} xCD3 ^{mid} (32/33/3435 ENLQ (LC); DKTHT linkers on HC/LC) IgG4 FALA BP # 27	1	229	<p>ACAAAGCCCTGACAGAGCGGCAACAGCCAGGAAAGCGTGACCGGACGACGAGCAAGGACTCCACCTACAGCCTG AGCAGCACCCCTGACACTGAGCAAGCGCCGACTACGAGAAGCAACAAGGTGTACGCTGCGAAAGTGACCCACCAAGG CCTGTCTAGCCCGGTGACCAAGAGCTTCAACCGGGGAGTGTT</p> <p>GACATCGTGATGACCCAGACCCCTGAGCCTGAGCGTGACACCTGGACAGCCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGACGAGAACCTGACAGCACTACCTGAGCTGATCTGCAAGCCCGGCGGAGAGCCCGCAG TCCCTGATCTCAAAGGTGTCACAGATTACGCGGCTGCCCCGACAGATTTCTCCGGCAGCGGCTCTGGCACCCGACT TCACCTTGAAGTACGCGGTGGAAGCCGAGGACGCTGGCGGTGTAATTTGGGCCAGGGCAGCCAGTACCCCT TCACCTTGGCAGCGGCAACAAGTGGAAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCA GCAGCCTGTCTGCCAGCCTGGGCGACAGAGTGACCATACCTGTGAGGCCAGCCAGCAATCTACGTGTGGCTGA ACTGGTATCAGCAGAAAGCCCGGCAAGGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCAACCCGGCGTGC CCAGCAGATTTCTGGCAGCGGCTCCGGCACCGACTTACCTTGACATCAGCTCCCTGACGCCGAGGACATTGC CACTACTACTGCCAGCAGGCGCAGACCTACCTTACACCTTGGCCAGGCAACCAAGCTGGAATCAAGGATAA GACCCACACCGGTAGCGTGGCTCCAGCGTGTTCATCTTCCACCTAGCAGCAGCAGCTGAAGTCCGGCACA GCCTCTGTGCTGCTGCTGAACAATTCTACCCCGGAGGCCAAAGTGCAGTGAAGGTGGAACAACGCCCTGC AGAGCGGCAACAGCCAGGAAAGCTGACCCGAGCAGACAGGACTCCACCTACAGCCTGAGCAGCAGCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAAGTGACCCACCAAGGCGCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGGCGAGTGTT</p>
	2	230	<p>CAGGTGACGCTGGTGCACTGTGGCGCGAGGTGCTGAAACCTGGCGCTCTGTGAAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAAGTACTACATCCACTGGTGGCCAGGCCCTTGACAGGACTTGAATGGATCGGCGAGC ATACCCCGGCAACGTGAACACCACTACGCCAGAAAGTTCAGGGCAGAGCCCTGACCGTGGACACCCAGC ATCAGCACCGCTACATGAACTGAGCGGCTGAGAAGCAGCAGACCCGCTGTACTACTGCACCCCGTCCAC TACGGCCTGGAATTGAACTTCGACGTGTGGGCAAGGCCACACCGTGACAGTGTAGCGACAAACCCATATACC CAGGTGACGCTGGTGAATCTGGCGCGGAGTGTGCAAGCTGGCAAGACCTGAGACTGAGCTGTGCCCGCAGC GGCTTCACTTCAACAAGCCTGGATGCACTGGGTGCGCCAGGCCCTGGAAAGCAGCTGGAATGGTGGCCCCAG ATCAAGGACAAAGACCAACAGTACGCCACCTACTACGCCGACAGCGTGAAGGCCCGGTTACCATCAGCCGGGAC GACAGCAAGAACACCTGTACCTGCAGATGAACAGCCTGGCGGCCGAGGACACCCCGTGTACTACTGTGGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGGAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCCAGCACAAGGGGCCATCGGTGTTCCTTGGCCCTTGACGAGAAAGCAACAGCAATCTACAGCCGCCCT GGGTGCTGCTGAAAGGACTACTTTCGAGCCCTGACCGTGTCTTGGAACTCTGGCGCTCTGACAAAGCGGCGTG CACACTTTCAGCGCTGCCAGAGCAGCGGCTGTACTCTGTAGCAGCGCTGTGACAGTCCCCAGCAGCAGCC TGGGCACCAAGACCTACACTGTAACTGGGACCAAGCCCAAGCAACCAAGTGAACAGCGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGTCCGGGAGCCCTCCGTGTCTTCCCTCCCAAG CCCAAGGACACCTGTATGACCGGACCCCGAAGTGAACCTGCTGGTGGTGGATGTGCCAGGAAGATCCC GAGGTGCACTTCAATTGTAATGGAGCGGCTGGAAGTGCACAACGCCAAGCAACCCAGAGCAAGTTC AACAGCACCTACCGGTGGTGTCCGTGTGACCGTGTGACCAAGACTGGGTGAACCGCAAGAGTACAAGTGC AAGGTGTCCAAACAGGGCCTGCCAGCTCCATCAGAAACCAATCAGCAAGGCCAAGGGCCAGCCCGCGAGCCT CAAGTGTGTAACCTGCCCCCTAGCCAGGAAGATGACCAAGAACCAAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTTACCCCAAGCAGCATTTGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACACTACAAGACCAACCCCT</p>

			<p>GACCCACACCCGTACGGTGGCCGCTCCACGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCACA GCCTCTGTCTGTGCTGTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGAAGGTGGAACAAAGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCAGCACCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACGAGGCCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	234		<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTCTGTGAACCTGGCGCCTCTGTGAAGGTGTCTGTGAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGTGGTGGCCAGGCCCTTGACAGGGACTGGAAATGGATCGGCAGC ATCTACCCCGCAACCGTGAACACCAACTACGCCAGAACTTCCAGGGCAGAGCCACCTGACCCGTGGACACCAGC ATCAGCACCGCTACATGGAATGAGCCGGTGAAGAGCAGCAGCACCCCGTGTACTACTGACCCCGTCCAC TAGGGCTGGATTGGAATCTGACCGTGTGGGCAAGGGCACCAACCGTGACAGTGTCTAGCGACAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGGAGTGGTGCAGCCTGGCAGAAAGCCTGAGCTGAGCTGTGCCGCCAGC GGCTTACCTTACCAAGGCCTGGATGCACTGGGTGCGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGGCCAG ATCAAGGACAAGACAAGTACGCCACCTACTACGCCGACAGCGTGAAGGGCCGGTTACCATCAAGCCGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCGTGACCGTGTCTAGTGATAAGACCCACA CCGCCAGCAAAAGGGCCCATCGGTGTTCCCTCTGGCCCTTGCAGCAGAAAGCAGCGAATCTACAGCCGCCCT GGGTGCCCTGTGAAGGACTACTTCCGAGCCCGTACCGTGTCTGGAACTCTGGCGTCTGACAAAGCGCGTG CACACCTTCCAGCCGTCTCCAGAGCAGCGGCTGTACTCTGAGCAGCGTGTGACAGTCCCAGCAGCAGC TGGCACCAAGACCTACACCTGTAACGTGGACACAAAGCCCAAGCAACCAAGGTGGACAAAGCGGTGGAAATCTA AGTAGGGCCCTCCCTGCTTGGCCAGCCCTGAAGTGCCTGGCGGACCCCTCCGTGTCTCTGTTCCCTCCCAAG CCCAAGGACACCTGATGATCAGCCGACCCCGAAGTGAACCTGCGGTGGTGGTGTCTGCCAGGAATCCC GAGTGCAGTTCAATTGTAACGTGGACGCGGTGGAAGTGCAACGCCAAGACCAAGCCAGAGAACAGACATTC AACAGCACCTACCGGGTGGTGTCCGTGTGACCGTGTGACCAAGGACTGGCTGAACGGCAAGAGATCAAGTGC AAGGTGTCCAAACAAGGGCCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGGAGCCT CAAGTGTGTACCCCTGCTAGCCAGGAAGATGACCAAGAACCCAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCCAAGCAGATTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTAAGACCAACCCCTCT GTGCTGGACAGCGACGGCTCATTTCTGTTGTCCAAAGTGAACCGTGGACAAAGCCGTGGCAGGAAGGCCAAC GTGTTCAGCTGTCCGTGATGCACGAGGCCCTGCACCAACCACTACACCAAGATCCCTGTCTCTGTCCTGGGC GAAGTGCAGCTGGTGAATCTGGCGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGAGCTGTGCCCGCCAGC GGCTTCAACATCAAGGACACCTACATCCACTGGGTGGCCAGGCCCTTGGCAAGGGAATGGGTGGCCAGA ATCTACCCCAACCAACGGCTACACAGATACCGCGACAGCGTGAAGGCCCGGTTCAACCATCAGCCCGCACACAGC AAGAACACCCGCTACCTGCAGATGAACAGCTCGCGCGGAGGACACCCGCTGTACTGTAGTAGTGGGA GGCAGCGCTTCTACGCCATGGAATATTGGGGCCAGGGCACCCCTGTGACCGCTGTCTAGTGCCTGACCAAGGGCC CATCGGTGTCCCTCTGGCCCTTGCAGCAGAACCAAGCAGCAATCTACAGCCCGCTGGGTGCCTCGTGAAGGA CTACTTCCCGAGCCCGTGAACCGTGTCTTGAACTCTGGCGCTCTGACAAAGCGGCTGCACACCTTTCAGCCGTG CTCCAGAGCAGCGGCTGTACTCTGTGACAGCGTCTGACAGTGGCCAGCAGCAGCCTGGGCACCAAGACCTAC ACCTGTAAACGTGGACCAAGCCCAAGCAACCAAGGTGGACAAAGCGGTGGAAATCTAAGTACGGCCCTCCCTGC CCTCTTGGCCAGCCCTGAAGCTGCGGGGGAACCTCGTGTCTGTTCCCTCCCAAGGCCAAGGACACCCCTGA TGATCAGCCGACCCCGAAGTGAACCTGCGTGGTGGTGTGTCCTCCAGGAAGATCCCGAGGTGCGAGTTCAATT</p>
3	235		

			GGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCACAGAGAGGAACAGTTCAACAGCACCTACCGG GTGGTGTCCGTGCTGACCGTGTGCAACAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGGTGTCCAACAAG GGCTTGGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAAGGCCGAGCCCGGAGCCTCAAGTGTATACCTG CCCCCTTGGCAGGAAGATGACCAAGAACAGGTGTCCCTGTGGTGTCTGTGAAGGCTTCTACCCAGCGACA TTGCCGTGGAATGGGAGACAACGGCCAGCCCGAGAACTACAAGACACCCCTGTGTGGACAGCGACG GTCAATTCTTCTGTACTCCAAGCTGACCGGTGGAACAGAGCCGGTGGCAGGAAGGCAACGTGTTCAGTGTCTCCGT GATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCTGTCCCTGGGC GACATCCAGATGACCCAGAGCCCCAGCAGCTGTGCGAGCGTGGCGACAGATGACCATCACCTGTAGAGCC AGCCAGGACGTGAACACCGCGTGGCTGGTATCAGCAGAAAGCTGGCAAGGCCCCCAAGCTGTGTATACAGC GCCAGCTTCTGTACAGCGGGTGGCCAGAGATTACGGGAAGCAGAAAGCGGACCGGACTTCAACCTGACCATC AGTCCCTGCAGCCGAGGACTTCGCCACTACTACTGCCAGCAGCTACACACCCCCCACAATTGGCCAGG GCACCAAGGTGGAATCAAGCGTACGGTGGCCGTCCAGCGTGTCTTCCACCTAGCGACGAGCAGCTGA AGTCCGGCACAGCCTGTGTGTGTCTGTGAACAACTTCTACCCCGGAGGCCAAAAGTGCAGTGGAAAGGTGG ACAACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTG AGCAGCACCTGACACTGAGCAAGGCCGACTACGGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACACAGG CCTGTACGCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT
anti- Her2/CD3/3CD2 8 IgG4 FALA BP # 29	1	237	GACATCGTATGACCCAGACCCCTGAGCCTGAGCGTGAACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCAACAACGCCAACACCTACCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCAG TCCTGATCTACAAGGTGTCCAACAGATTACGGCGTGGCCGACAGATCTCCGGCAGCGGCTCTGGCACCCGACT TCACCTGAAGATCAGCCGGGTGGAAGCCGAGGACGTGGCGTGTACTATTGGGCCAGGGCACCCAGTACCCCT TCACCTTGGCAGCGGCAACCAAGGTGGAATCAAGGGCCAGCCCAAGGCCGCCCGCACATCCAGATGACCCAGA GCCCAAGCAGCCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTCAAGGCCAGCCAGCAATCATCTGT GGCTGAACCTGGTATCAGCAGAAAGCCCGGCAAGGCCCCCAAGCTGTGTATCTACAAGGCCAGCAACCTGCACACCG GGTGCCCAAGCAGATTTCTGGCAGCGGCTCCGGCACCGACTTACCTGACATCAGCTCCCTGCAGCCCCGAGGA CATTGCCACCTACTTGCCAGCAGGGCCAGACCTACCTTACCTTGGCCAGGGCACCAAGCTGGAATCAAG ACCAAGGCCCCAGCCGTACGGTGGCCGTCCAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCG GCACAGCCTGTGTGTGTGTGAACAACTTCTACCCCGGAGGCCAAAAGTGCAGTGGAAAGTGGACAACG CCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGC ACCTTGACACTGAGCAAGGCCGACTACGGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACACAGGCGCTGTCT AGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT
	2	238	CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTCTGTGAACCTGGCGCTCTGTGAAGGTGTCTTGCAGAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTAGCCCAAGAGTTCCAGGGCAGAGCCCTGACCCGTGGACACCAAGC ATCAGCACCCGCTACATGGAACTGAGCCGGTGAAGCGACACCGCGGTACTACTGCAACCCCGTCCAC TACGGCCTGGAATTGAACTTCGCTGTGGGCAAGGGCACACCGCTGACAGTGTAGCAGCGAGGTGCAGCTG GTGGAATCTGGCGGCGAGTGTGACGCTGGCAGAAAGCTGAGCTGAGTGTGCCCGCAGCGGCTTCACCTTC ACCAAGGCCTGGATGCATGGGTGGCCAGGCCCTGGAAAGCAGCTGGAATGGGTGGCCAGATCAAGGACAA GAGCAACAGCTACGCCACCTACTACGCCGACAGCGGTGAAGGGCGGTTACCATCAGCCCGGACGACAGCAAGAA

HER230R/55Q/1 02E/ CD28 _{sup} xCD3 _{mild} (32/33/3435 ENLR (LC); DKTH linkers on HC/LC) IgG4 FALA BP # 31	1	241	<p>ACAAAGCCCTGCAGAGCGGCAACAGCCAGGAAAGCGTGACCGGACGAGGACAGCAAGGACTCCACCTACAGCCTG AGCAGCACCCCTGACACTGAGCAAGCGCCGACTACGAGAAGCACAAAGGTGTACGCTGCGAAAGTGACCCACCAAGG CCTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p> <p>GACATCGTGATGACCAAGACCCCTGAGCCTGAGCGTGAACCTGGACAGCCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGACGAGAACCTGCTGCTACCTACCTGAGTGTGATCTGCGAAGCCCGGCCAGAGCCCCCAG TCCCTGATCTCAAAGGTGTCACAGATTACGCGGCTGCCCCGAGATTTCCGGACGCGCTCTTGCCACCCGACT TCACCTTGAAGATCAGCCGGGTGGAAGCCGAGGACGCTGGCGGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTTGGCAGCGGCAACAAAGTGGAAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGGCGACAGAGTGACCATACCTGTCAAGCCAGCCAGCAACATCTACGTGTGGCTGA ACTGGTATCAGCAGAAAGCCCGGCAAGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCCGGCTGC CCAGCAGATTTCTGGCAGCGGCTCCGGCACCGACTTACCTTACCTTGGCCAGGCAACCAAGCTGGAATCAAGGATAA CACTACTACTGCCAGAGGCGAGACCTACCTTACCTTGGCCAGGCAACCAAGCTGGAATCAAGGATAA GACCCACACCGGTAGCGTCCAGCGGTTCATCTTCCACCTAGCAGCAGCAGCTGAAAGTCCGGCACA GCCTCTGTGCTGCTGTGAACAATTCTACCCCGGAGGCCAAAGTGCAGTGGAAAGGTGGAACAACGCCCTGC AGAGCGGCAACAGCCAGGAAAGCTGACCCGAGCAGGACAGGACTCCACCTACAGCCTGAGCAGCAGCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAAGTGACCCACCAAGGCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
	2	242	<p>CAGGTGCAGCTGGTGCACTGGCGCGAGGTGCTGAAACCTGGCGCTCTGTGAAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAAGTACTACATCCACTGGTGGCCAGGCCCTTGACAGGACTTGAATGGATCGGCGAGC ATACCCCGGCAACGTGAACCAACTACGCCAGAGTTCCAGGGCAGAGCCCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGAACTGAGCCGGTGAAGCGACACACCGCGTGTACTACTGCACCCCGTCCCAC TACGGCCTGGATTGAACTTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTAGCGACAAACCCATATACC CAGGTGCAGCTGGTGAATCTGGCGGCGGAGTGTGCAAGCTGGCAAGAGCCTGAGACTGAGCTGTGCCCGCAGC GGCTTCACTTCAACCAAGCCTGGATGCACTGGGTGGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGCCCCAG ATCAAGGACAAAGACCAACAGTACGCCACCTACTACGCCGACAGCGTGAAGGCCCGGTTCACCATCAGCCGGAC GACAGCAAGAACACCTGTACCTGCAGATGAACAGCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCGGGC GTGTACTATGCCCTGAGCCCCCTCGATTACTGGGGCCAGGGAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCCAGCAACAAAGGGCCCATCGGTGTCCCTTGGCCCCCTTGACGACAGAAACACAGCAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTCCGAGCCCCGTGACCGTGTCTTGAACTCTGGCGCTCTGACAAAGCGCGGTG CACACTTTCAGCCGTGCTCCAGAGCAGCGGCTGTACTCTGTAGCAGCGCTGTGACAGTCCCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGTAACTGGGACCAACAGCCACCAACCAAGGTGGACAAAGCGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCCCTGAAGTCCGGCGGACCCCTCCGTGTCTTCCCTCCCAAG CCCAAGGACACCTGTATGACCGGACCCCCGAAGTGAACCTGCTGGTGGTGGATGTGCCAGGAAGATCCC GAGGTGCAGTTCAATTGTAACGTGAGCGGCTGGAAGTGCACACGCCAAGACCCAGCAGCAGCAAGTTC AACAGCACCTACCGGTGGTCCGTGCTGACCGTGCACCAAGACTGGCTGAACCGCAAGAGTACAAGTGC AAGGTGTCCAAACAGGGCCTGCCAGCTCCATCAGAAACCAATCAGCAAGGCCAAGGGCCAGCCCCCGAGCCT CAAGTGTGTACCTGCCCTAGCCAGGAAGATGACCAAGAACCAAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTTACCCCCAGCGACATTGCCGTGGAATGGGAGAGCAACGGCCAGCCCCGAGAACAACTACAAGACCAACCCCCCT</p>

				GTGCTGGACAGCGACGGCTCATTTCTTCTGGTGTCCAAAGTGAACGGTGGACAAAGAGCCGGTGGCAGGAAGGCAAC GTGTTACAGCTGCTCCGTGATGACGAGGCGCTGCACAAACCACTACACCCAGAAAGTCCCTGTCTGTCTGCTGGC
	3	243		GAAGTGCAGCTGTGTGGAATCTGGCGGGGGAATGGTGACGCCTGGCGGATCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCAACATCCGGGACACCTACATCCACTGGGTGCGCCAGGCCCTGGCAAGGGAAGTGGGTGGCCAGAG ATCTACCCCAACCCAGGGTACACAGATACGCGACAGCGTGAAGGCGCGTTCCACATAGCGCGGACACCGAGC AAGAACCCGCTACTGCAGATGAACAGCTGCGGGCCGAGGACACCGCTGTACTACTGTAGTAGATGGGA GGCGAAGGCTTCTACGCCATGGACTATTGGGGCCAGGCCCTGTGACCCGTGTACTGTGCTGACCAAGGGC CCATCGGTGTTCCCTCTGGCCCCCTTGGACAGAGAACACAGCGAATCTACAGCCGCCCTGGGTGCTGCTGTAAGG ACTACTTTCGAGAGCCCGTGAACCGTGTCTGGCACTCTGGCGCTCTGACAAAGCGCGTGCACACCTTTCAGCCGT GCTCAGAGCAGCGGCTGTACTCTGTAGCAGGCTGTGACAGTGCCCAAGCAGCAGCTGGGCAACCAAGACCTA CACCTGTAACTGTGACCAAGCCCCAGCAACACCAAGGTGGACAAAGCGGTGGAATCTAAGTACGGCCCTCCCTG CCCTCTTGGCCAGCCCTGAAGCTGCGGGGAGCCCTCCGTGTCTGTCTTCCGCCAAAGCCAAAGGACACCCCTG ATGATCAGCGGACCCCGAAGTGAACCTGCGTGGTGGTGGTGTGTCAGGAAGATCCCGAGGTGCAGTTCAAT TGGTACGTGGACGGCTGGAAGTGCACAAACGCCAAGACCAAGCCACAGAGAGAAACAGTTCAACAGCACCTACCG GGTGGTGTCCGTGCTGACCGTGTGACCCAGGACTGGCTGAACGGCAAGAGTACAAGTGAAGGTGTCCAACAA GGGCTTGCCAGCTCCATCGAGAAAACCATCAGCAAGGCCAAAGGCCAGCCCGGAGCTCAAGTGTATACCT GCCCTTGGCAGGAAGAGATGACCAAGAACAGGTGTCCCTGTGTGTCTGTGTAAGGCTTCTACCCACAGCGAC ATTGCCGTGGAATGGGAGAGCAACGGCCAGCCCGGAACAACTACAAGACACCCCTGTGTGCTGGACAGCGAC GGCTCAITTCCTGTACTCCAAGCTGACCGTGGACAAAGCGCGTGGCAGGAAGGCAACGTGTTCAGCTGCTCCG TGATGACGAGGCCCTGCACAAACCACTACACCCAGAAAGTCCCTGTCTGTCTCCCTGGGC
	4	244		GACATCCAGATGACCCAGAGCCCCAGCAGCCTGTCTTGGCAGCGTGGGCGACAGAGTGACCATCACCTGTAGAGCC AGCCAGGACGTGAACACCGCGTGGCTGGTATCAGCAGAAGCCTGGCAAGGCCCAAGCTGTGATCTACAGC GCCAGCTTCTGTACAGCGGCTGCCAGCAGATTCAGCGGAAGCAGAAAGCGGCAACCGACTTCACTGACCATC AGTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGCTACACCAACCCCGCCACATTTGGCCAGG GCACCAAGGTGGAATCAAGCGTACGGTGGCGCTCCAGCGTGTCTATCTTCCACCTAGCGACGAGCAGCTGA AGTCCGGCACAGCCTCTGTGTGTGCTGTGTAACAACTTCTACCCCGCAGGCCAAAGTGCAGTGGAAAGTGG ACAACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGGACAGCAAGGACTCCACCTACAGCCTG AGCAGCACCCCTGACACTGAGCAAGGCCGACTACGAGAAGCAACAGGTGTACGCTGCGAAAGTGACCCACAGGG CCTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT
CD38VH1 CD28sup CD3mid_ENLQ DKTHT_IgG4 FALA BP # 1	/ x ENLQ IgG4	1	245	GACATGATGATGACCCAGACCCCTGTAGCCTGAGCGTGAACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGTGGTCAGCAACCTGTTCACTTACCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCAG TCCCTGATCTACAAGGTGTCCAACAGATTCAGCGGCTGCCAGCAGATTCCTCGGACAGCGGCTCTGGCACCCGACT TCACCTGAAGATCAGCCGGGTGGAAGCCGAGGACGTGGCGTGTACTATTGTGGCCAGGGCAACCCAGTACCCCT TCACCTTTGGCAGCGGCAACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATCCAGATGACCCAGGCCCA GCAGCCTGTCTGCCAGCGTGGGCAAGAGTGACCATCTACCTGTCAAGGCCAGCCAGAACATCTACGTGTGGCTGA ACTGATATCAGCAGAAAGCCCGCAAGGCCCTCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCGCGCTGC CCAGCAGATTTTCTGGCAGCGGCTCCGGCACCGACTTCACTTCACTGCAATCAAGTCCCTGCAGCCCGAGGACATTGC CACCTACTACTGCCAGCAGGGCGAGACCTTACCCCTACACCTTGGCCAGGGCAACCAAGCTGGAAATCAAGGATAA

			<p>GACCCACACCCGTACGGTGGCCGCTCCACAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCACA GCCTCTGTCTGTGCTGTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGAAGGTGGAACAAAGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCAGCACCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACAGGCCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	246		<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGCTGAAACCTGGCGCCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGGTGGCCAGGCCCTTGACAGGACTGGAAATGGATCGGCAGC ATCTACCCCGCAACCGTGAACACCAACTACGCCAGAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCAGC ATCAGCACCGCTACATGGAATGAGCCGCTGAGAGCGACGACACCGCCGTGTACTACTGACCCCGTCCAC TAGGGCTGGATTGGAATCTCGACCTGTGGGGCAAGGGCACCAACCGTGACAGTGTCTAGCGACAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGGAGTGGTGACGCTGGCAGAAAGCCTGAGCTGAGCTGTGCCGCCAGC GGCTTACCTTCAACAGGCCTGGATGCATGGGTGCGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGGCCAG ATCAAGGACAAGACAAGTACGCCACCTACTACGCCGACAGCGTGAAGGGCCGGTTACCATCAAGCCGGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGTACCGTGTCTAGTGATAAGACCCACA CCGCCAGCAAAAGGGCCATCGGTGTTCCCTTGGCCCTTGCAGCAGAAAGCAGCGAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTTCGAGCCCGTACCGTGTCTGGAACCTGTGGCGTCTGACAAGCGCGGTG CACACCTTTCAGCGGTCTCCAGAGACGCGCCTGTACTCTGAGCAGCGTGTGACAGTGCCAGCAGCAGCAGC TGGCACCAAGACCTACACCTGTAACTGGGACCAAGCCACCAAGCTGACCAAGCTGGACAAAGCGGTGGAAATCTA AGTAGGGCCCTCCCTGCCCTTGGCCAGCCCTGAAGTCCCGCGGACCCCTCCGTGTCTCTGTTCCCTCCCAAG CCCAAGGACACCTGTAGTACGCGGACCCCGAAGTGACCTGCGTGGTGGTGTGTGTCTCCAGGAATCCC GAGTGCAGTTCAATTGTGACGTGGACGCGGTGGAAGTGCAACGCCAAGACCAAGCCAGAGAGAACAGATTC AACAGCACCTACCGGGTGTCTCGTGTGACCGTGTGACCAAGGACTGGCTGAAACGGCAAGAGTACAAGTGC AAGGTGTCCAAACAAGGGCCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGCAGCCT CAAGTGTGTACCCCTGCCCTAGCCAGGAAGATGACCAAGAACCCAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCACGCAATTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCAACCCCTCT GTGCTGGACAGCGACGGCTCATTTCTCTGTGTCCAAAGTGAACGTGACCGTGGACAAGAGCCGTGGCAGGAAGGCAAC GTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACTACACCAAGAGTCCCTGTCTCTGTCCCTGGGC</p>
3	247		<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAAGTCTGAAACCTGGCGCCTCCGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACGCCATGCATGGGTCAAAGAGCCCTTGGCCAGAGACTGGAAATGGATCGGCTAC ATCTACCCCGCCAGGGCGCACCAACTACAACCAAGTTCCAGGGCAGAGCCACCTGACCCCGCATACAAGC GCCAGCACCGCTACATGGAACCTGAGCAGCTGCGGAGGATACCGCCGTGTACTTCTGTGCGAGAACAGGC GGCCTGAGGGGGCCTACTTTACTATTGGGGCCAGGGCAGCTCTGACCGTGTCTACCGCTAGCAACAAAGGCC CATCGGTGTCCCTCTGGCCCTTGCAGCAGAACCAAGCAGCAATCTACAGCCGCCCTGGGTGCCTCGTGAAGGA CTACTTTCGAGCCCGTGAACGTGTCTTGAACCTCTGGCGCTCTGACAAAGCGGTGTCACACCTTTCCAGCCGTG CTCCAGAGCAGCGCCTGTACTCTGTGACAGCGTCTGACAGTGGCCACGACAGCAGCTGGGCACCAAGACCTAC ACCTGTAACTGTGACCAAGCCCAAGCAACCAAGGTGGACAAAGCGGTGGAAATCTAAGTAGGCCCTCCCTGC CCTCTTGGCCAGCCCTGAAGCTGCGGGGACCCCTCGTGTCTCTGTTCCCTCCCAAGGCCAAGGACACCCCTGA TGATCAGCCGACCCCGAAGTACCTGCGTGGTGGTGTGTCCAGGAAGATCCCGAGGTGCGAGTTCAATT</p>

			GGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTACCGG GTGGTGTCCGTGCTGACCGTGTGACACAGGACTGGCTGAACGGCAAGAGTACAAGTCAAGGTGTCCAACAAG GGCTTGGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGGCCGAGCCTCAAGTGTATACCTG CCCCCTTGGCAGGAAGATGACCAAGAACAGGTGTCCCTGTGGTGTCTGTGAAGGCTTCTACCCAGCGACA TTGCCGTGGAATGGGAGACAACGGCCAGCCCGAGAACAACTACAAGACACACCCCTGTGTGGACAGCGACG GTCAATTCTTCTGTACTCCAAGCTGACCGGTGGAACAGAGCCGGTGGCAGGAAGGCAACGTGTTCAGCTGTCCGT GATGCACGAGGCCCTGCACAACCACTACACCCAGAAAGTCCCTGTCTGTCCCTGGGC
	4	248	GACATCGTGTGACACAGAGCCCTGCCACCTGTCTGTAGCCCTGGCGAGAGAGGCCACCATCAGCTGTAGAGCC AGCCAGAGCGTGTCCAGCTACGGCCAGGGCTTCATGCACTGTATCAGAGAACCCCGGCCAGCCCCCAGACTG CTGATCTATGGCGCCAGCAGCAGAGCCACAGGCATCCCCGCCAGATTCTTGGCTCTGGCAGCGGACCGACTTCA CCCTGACAAATCAGCCCCCTGGAAACCGAGGACTTCGCCGTGTACTGTCAGCAGAAACAAAGAGGACCCCTGGA CCTTCGGCGGAGGCCACCAAGCTGGAAATCAAGCTACGGTGGCCGCTCCAGCGTGTTCATCTTCCACCTAGCGA CGAGCAGCTGAAGTCCGGCACAGCTCTGTGTGTGCTGTGAACAATTCTACCCCGGAGGCCAAGGTGCAG TGGAAAGTGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCAC CTACAGCTGAGCAGCACCTGACCCCTGTCCAAGCGCGATTACGAGAAAGCAAGGTGTACGCGTACGCGCTGCGAAGTGAC CCACAGGGCCTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGGAGTGC
CD38 ^{hly992} / CD28 ^{sup} x CD3 ^{mid} _ENLQ DK ^{TH1} IgG4 FALA BP # 5	1	249	GACATCGTGTGATGACCCAGACCCCTGTAGCCCTGAGCGTGAACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCACGAGAACCTGCAGACCTACCTGAGCTGGTATCTGCAGAACCCCGGCCAGAGCCCCAG TCCTGATCTACAAGGTGTCCAACAGATTACGGCGCTGCCGACAGATTCTCCGGCAGCGGCTCTGGCACCCGACT TCACCTGAAGATCAGCGGGGTGGAAAGCCGAGGACGTGGCGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTGGCAGCGGCCACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTCAAGCCAGCCAGCAACATCTACGTGTGGTGA ACTGGTATCAGCAGAAAGCCCGGCAAGGCCCCCAAGCTGTGTATCTACAAGGCCAGCAACCTGCAACCCGGCTGC CCAGCAGATTTCTGGCAGCGGCTCCGGCACCCGACTTACCTTACCAATCAGCTCCCTGCAGCCCGAGGACATTGC CACCTACTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTTGGCCAGGCCACCAAGCTGGAAATCAAGGATAA GACCCACACCCGTACGGTGGCCGCTCCAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAAGTCCGGCACA GCCTCTGTGTGCTGCTGTGAACAATTCTACCCCGCGAGGCCAAAGTGCAAGTGGAGGACAAACCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGACAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAGCACAAGGTGTACGCTGTGCGAAGTGACCCACAGGGCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGGAGTGT
	2	250	CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTCTGTGAACCTTGGCGCCTCTGTGAAGGTGTCTTGC AAGGCCAGC GGCTACACCTTTACAGCTACTACATCCACTGGGTGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTAGCCCAAGAGTTCCAGGGCAGGCCACCTGACCCGTGGACACCAAGC ATCAGCACCCGCTACATGGAACTGAGCCGGTGAAGCGACACCGCGTGTACTACTGCAACCCCGTCCAC TACGGCTGGAATTGGAATTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTAGCGCAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGAGTGGTGCAGCCTGAGAGAGCCTGAGAGTGTGCTGCCCGCAGC GGCTTCACTTCAACCAAGGCCTGGATGCATGGGTGCCAGGCCCTTGGAAGCAGCTGGGAATGGGTGGCCCCAG ATCAAGGACAAGAGCAACAGCTACGCCACCTACTACGCCGACAGCGTGAAGGGCCGCTTACCATCAGCCGGGAC

178

CD38 ^{hyb} 5739 / CD28 ^{sup} x CD3 ^{mid} ENLQ DKTHT IgG4 FALA BP # 6	1	253	<p>GACAAAGCCCTGACAGCGGCAACAGCCAGGAAAGCGTGACCGGACAGGACAGCAAGGACTCCACCTACAGCCT GAGCAGCACCCCTGACACTGAGCAAGGCCGACTACGAGAAAGCACAAAGGTGTACGCTGCGAAAGTGACCCACAGG GCCGTGTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p> <p>GACATCGTGATGACCCAGACCCCTGAGCCTGAGCGTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCACGAGAACCTGACAGCACTACCTGAGCTGATCTGCAAGCCCGGCCAGAGCCCCCAG TCCCTGATCTCAAAGGTGTCACAGATTACAGCGGCTGCCCCAGAGATTCTCCGGCAGCGGCTCTGGCACCCGACT TCACCTGAAGATCAGCCGGGTGGAAGCCAGGACGCTGGCGGTGTAATTTGGGCCAGGGCAGCCAGTACCCCT TCACCTTGGCAGCGGCAACAAAGTGGAAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCCTGGGCGACAGAGTGACCATACCTGTACGGCCAGCCAGCAATCTACGTGTGGCTGA ACTGGTATCAGCAGAAAGCCCGGCAAGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCCGGCTGC CCAGCAGATTTCTGGCAGCGCTCCGGCACCGACTTACCTTGACAATCAGCTCCCTGCAGCCCGAGGACATTGC CACTACTACTGCCAGCAGGCGACACCTACCCCTACACCTTTGGCCAGGCAACCAAGCTGGAATCAAGGATAA GACCCACACCCGTAGCGTGGCTCCAGCGTGTTCATCTTCCACCTAGCGACGACGACTGAAGTCCGGCACA GCCTCTGTGCTGCTGCTGAACAATTCTACCCCGGAGGCCAAAGTGCAGTGGAAAGGTGGACAACGCCCTGC AGAGCGGCAACAGCCAGGAAAGCTGACCCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACGCTGCGAAAGTGACCCACCAAGGGCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p> <p>CAGGTGCAGCTGGTGCACTGTGGCGCGAGGTGTAACCTGGCGCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAAGTACTACATCCACTGGTGGCCAGGCCCTTGACAGGGACTGGAATGGATCGGCGAGC ATACCCCGGCAACGTGAACACCACTACGCCAGAGTTCCAGGGCAGAGCCCTGACCCGTGGACACCCAGC ATCAGCACCGCTACATGAACTGAGCGGCTGAGAAGCAGCAGCACCGCGTGTACTACTGCACCCGTTCCAC TACGGCTGATTTGAACTTCGACGTGTGGGCAAGGCCACACCGTGACAGTGTAGCGACAAACCCATATACC CAGGTGCAGCTGGTGAATCTGGCGGCGGAGTGTGCAAGCTGGCAAGACCTGAGACTGAGCTGTGCCCGCAGC GGCTTCACTTCAACAGCCCTGGATGCACTGGGTGGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGCCCCAG ATCAAGGACAAAGACCAACAGTACGCCACCTACTACGCCGACAGCGTGAAGGCCCGGTTACCATCAGCCGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCTTGGCGGCCGAGGACACCCCGTGTACTACTGTGGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGTGACCGCTGTAGTATAAGACCCACA CCGCCAGCACAAAGGGCCCATCGGTGTCCCTTGGCCCTTGACGACAGAAACCAAGCAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTCCGAGCCCTGACCGTGTCTTGAACTCTGGCGCTCTGACAAAGCGGCGTG CACACTTTCAGCCGTGCTCCAGAGCAGCGGCTGTACTCTGTAGCAGCGCTGTGACAGTCCCCAGCAGAGCC TGGGCACCAAGACCTACACCTGTAACTGGGACCAACAGCCCAAGCAACCAAGTGGACAAAGCGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCTGAAGTCCGGCGGACCTCCGTGTCTCCCTCCCTCCCTCCCTCCCT CCCAAGGACACCCCTGATGACGCCGACCCCGAAGTGAACCTGCTGGTGGTGGATGTGCCAGGAAGATCCC GAGGTGCAGTTCAATTGGTACGGCGGTGGAAGTGCAACACGCCAAGCAACGCCAGAGAGAGCAAGTTC AACAGCACCTACCGGGTGGTCCGTGCTGACCGTGCACCAAGACTGGCTGAACCGCAAGAGTACAAAGTGC AAGGTGTCACAAAGGGCTGCCAGCTCCATCAGAAACCAATCAGCAAGGCCAAGGGCCAGCCCCGCGAGCCT CAAGTGTACCTGCCCTAGCCAGGAAGATGACCAAGAACCAAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTTACCCCAAGCGACATTGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCAACCCCT</p>
	2	254	

			<p>GTGCTGGACAGCGACGGCTCATTTCTTCTGGTGTTCCAAAGCTGACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAAC GTGTTACAGCTGCTCCGTGATGACGAGGCGCTGCACAAACCACTACACCCAGAAAGTCCCTGTCTCTGCTCCCTGGG</p>
	3	255	<p>CAGGTTACAGCTGACAGCTGTGGCCCGAACTCTGTAGACTTGGACCTTGTGAAGGTGTCTGCAAGGCCAGCG GCTACGCCCTTTACCACCTACCTGGTGAATGGATCAACGAGAGGCTTGGACAGGGCCCTCGAGTGGATCGGAGTGA TCAATCTTGGCAGCGCAACCACTACACGAGAGTTTCAAGGCAAGCCACACTGACCGTGGACAGAAAGC AGCACACAGCCTACATGACACCTGAGCGCCCTGACCTGTATGACAGCGCGTGTCTTCTGCGCCAGATACGCCCT ATGGCTATTGGGGCCAGGGCACAAACCTGACCCGTGACCTGTGCTGACCAAGGGCCCACTGGGTTCCTCTCTGGC CCCTTGACAGAAAGCACCAGCAATCTACAGCGCCCTGGGCTGCCGTGGAAGGACTACTTTTCCGAGCCCGTG ACCGTGTCTGGAACTCTGGCGCTCTGACAAAGCGCGTGCACACTTTCCAGCCGTGCTCCAGAGCAGCGCCCTGT ACTCTTGACAGCGTGTGACAGTGCCCAAGAGCCCTGGGCCACCAAGACCTACACCTGTAACTGTGGACCA AGCCAGCAACACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCCCTCCCTGCCCTCCTTGGCCAGCCCTG AAGCTGCCGGGACCCCTCCGTGTCTGTTCCTCCCAAGCCCAAGGACACCTGATGATCAGCCGACCCCGA AGTGACCTGGTGGTGGATGTGTCTCCAGGAAGATCCGAGGTGACGTTCAATTGGTACGTGGACGGCGTGG AGTGACAAACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACTACCGGGTGGTGTCCGTGACCGT GCTGCACAGGACTGGCTGAACGGCAAGAGTCAAGTGCAAGGTGTCCAAAGGGCTGCCAGCTCCATCGA GAAACCATCAGCAAGGCCAAGGCCAGCCCGCAGCTCAAGTGTATACCTGCCCTTGGCCAGGAAGAGAT GACCAAGAACCAAGGTGTCCCTGTGGTGTCTGTGAAAGGCTTCTACCCAGCGACATTTGCCGTGGAATGGAGAG CAACGGCCAGCCGAGAACAACTACAAGACCAACCCCTGTGCTGGACAGCGAGGCTCAATTTCTCTGTACTCC AAGCTGACCGTGGACAAGAGCCGTGGCAGGAAGCAACCTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGTCAC AACCATACACCCAGAGTCCCTGTCTGTCCCTGGG</p>
	4	256	<p>GACATCGTGATGACCCAGAGCCAGAAATTCATGAGCCAGCGTGGGCGACAGAGTGTCCATCATGTAAAGCC AGCCAGAACGTGGGCACAGCCGTGGTGTGATCAGCAGAGCCCTGGCCACTCTCTAAGCAGCTGATCTACAGC GCCAGCAACAGATACACCGCGTGGCGATAGATTCACAGGATCTGGGCGCGGAACCGACTTCAACCTGACCATC AGCAACATCCAGAGCGAGGACCTGGCCGACTACTTCTGCCAGCAGTACAGCACATACCCCTTCACTTTGGCAGCG GCACCAAGCTGGAATCAAGCGTACGGTGGCCGCTCCAGCGTGTTCATCTTCCCACTAGCGACGACGAGCTGA AGTCCGGCACAGCCTCTGTCTGTGCTGTGTAACAACTTCTACCCCGCGAGGCCAAAGTGCAAGTGAAGGTGG ACAACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTG AGCAGCACCTGACACTGAGCAAGGCCGACTACGAGAAGCAAGGTGTACGCTGCGAAGTGACCCACCAAGGG CCTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTG</p>
CD38hyb6284 / CD28sup x CD3mid_ENLO DK'THT IgG4 FALA BP # 7	1	257	<p>GACATCGTGATGACCCAGACCCCTTGAGCCTGAGCGTGACACCTGGACAGCCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGTGTCAGAGAACCTGCAGACCTACCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCAG TCCCTGATCTACAAGGTGTCCAACAGATTCAGCGCGTGGCCGACAGATTTCCGGCAGCGGCTCTGGCAGCCGACT TCACCTGAAGATCAGCGGTGGGAAGCCGAGGACGTGGCGTGTACTATTGTGGCCAGGGCAACCAAGTACCCCT TCACCTTTGGCAGCGGCAACAAAGGTGGAAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGCGACAGGTGACCATCACCTGTCAAGGCCAGCCAGAACATGATACCTGTGGCTGA ACTGATATCAGCAAGAGCCCGCAAGGCCCAAGCTGTGATCTACAAGGCCAGCAACCTGACACCCGGCGTGC CCAGCAGATTTTCTGGCAGCGGCTCCGGCAGCGACTTACCCCTGACAATCAAGCTCCCTGCAGCCCGAGGACATTGC CACCTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTGGCCAGGGCACCAAGCTGGAAATCAAGGATAA</p>

			<p>GACCCACACCCGTACGGTGGCCGCTCCACAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCACA GCTCTGTGCTGCTGCTGTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGAAGGTGGACAACAGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCAGCACCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGAACCCACAGGCCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	258		<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGTGAAACCTGGCGCCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGGTGGCCAGGCCCTTGACAGGACTGGAAATGGATCGGCAGC ATCTACCCCGCAACCGTGAACACCAACTACGCCAGAGTTCCAGGCCAGAGCCACCTGACCCGTGGACACCAGC ATCAGCACCGCTACATGGAACCTGAGCCGCTGAGAGCGACGACACCGCCGTGTACTACTGACCCCGTCCAC TAGGGCTGGATTGGAACCTTCGACGTGTGGGGCAAGGGCACCAACCGTGACAGTGTCTAGCGACAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGGAGTGGTGACGCTGGCAGAAAGCCTGAGCTGAGCTGTGCCGCCAGC GGCTTCACTTACCAAGGCCTGGATGCATGGGTGCGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGGCCAG ATCAAGGACAAGACAAGTACGCCACCTACTACGCCGACGCGTGAAGGGCCGGTTACCATCAAGCCGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCGTGACCGTGTCTAGTGATAAGACCCACA CCGCCAGCAAAAGGGCCCATCGGTGTTCCCTTGGCCCTTGCAGCAGAAAGCAGCGAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTTCGAGCCCGTACCGTGTCTGGAACTCTGGCGCTCTGACAAGCGCGGTG CACACCTTTCAGCGGTCTCCAGAGACAGCGCCTGTACTCTGAGCAGCGTGTGACAGTGCCAGCAGCAGC TGGCACCAAGACCTACACCTGTAACTGGGACACCAAGCCCAAGCAACCAAGGTGGACAAAGGGTGGAAATCTA AGTACGGCCCTCCCTGCCCTCTTGGCCAGCCCTGAAGTGCCTGGCGGACCCCTCCGTGTCTTCCCTCCCAAG CCCAAGGACACCTGTATGATCAGCCGACCCCGAAGTGACCTGCGTGGTGGTGTGTGTCCAGGAATCCC GAGTGCAGTTCAATTGTGACGTGGACGGCGTGGAAAGTGCACACGCCAAGACCAAGCCAGAGAGAACAGTTC AACAGCACCTACCGGGTGGTGTCCGTGTGACCGTGTGACCAAGGACTGGCTGAAACGGCAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGCAGCCT CAAGTGTGTACCCCTGCCCTAGCCAGGAAGATGACCAAGAACCCAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCCAAGCAGATTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCAACCCCTCT GTGCTGGACAGCGACGGCTCATTTCTCTGTGTCCAAGTGAACCGTGGACAAGACCGGTGGCAGGAAGGCAAC GTGTTCAAGCTGCTCCGTGATGCACGAGGCCCTGCACAAACCACTACACCAAGATCCCTGTCTCTGCCCTGGC CAGGTTCAAGCTGTGCTGCTGGCGCCGAACTGTTCAGACCTGGCGTGTCCGTGAAGATCAGCTGTACAGGCAGCG GCTACAGCTTCAACCACTAGCCGTGCACTGGGTCAAGCAGAGCCACGTGAAGTCCCTGGAAATGGATCGGCGTGA TCAGCCCTACTACGGCGACACCACTACAAACAGAACTTCAACGGCAAGGCCACCATGACCGTGGACAAGTCTA GCAGCACCGCTACATGGAACCTGGCAGACTACCGAGGACGAGCCTACTCTTTGCGCCAGAGATTCG AGGGCTTTACTACAGATGGACTACTGGGGCCAGGGCACCAGGTGACATTTCTTGTGCTGCAACAAAGGCC ATCGGTGTCCCTCTGGCCCTTGCAGCAGAACCAACCGGAATCTACAGCCGCCCTGGGTGCTCGTGAAGGAC TACTTTCCGAGCCGTGACCGTGTCTTGGAACTCTGGCGCTGTGACAAGCGCGGTGCACACCTTTCCAGCCGTGC TCCAGAGCAGCGGCCCTGTACTCTGTGACAGCGTGTGACAGTGGCCACAGCAGCCTGGGCAACCAAGACCTACA CCTGTAAAGTGGACCAAGGCCAGCAACCAAGGTGGACAAGCGGGTGAATCTAAGTACGGCCCTCCCTGCC CTCCTTGCCAGCCCTGAAGTGTCCGGCGGACCTCCGTGTCTTCCCTTCCCAAGCCCAAGGACACCCCTGAT GATCAGCGGACCCCGAAGTGAACCTGCGTGGTGGATGTGCCAGGAAGATCCCGAGGTGCAGTTCATTAATTG</p>
3	259		

			<p>GTACGTGGACGGCGTGGAAAGTGCACAACGCCAAGACCAAGCCAGAGAGGAAACAGTTTCAACAGCACCTACCGGG TGCTGCCGTGCTGACCGTGTGCACACAGGACTGGCTGAACGGCAAGAGTACAAAGTGAAGGTGTCCAACAAGG GCCTGCCAGCTCCATCGAGAAACCATCAAGCAAGGCCAAGGCCAGCCCGGAGCCTCAAGTGTATACCTTGC CCCCTTGCCAGGAAGATGACCAAGAACAGGTGTCCCTGTGGTGTCTCGTGAAGGCTTCTACCCAGCGACAT TGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACACCCCTGTGTCTGACACGACGACGG CTCAATTCTTCTGTACTCCTCAAGCTGACCGTGGAACAAGCCGTGGCAGGAAGCAACGTGTTCAGCTGCTCCGTG ATGCACGAGGCCCTGCACAACCACTACACCCAGAAAGTCCCTGTCTGTCCCTGGGC</p>
	4	260	<p>GACGTGGTCAATGATCCAGACACCTCTGAGCCTGTGTCTCTGGAGATCAGGCCAGCATCAGCTGCAGACCTA GCCAGTCTCTGGTGCACAGCAACGGCAACACCTACCTGAACCTGTATCTGCAGAGGCCGGACAGAGCCCCAAGC TGCTGATCTACAAGGTGCCAAGCGGTTACGGGGTGCCTGATAGATTTCTGGCAGCGGCTCTGGCACCGACTT CACCTGAAGATTAGCAGAGTGAAGCCGAGGACCTGGCGTGTACCTGTCTCAGAGCACACACGTGCCCT GACCTTGGCAGCGGAACCCAGCTGGAATCAAGCTACGGTACGGCTCCACGCTGTTCTCTCCACCTAGC GACGAGCAGCTGAAGTCCGGCACAGCCTCTGTCTGTGTGCTGTGAACAATTCTACCCCGCAGGCAAAAGTGC AGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGGACGAGCAAGGAACTCC ACCTACAGCCTGAGCAGCACCTGACACTGAGCAAGCGGACTACGAGAAGCAAAAGGTGTACGCTGCGGAAGTG ACCCACAGGGCCTGTCTAGCCCCGTGACCAAGAGTTCAACCGGGCGAGTGT</p>
CD38 ^{hhy} 1195 / CD28 ^{sup} x CD3 ^{mid} _ENLQ DK TH T IgG4 FALA BP # 8	1	261	<p>GACATCGTGTGATGACCCAGACCCCTCTGAGCCTGAGCGTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCACGAGAACCTGCAGACCTACCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCAG TCCTGATCTACAAGGTGTCCAACAGATTACGGCGTGTCCCGACAGATTCTCCGGCAGCGGCTCTGGCACCGACT TCACCTGAAGATCAGCGGGGTGAAGCCGAGGACGTGGCGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTGGCAGCGGCACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTCAAGCCAGCCAGCAATCATCTGCTGGCTGA ACTGGTATCAGCAGAAAGCCCGGCAAGGCCCCCAAGCTGTGTATCTACAAGGCCAGCAACCTGCAACCCGGCTGC CCAGCAGATTTCTGGCAGCGGCTCCGGCACCCGACTTCACTCCATGACATCAGCTCCCTGCAGCCCGAGGACATTGC CACCTACTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTTGGCCAGGGCACCAAGCTGGAAATCAAGGATAA GACCCACACCCGTACGGTGGCCGCTCCAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAAGTCCGGCACA GCCTCTGTGTGTGCTGTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAAGTGAAGGTGGACAAACGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGCAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGCAGAAAGTGACCCACAGGGCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
	2	262	<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTCTGTGAAACCTGGCGCTCTGTGAAAGGTGTCTTGCAGAGGCCAGC GGCTACACCTTTACAGCTACTATCTCCACTGGTGGCCAGGCCCTTGACAGGACTGGAATGGATCGGCAGC ATCTACCCCGGCAACGTGAACACCAACTAGCCCAAGAGTTCCAGGGCAGAGCCCTGACCCGTGGACACCAAGC ATCAGCACCCGCTACATGGAACTGAGCCGGTGAAGCGACACCGCGTGTACTACTGCAACCCCGTCCAC TACGGCCTGGAATTGGAATCTGACCTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGCAAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGAGTGTGACGCTGCGAGAAGCCTGAGACTGAGCTGTGCCCGCAGC GGCTTCACTTCAACCAAGGCCTGGATGCATGGGTGCGCCAGGCCCTTGAAAGCAAGCTGGAATGGGTGGCCCCAG ATCAAGGACAAGAGCAACAGCTACGCCACCTACTACGCCGACAGCGTGAAGGCCCGGTTCACCATCAGCCGGGAC</p>

183

CD38 ^{hly} 1370 / CD28 ^{sup} x CD3 ^{mid} ENLQ DK TH IgG4 FALA BP # 9	1	265	<p>AACGCCCTGCAGAGCGGCAACAGCCAGGAAAGCGTGACCGAGCAGACGAAAGGACTCCACCTACAGCCTGAG CAGCACCTGTACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGCAGAAAGTGACCCACAGGGCCT GTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p> <p>GACATCGTGATGACCCAGACCCCTGTAGCCTGAGCGTGCACCTGGACAGCCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCGCTGGTGCACGAGAACCTGACAGCCTACCTGAGCTGATCTGCAGAACCCGGCCAGAGCCCCCAG TCCCTGATCTCAAAGGTGTCCAAAGATTACAGCGGCTGCCCCAGATATTCCTGGCAGCGGCTCTGGCACCAGCT TCACCTGAAGATGACCGGGTGAAGCCGAGGACGTGGCGGTGTAATTTGGGCCAGGGCAGCCAGTACCCCT TCACCTTTGGCAGCGGCAACAAAGTGGAAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCTGTCTGCCAGCGTGGCGACAGAGTACCATACCTGTCAAGGCCAGCCAGCAATCTACGTGTGGCTGA ACTGGTATCAGCAGAAAGCCCGGCAAGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCCGGCGTGC CCAGCAGATTTCTGGCAGCGGCTCCGGCACCGACTTACCTTGACATCAGCTCCCTGCAGCCCGAGGACATTGC CACTACTACTGCCAGAGGGCCAGACCTACCTTACACCTTTGGCCAGGCAACCAAGCTGGAATCAAGGATAA GACCCACACCGGTAGCGTGGCGCTCCAGCGTGTTCATCTTCCACCTAGCGACGACGAGCTGAAGTCCGGCACA GCCTCTGTGCTGCTGTGAACAATTCTACCCCGGAGGCCAAAGTGCAGTGAAGGTGGAACAACGCCCTGC AGAGCGGCAACAGCCAGGAAAGCTGACCCAGCAGGACAGAGGACTCCACCTACAGCCTGAGCAGCACCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAAGTGACCCACCAAGGGCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
	2	266	<p>CAGGTGCAGCTGGTGCACTGTGGCGCGAGGTGCTGAAACCTGGCGCCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAAGTACTACATCCACTGGTGGCCAGGCCCTTGACAGGGACTTGAATGGATCGGCGAGC ATACCCCGGCAACGTGAACCACTACGCCAGAAAGTTCAGGGCAGAGCCCTGACCGTGGACACCCAGC ATCAGCACCGCTACATGAACTGAGCGGCTGAGAAGCAGCAGCAGCCGCTGTACTACTGCACCCCGTCCAC TACGGCCTGGATTGAACTTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTCTAGCGACAAAACCCATATACC CAGGTGCAGCTGGTGAATCTGGCGGCGGAGTGTGCAAGCCTGGCAGAAAGCCTGAGACTGAGTGTGCCCGCAGC GGCTTCACTTCAACAGGCTGGATGCACTGGGTGGCCAGGCCCTGGAAAGCAGCTGGAATGGTGGCCCCAG ATCAAGGACAAAGAGCAACAGTACGCCACCTACTACGCCGACAGCGTGAAGGCCCGGTTCACCATCAGCCGGAC GACAGCAAGAACCCCTGTACCTGCAGATGAACAGCCTGGCGGCCGAGGACACCCCGTGTACTACTGTGGGGC GTGTACTATGCCCTGAGCCCCCTCGATTACTGGGGCCAGGGAACCTCTGTGACCGTGTCTAGTATAAGACCCACA CCGCCAGCACAAAGGGCCCATCGGTGTTCCTTGGCCCCCTTGACGACAGAAACACAGCAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTTCGAGCCCCGTGACCGTGTCTTGGAACTCTGGCGCTCTGACAAAGCGGCGTG CACACTTTCAGCGGTGCTCCAGAGCAGCGGCTGTACTCTGTAGCAGCGTGTGACAGTCCCCAGCAGCAGCC TGGGCACCAAGACCTACACCTGTAACTGGGACCAAGCCCCAGCAACCAAGGTGGAACAGCGGTGGAATCTA AGTACGGCCCTCCCTGCTTGGCCAGCCCCCTGAAGTGTCCGGCGGACCTCCGTGTCTTCCCTCCCAAG CCCAAGGACACCTGTATGACCGGACCCCCGAAGTGAACCTGCTGGTGGTGGATGTGCCAGGAAGATCCC GAGGTGCAGTTCAATTGTAACGCGGTGGAAGTGCACACGCCAAGACCCAGAGCCAGAGCAAGTTC AACAGCACCTACCGGTGGTGTCCGTGTGACCGTGTGACCAAGACTGGCTGAACCGCAAGAGTACAAGTGC AAGGTGTCCAAACAGGGCCTGCCAGCTCCATCAGAAACCAATCAGCAAGGCCAAGGGCCAGCCCCGCGAGCCT CAAGTGTACCTGCCCCCTAGCCAGGAAGATGACCAAGAACCAAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTTACCCCCAGCGACATTGGCCGTGAATGGGAGAGCAACGGCCAGCCCCGAGAACAACTACAAGACCAACCCCCCT</p>

			<p>GTGCTGGACAGCGACGGCTCATTTCTTCTGGTGTTCAAGCTGACCGTGGACAAAGAGCCGGTGGCAGGAAGGCAAC GTGTTACAGCTGCTCCGTGATGACGAGGCGCTGCACAAACCACTACACCCAGAAAGTCCCTGCTCTGTCCTCGGCG</p>
	3	267	<p>CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCGTGGTGCAGCCTGGCAGGTCTCTGAGACTGAGCTGTGCCGCCAGC GGCTTCACCTTCAGCAGCTACGGAATGCACTGGGTGCAGGCGCTGGCAAGGACTGGAATGGGTGGCCGTG ATTGTGACGACGGCAGCAACAAGTACTACGCCGACAGCGTGAAGGCGCGTTCCACATCAGCGGCGACAAACAGC AAGAACAACCTGTACTGTCAGATGAACAGCTCGGGCCGAGGACACCGCGTGTACTACTGCGCCCAAGATGTTT AGAGGCGCTTCGACTACTGGGGCCAGGGCACACTCTGAGCCGTGTCTGAGTGTGACCAAGGGGCCCATCGGTG TTCCCTCTGGCCCCCTTGACGAGAAGACCAAGCAATACAGCGCCCTGGGTGCTCGTGAAGGACTACTTTT CCGAGCCCGTGACCGTGTCTGGAACCTCTGGCGCTCTGACAAAGCGCGTGCACACCTTTCCAGCCGTGCTCCAGAG CAGCGGCTGTACTCTGAGCAGCGTGTGACAGTGCACAGAGCCTGGGCAACCAAGACCTACACCTGTAA CGTGGACCAACAGCCAGCAACACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCCCTCCCTGCCCTCCTTG CCAGCCCTGAAAGCTCGCGGCGACCTCCGTGTTCTTCCCCCAAGGCCAAGGACACCTGATGATCAGC CGACCCCGGAGTGCACACCGCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTACCGGGTGTGTG GACGGCGTGAAGTGCACACCGCAAGACCAAGCCAGAGAGGAACAGTTCAAGGTGTCACCAAGGGCTGCC CGTGTGACCGTGTGACACAGGACTGGCTGAACGGCAAGAGTCAAGTCAAGGTGTCACCAAGGGCTGCC CAGCTCATCGAAGAAACCATCAGCAAGGCCAAGGCCAGCCCGCGAGCCTCAAAGTGTATACCTTGCCCCCTTG CCAGGAAGAGATGACCAAGAACAGGTGTCCCTGTGTGTCTCTGTGAAAGGCTTCTACCCCAAGGACATTGGCCGT GGAATGGGAGAGCAACGGCCAGCCGAGAAACAACTACAAAGACCAACCCCTGTGCTGACAGCGAGCGCTCAT TTCTCTGACTTCAAGCTGACCTGACCAAGAGCGCGTGGCAGGAAGCAACGTGTTTCAGCTGCTCCGTGATGAC GAGGCCCTGCACAAACCACTACACCCAGAAAGTCCCTGTCTGTCCCTGGGC</p>
	4	268	<p>GCCATCCAGATGACCCAGAGCCCGCAGCCTGTCTGCCAGCGTGGCGCAGAGTGACCATCACCTGTAGAGCC AGCCAGGGCATCCGGAACGACCTGGGTGGTATCAGCAGAGCCTGGCAAGGCCCAAGCTGTGATCTACGCC GCTAGCTCTCTGAGTCCGGGTGCCAGCAGATTTTCTGGCAGCGGCTCCGGCACCAGCTTCAACCTGACAACTCT CTGGCTGCAGCCGAGGACAGCGCCACCTACTACTGTCTGCAAGACTACTACCCCACTTCGGCCAGGG CACCAAGGTGGAATCAAGCGTACGGTGGCGCTCCAGCGTGTCTATCTCCCACTAGCGACGAGCAGCTGAA GTCCGGCACAGCCTCTGTGTGCTGTGCTGAACAACTTCTACCCCGCAGGCAAGAGTGCAGTGAAGTGGAC AAGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGCAGCAAGGACTCCACCTACAGCCTGAG CAGCACCCCTGACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCGTGCGAAGTGACCCACAGGGCCT GTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
CD38 ^{hu} 5739 / CD28 ^{sup} _x CD3 ^{mid} _ENLO DK'THT_ IgG4 FALA	1	269	<p>GACATGTTGATGACCCAGACCCCTTGAGCCTGAGCCTGAGCCTGACACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGTGTCAGCAACCTGCAGACCTACCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCCAG TCCCTGATCTACAAAGGTTCACAGATTCAGCGGCTGCCGACAGATTTCTCCGGCAGCGGCTCTGGCACCCGACT TCACCTTGAAGATCAGCGGCTGGAAGCCGAGGACCTGGCGGTGTACTATTGTGGCCAGGGCAACCAAGTACCCCT TCACCTTTGGCAGCGGCAACCAAGGTGGAATCAAGGACAAACCCATACCCAGATCCAGATACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGGCGACAGTGAACCATACCTGTCAAGGCCAGCCAGAACATCTACGTGTGGCTGA ACTGTTATCAGCAAGCGCCGCAAGGCCCCCAAGCTGTGATCTACAAGGCCAGCAACCTGCACACCGCGCTGC CCAGCAGATTTTCTGGCAGCGGCTCCGGCACCGACTTCAACCTGACATCAAGTCCCTGCAGCCCCGAGGACATTGC CACCTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTTGGCCAGGGCAACCAAGCTGGAATCAAGGATAA</p>

			<p>GACCCACACCCGTACGGTGGCCGCTCCACAGCGTGTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCACA GCTCTGTGTCGTGCTGTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGAAGGTGGACAACAGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCAGCACCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACGCGTGCAGAGTGAACCCACAGGCCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
2	270		<p>CAGGTGCAGCTGGTGCAGTCTGGCGCGAGGTGTGAAACCTGGCGCCCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACACCTTTACCAGTACTACATCCACTGGGTGGCCAGGCCCTTGACAGGGACTGGATGGATCGGCAGC ATCTACCCCGCAACCGTGAACACCAACTACGCCAGAAAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCAGC ATCAGCACCGCTACATGGAACCTGAGCCGGTGAAGAGCAGCAGACCCCGTGTACTACTGACCCCGTCCAC TAGGGCTGGATTGGAACCTTCGACGTGTGGGGCAAGGGCACCAACCGTGACAGTGTCTAGCGACAAACCCATACC CAGGTGCAGCTGGTGAATCTGGCGGGGAGTGGTGCAGCCTGGCAGAAAGCCTGAGCTGAGCTGTGCCGCCAGC GGCTTACCTTACCAAGGCCTGGATGCACCTGGGTGCGCCAGGCCCTTGAAAGCAGCTGGAATGGTGGGCCAG ATCAAGGACAAGACAAGCTACGCCACCTACTACGCCGACAGCGTGAAAGGCCGGTTACCATCAAGCCGGAC GACAGCAAGAACACCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCCCGTGTACTACTGTCCGGGC GTGTACTATGCCCTGAGCCCTTCGATTACTGGGGCCAGGAAACCTCTGTACCGTGTCTAGTGATAAGACCCACA CCGCCAGCAAAAGGGCCCATCGGTGTTCCTCTGGCCCTTGCAGCAGAAAGCAGCAGCAATCTACAGCCGCCCT GGGTGCCCTCGTGAAGGACTACTTTCGAGCCCGTACCGTGTCTGGAACCTCTGGCGCTCTGACAAGCGCGGTG CACACCTTTCAGCGGTCTCCAGAGACGCGCCTGTACTCTGAGCAGCGTGTGACAGTGCCAGCAGCAGCAGC TGGCACCAAGACCTACACCTGTAAACGTGGACACCAAGCCACCAAGCTGGACAAAGCGGTGGAAATCTTA AGTAGGGCCCTCCCTGCCCTCTTGGCCAGCCCTGAAGCTGCCGGCGGACCCCTCCGTGTCTCTCCCTCCCAAG CCCAAGGACACCTGTATCAGCCGACCCCGAAGTACCTGCGTGGTGTGTGTCTCCAGGAATCCC GAGTGCAGTTCAATTGTACGTGGACGCGGTGGAAGTGCAACCGCAAGACCAAGCCAGAGAGAACAGTTC AACAGCACCTACCGGGTGTGTCGTGTGACCGTGTGACCAAGGACTGGCTGAAACGGCAAGAGTACAAGTGC AAGGTGTCCAAACAAGGGCCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGCAGCCT CAAGTGTGTACCCCTGCCCTAGCCAGGAAGATGACCAAGAACCCAGGTGTCCCTGAGCTGTGCCGTGAAAGGC TTCTACCCCAAGCAATTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAAACAACTACAAGACCAACCCCT GTGCTGGACAGCGACGGCTCATTTCTCTGTGTCCAAAGTGAACCGTGGACAAGAGCCGTGGCAGGAAGGCAAC GTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAAACCACTACACCAAGAGTCCCTGTCTCTGCCCTGGC</p>
3	271		<p>CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAAGTGAACCTGGCGCCTCTGTGAAGGTGTCTGCAAGGCCCTCTG GCTACGCCCTTACCACTACCTGTGGAATGGATCAGACAGAGCCCTGGACAGGGCCTCGAATGGATGGCGGTGA TCAATCTTGCGACGCGCAGCACCATTACGCCAGAAATTCAGGGCAGAGTGACCATGACCGTGGACAGAAGCA GCACCAACCGCTACATGGAACCTGAGCACTGAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGC ACGGCTATTGGGGCCAGGGAACCTGTGTTACCGTTAGCTGTGCTGCAACCAAGGGCCATCGGTGTCTCTCTGGC CCCTTGACAGCAAGCACCAAGCGAATCTACAGCCCGCTGGGTCCCTGTAAGGACTACTTTCCCGAGCCCTGT ACCGTGTCTGGAACCTTGCGCTCTGACAAGCGCGTGCACACTTCCAGCCGTGCTCCAGAGCAGCGGCTGT ACTCTGTGACAGCGTGTGACAGTGGCCCAAGCAGCAGCTGGGCAACCAAGACCTACACCTGTAACTGTGACCA AGCCAGCAACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCCCTCCCTGCCCTCTTGGCCAGCCCTGT AAGCTGCCGGCGGACCCCTCCGTGTCTGTTCCTCCCAAGCCCAAGGACACCTGTGATGATCAGCCGGAACCCCGA AGTGACCTGCGTGTGTGTGATGTGTCCCAAGGAAGATCCCGAGGTGCAGTTCAATTGGTACGCTGGACGGCGTGA</p>

			<p>AGTGCAACACGCCAAGACCAAGCCAGAGAGGAAAGATTCAACAGACCTACCGGGTGGTGTCTCCGTGCTGACCGT GCTGCACAGGACTGGCTGAACGGCAAGAGATCAAGTCAAGGTGTCCAAAGGGCTGCCAGCTCCATCGA GAAACCATCAGCAAGGCCAAGGCCAGCCCGAGCCTCAAGTGTATACCTGCCCTTGGCAGGAAGAGAT GACCAAGAACACAGGTGTCCCTGTGTCTGTGAAAGGCTTACCCAGCGACATTGCCGTGGAATGGAGAG CAACGGCCAGCCGAGAACAACTACAAGACACCCCTGTGTGACAGCGACGGCTCATCTTCTCTGTACTCC AAGCTGACCCGTGGACAAGACCGGTGGCAGGAAGCAAGCTGTCTGCTCCCTGGGC AACCATAACCCAGAGTCCCTGTCTGTCTCCCTGGGC</p>
	4	272	<p>GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCGAGCTGGAGACAGAGTGACCATCACCTGTAGAGCC AGCCAGAATGTGGGAACAGCCGTGGCTGGTATCAGCAGAAAGCTGGCAAGAGCCCCAAGCAGTGTATACAGC GCCAGCAACAGATACACCGGGTGGCCAGCAGATTTTCTGGCAGCGGCTCTGGCACCGACTTACCTTGACCATAT CTAGCTGCAGCCTGAGACCTGGCCACCTACTACTGTACAGTACAGACATACCTTACCTTCGGCCAGGG CAACAAAGCTGGAATCAAGCGTACGGTGGCCGCTCCAGCGTGTCTTCCACCTAGCAGCAGCAGCTGAA GTCCGGCACAGCCTCTGTCTGTCTGTCTGTGAACAACTTCTACCCCGGAGGCCAAAGTGCAGTGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAAGCGTGAACCGAGCAGCAGCAAGGACTCCACCTACAGCCTGAG CAGCACCTGACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGCAGAGTGACCCACAGGGCCT GTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
CD38 ^{hu6284} / CD28 ^{sup} x CD3 ^{mid} ENLQ DK3 TH IgG4 FALA	1	273	<p>GACATCTGTGATGACCCAGACCCCTGTAGCCTGAGCGTGAACCTGGACAGCCTGCCAGCATCAGCTGCAAGAGC AGCCAGAGCCTGGTGCACGAGAACCTGCAGACCTACCTGAGCTGGTATCTGCAGAAAGCCCGGCCAGAGCCCCAG TCCTGATCTACAAGGTGTCCAACAGATTCAGCGGTGCCCCGACAGATCTCCGGCAGCGGCTCTGGCACCCGACT TACCTTGAAGATCAGCGGGGTGGAAGCCGAGGACGTGGCGTGTACTATTGTGGCCAGGGCACCCAGTACCCCT TCACCTTGGCAGCGGCACCAAGGTGGAATCAAGGACAAACCCATACCGACATCCAGATGACCCAGAGCCCCA GCAGCCTGTCTGCCAGCGTGGCGACAGAGTGACCATCACCTGTCAAGGCCAGCCAGCAATCATCTGCTGGCTGA ACTGGTATCAGCAGAAAGCCCGCAAGGCCCCCAAGCTGCTGATCTACAAGGCCAGCAACCTGCAACCCGGCTGC CCAGCAGATTTTCTGGCAGCGGTCCCGCACCCGACTTACCTTACATCAGCTCCCTGCAGCCCGAGGACATTGC CACCTACTACTGCCAGCAGGGCCAGACCTACCCCTACACCTTGGCCAGGCAACCAAGCTGGAAATCAAGGATAA GACCAACACCGTACGGTGGCCGCTCCAGCGTGTCTTCCACCTAGCAGCAGCAGCTGAAAGTCCGGCACACA GCCTCTGTCTGTGCTGTGAACAACTTCTACCCCGCGAGGCCAAAGTGCAGTGAAGGTGGACAACGCCCTGC AGAGCGGCAACAGCCAGGAAGCGTGACCGAGCAGCAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCTTGCAGAAAGTGACCCACAGGGCCTGTCTAGCCCC GTGACCAAGAGCTTCAACCGGGCGAGTGT</p>
	2	274	<p>CAGGTGCAGTGGTGCACTGTGGCGCAGGTCTGTGAAACCTGGCGCTCTGTGAAAGGTGTCTTGCAAGGCCAGC GGCTACACCTTTACAGCTACTACATCCACTGGGTGCCAGGCCCTTGACAGGACTTGAATGGATCGGCAGC ATCTACCCCGGCAACGTTGAACACCAACTAGCCCAAGAGTTCCAGGGCAGAGCCACCTGACCCGTGGACACCAAGC ATCAGCACCCGCTACATGGAACTGAGCCGGTGAAGCGACGACACCGCGTGTACTACTGCAACCCCGTCCAC TACGGCTGGAATTGGAATTCGACGTGTGGGCAAGGGCACACCGTGACAGTGTAGCGCAAAACCCATACC CAGGTGCAGTGGTGAATCTGGCGGGAGTGGTGCAGCCTGAGAGAGCCTGAGAGTGTGCTGCGCCAGC GGCTTCACTTCAACCAAGGCCTGGATGCATGGGTGCCAGGCCCTTGAAAGCAGCTGGAATGGGTGGCCCCAG ATCAAGGACAAGAGCAACAGCTACGCCACCTACTACGCCGACAGCGTGAAGGCCCGGTTCACCATCAGCCGGGAC</p>

			<p>GACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGGGGG GTGTACTATGCCCCGTAGCCCCCTTCGATTACTGGGGCCAGGAAACCTCTGTGACCGTGTCTAGTGATAAGACCCACA CCGCAGCACAAAGGGCCCATCGGTGTTCCTCTGGCCCTTGCAGCAGAAAGACACGGAATCTACAGCGCCCT GGGTGCTCTGTGAAGACTACTTCCGAGCCCGTGCCTGTCTGAACTCTGGCGTCTGACAAGCGCGGTG CACACCTTCCAGCCGTGCTCCAGAGCAGCGCGTGTACTCTGAGCAGCGTGTGACAGTCCCAGCAGCAGCC TGGGCAACCAAGACCTACACCTGTAACTGTGAGCCACACCCAGCAACCAAGGTGGCAAGCGGTGGAACTTA AGTACGGCCCTCCCTGCCCTCTTGGCCAGCCCTGAAGCTGCCGGGACCCCTCCGTGTCTCTCTCCCTCCCAAG CCCAAGGACACCCTGATGATCAGCCGACCCCGAAGTACCTGCTGGTGTGGTGTGTGCCAGGAAGATCCC GAGTGCAGTTCAATTGTGACGTGGACGGCGTGGAAGTGCACACGCCAAGCAAGCCAGAGAGAAACAGTTTC AACAGCACCTACCGGGTGTCTCGTGTGACCTGTGACCTGCTGACCAAGACTGGCTGAACGGCAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCCTGCCAGCTCCATCGAGAAACCATCAGCAAGGCCAAGGCCAGCCCGGAGCCT CAAGTGTGTAACCTGCCCTAGCCAGGAAGAGATGACCAAGAACAGGTGTCCCTGAGCTGTGCCGTGAAGGC TTTACCCCAAGCAGATTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCAACCCCTCT GTCTGGACAGCGACGGCTATTCTCTGTGTCTCAAGTGAACCTGAGCAAGAGCCGTGGCAGGAAGGCAAC GTGTCAAGCTGCTCCGTGATGACAGAGGCCCTGCACAAACCTACACCCAGAACTGCTCTGTCTGCTCCCTGGGC</p>
3	275		<p>CAGGTTACAGCTGGTTACGTGGCGCCGAAAGTGAAGAAACCTGGCGCCTCTGTGAAGGTGTCTGCAAGGCCAGC GGCTACAGCTTCAACCAATTACCGCGTGCACTGGGTCCGACAGGCTCCAGGACAAAGGACTGGAATGGATGGCGGTG ATCAGCCCTACTACGGCGATACACATACGCCAGAAATTCAGGGCAGAGTGACCATGACCGTGGACAAGAGC AGAGCACCCGCTACATGGAACCTGAGCAGACTGAGAAGCAGCAGCACCCCTGTACTACTGCGCCAGAGAAGATTTC GAGGGCTTCTACTACAGATGGACTACTGGGGCCAGGGCACCCCTGGTTACAGTCTTCTGCGTGCACCAAGGGCC CATCGGTGTTCCCTCTGGCCCTTGCAGCAGAAAGCAGCAGAACTACAGCCGCCCTGGGTGCCCTGTGAAGGA CTACTTCCCGAGCCCGTGAACCGTGTCTGGAACCTCTGGCGCTGTGACAGCGCGGTGCACACCTTTCAGCCGTG CTCCAGAGCAGCGCCCTGTACTCTGTGACAGCGTGTGACAGTGCCTCAGCAGCCCTGGGCAACCAAGACCTAC ACCTGTAACTGTGACCAAGCCAGCAACCAAGGTGGACAAGCGGTGGAATCTAAGTACGGCCCTCCCTGC CCTCCTTGCCAGCCCTGAAGCTGCCGGCGGACCTCCGTGTCTCTGTTCCCGCCAAAGCCCAAGGACACCCCTGA TGATCAGCCGACCCCGAAGTGAACCTGCGGTGGTGGTGTGTCTCCAGGAAGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGAAGTGCAACAACGCCAAGACCAAGCCAGAGAGGAACAGTTCAACAGCACCTACCCG GTGGTGTCCGTGTGACCGTGTGACCAAGACTGGCTGAACGGCAAGAGTACAAGTGAAGGTGTCCAACAAG GGCTGCCCAGCTCCATCGAAGAAACCATCAGCAAGGCCAAGGGCCAGCCCGAGCCTCAAGTGTATACCCCTG CCCCTTGCCAGGAAGATGACCAAGAAACAGGTGTCCCTGTGTGTCTGTGTAAGGGCTTCTACCCAGCGACA TTGCCGTGGAATGGAGAGCAACGGCCAGCCCGAGAACTACAAGACCAACCCCTGTGTGTGACAGCGACG GCTCATTTCTCTGTAACCTGACCTGACCGGTGACAGCGGTGGCAGGAAGCAAGTGTTCAGCTGTCCCTGGGC GATGCACGAGGCCCTGCACAACTACACCCAGAAAGTCCCTGCTCTGTCTCCCTGGGC</p>
4	276		<p>GACGTGGTCAACAGAGCCCTCTGAGCCCTGTGACACTGGGACAGCTGCCAGCATCAGCTGTAGACCTA GCCAGAGCCTGGTGCACAGCAACGGCAACACCTACCTGAACCTGGTATCAGCAGAGCCCGGACAGAGCCCAAGC TGCTGATCTACAAGGTGTCCAAGCGGTTTACGGCGGTGCCCGATAGATTTTCTGGCAGCGGCTCTGGCACCGACTT CACCTGAAGATTAGCAGAGTGAAGCCGAGGACGTGGCGGTGTACTGTAGCCAGTCTACCCACCGTGCCACT GACCTTTGGCGCGGAACAAGGTGGAATCAAGCGTACGGTGGCGCTCCAGCGTGTTCATCTTCCACCTAGC GACGAGCAGTGAAGTCCGGCACAGCCCTCTGTCTGTGCTGTGCTGTGTAACACTTCTACCCCCCGGAGGCCAAAGTGC</p>

			AGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAAAGCGTGACCGAGCAGGACAGCAAGGACTCC ACCTACAGCCTGAGCAGCACCCCTGACACTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTG ACCCACCAAGGGCCTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGGAGTGT
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EXAMPLES

[0304] 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: Development of trispecific HER2/CD28xCD3 antibodies and variant anti-CD3 binding sites

[0305] Immuno-oncology is a promising, emerging therapeutic approach to disease management in cancer. The immune system is the first line of defense against cancer development and progression. There is now large evidence that T cells are able to control tumor growth and prolong the survival of cancer patients in both early and late stages of disease. However, T cells specific for tumors can be limited in a number of ways preventing them from controlling the disease.

[0306] In order to remove the limitations on T cells induced by uncontrolled tumors, novel antibodies were developed in the trispecific antibody format depicted in **FIG. 1A** to specifically activate the T cells to engage HER2 expressing cancer cells. These novel trispecific antibodies are able to bind to three targets: HER2, CD3, and CD28. Anti-HER2 and anti-CD3 binding sites were further optimized for high affinity binding and reduction in potential manufacturing liabilities.

[0307] HER2 amplification and overexpression can be found in molecular subtypes of breast cancer, and also in gastric, ovarian, lung and prostate carcinomas. Optimal activation of T cells requires two factors: (1) Antigen recognition and (2) Co-stimulation. Using the trispecific HER2/CD28xCD3 trispecific binding proteins described herein, Signal 1 is provided by an agonist anti-CD3 binding site, and Signal 2 is provided by an agonist anti-CD28 binding site (*see, e.g., FIG. 1D*). It is thought that the trispecific antibodies described in the subsequent Examples recruit T cells to the tumor via HER2 and activate the engaged T cells by binding to CD3 and CD28. The resulting activation induces the killing potential of the immune cells against the nearby tumor cells.

Materials and Methods

Production and characterization of antibodies

[0308] Trispecific antibody variants were produced by transient transfection of expression plasmids into Expi293 cells. 5 days after transfection, the supernatant from

transfected cells was collected, quantified and normalized by absorbance at 280 nm on Nano Drop. The binding of supernatant to corresponding antigens were determined by ELISA and the absorbance of parental HER2 WT tri Ab was set as 1.0. The fold changes of other variants were calculated by dividing the corresponding absorbance to that of parental Ab.

[0309] Trispecific antibody variants were purified using protein A affinity purification followed by SEC purification. The binding of purified antibodies to corresponding antigens were determined by ELISA. The EC₅₀ were determined based on the binding curve generated by Graphpad Prism7.

Results

[0310] Trispecific Ab variants were produced with several mutations in the binding arms in order to mitigate potential manufacturing liabilities, *e.g.*, deamidation sites. A binding ELISA assay was performed to assess binding of the indicated trispecific antibodies to each of the three targets: HER2, CD3, and CD28. In **FIG. 1B**, HER2/CD3xCD28 trispecific antibodies with the indicated anti-HER2 or anti-CD3 variants were compared to parental Trispecific Ab. Introducing some sets of mutations (*e.g.*, 32/33 QQ and 33/35QQ) into the VL domain of the anti-CD3 binding site led to dramatically reduced binding to CD3, whereas 32/35 QQ mutations retained near wild-type binding. MS peptide analyses showed that binding sites with the DNAQ mutations in CDR-L1 (SEQ ID NO:63) were still subject to greater than 15% deamidation, whereas ENLQ (SEQ ID NO:281), ENLF (SEQ ID NO:282), and ENLR (SEQ ID NO:283) led to less than 5% deamidation. Importantly, these variants also retained binding to CD3.

[0311] In addition, binding curves for the indicated antibodies binding to human HER2, human CD28, and CD3 are provided in **FIG. 1C**. The EC₅₀ values of selected trispecific antibody variants are provided in **Table E**.

Table E. A binding ELISA assay was performed on purified trispecific antibodies to determine their binding affinities for HER2, human CD3, and human CD28.

	Binding Affinity (ELISA)(nM)		
	EC50		
Trispecific antibody	HER2	Human CD3	Human CD28
HER2 (WT-trastuzumab) / CD28supxCD3mid (32/35 QQ (LC); DKTHT linkers on HC/LC) IgG4 FALA	162.3	566.4	1321
HER2 (30R/55Q/102E +LC-WT-trastuzumab) / CD28supxCD3mid (32/35 QQ (LC); DKTHT linkers on HC/LC) IgG4 FALA	93.66	364.8	871.9
HER2-30R/55Q/102E/ CD28supxCD3mid (32/33/35QSQ) DKTHT linker IgG4 FALA	83.89	3222	1024
HER2 (30R/55Q/102E+LC-WT-trastuzumab) / CD28supxCD3mid (DNAQ (LC); DKTHT linkers on HC/LC) IgG4 FALA	111.2	725.7	1053
HER2 (30R/55Q/102E +LC-WT-trastuzumab) / CD28supxCD3mid (32/35QQ (LC); L1 linker) IgG4 FALA	111.5	412.5	1345
HER230R/55Q/102E/ CD28supxCD3mid (32/33/3435 ENLR (LC); DKTHT linkers on HC/LC) IgG4 FALA	123.9	81.53	878.8
HER2 (30R/56A/102S +LC-WT-trastuzumab) / CD28supxCD3mid (32/35QQ185E) IgG4 FALA	516.0	5494	3631
HER2-30R/55Q/102E+LC-30Q/ CD28supxCD3mid (32/35QQ) 185S L1 linker IgG4 FALA	1540	10616	2036
HER2-30R/55Q/102E/ CD28supxCD3mid (32/33/35QSQ) 185S L1 linker IgG4 FALA	467.0	19382	1814
HER2-30R/55Q/102E/ CD28supxCD3mid (32/33/35QSQ) 185E L1 linker IgG4 FALA	478.6	19756	1739

HER2/ CD28supxCD3mid DKTHT linkers on HC/LC) IgG4 FALA	228.9	671.2	752
HER2/ CD28supxCD3mid (32/33/3435 ENLF (LC); DKTHT linkers on HC/LC) IgG4 FALA	195.9	773.3	1466
HER2/ CD28supxCD3mid (32/33/3435 ENLQ (LC); DKTHT linkers on HC/LC) IgG4 FALA	212.1	10558	2405
HER2/ CD28supxCD3mid (32/33/3435 ENLR (LC); DKTHT linkers on HC/LC) IgG4 FALA	166.2	381.9	1051
anti-Her2/CD3/3CD28 IgG4 FALA	176.1	516.2	870.6

[0312] Without wishing to be bound by theory, as depicted in **FIG. 1D**, it is believed that HER2/CD3/CD28 trispecific antibodies recruit T cells to cancer cells through the anti-HER2 and anti-CD3/CD28 arms. Further, it is believed that engaged T cells are activated by the anti-CD28/CD3 arms. Killing of cancer cells is believed, without wishing to be bound by theory, to occur through T cell mediated mechanisms (*e.g.*, Perforin, granzyme). Without wishing to be bound to theory, it is contemplated that similar mechanisms may allow for killing of other types of tumors by substituting antigen binding sites that recognize other tumor target proteins.

Example 2: Development of trispecific CD38/CD3xCD28 antibodies

[0313] Trispecific CD38/CD3xCD28 antibodies were developed and characterized for binding to CD38, CD3 and CD28 polypeptides.

Materials and Methods

Generation of CD38/CD28xCD3 trispecific antibodies

[0314] A panel of anti-CD38, anti-CD3, and anti-CD28 antibodies, as well as human IgG4 Fc domains were used to generate CD38/CD28xCD3 trispecific antibodies in the trispecific antibody format depicted in **FIG. 2A**.

[0315] Trispecific binding proteins 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 (2.5×10^6 cells/ml). An optimization of transfection to determine the best ratio of plasmids was often used in order to produce the trispecific binding protein with good yield and purity.

[0316] 4-5 days post transfection, the supernatant from transfected cells was collected and filtered through 0.45 μ m filter unit (Nalgene). The trispecific binding protein 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 μ m 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 binding protein before combining them. The purified antibody can be aliquoted and stored at -80°C long term.

ELISA binding assay

[0317] Binding affinities to each target antigen by the CD38/CD28xCD3 T cell engagers were measured by ELISA. Briefly, each antigen was used to coat the 96-well Immuno Plate (Thermo Fisher Scientific) overnight at 4°C using 200 ng/well in PBS(pH7.4) of each antigen. 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 μ l/well in duplicate), incubated at room temperature (RT) for one hour, followed by washing 5 times with PBS+0.25% Tween 20. 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 μ l of TMB Microwell Peroxidase Substrate (KPL, Gaithersburg, MD, USA) was added to each well. The reaction was terminated by adding 50 μ l 1M H_2SO_4 , and OD450 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. EC50 was calculated using the same software.

Measurement of trispecific antibody binding using SPR

[0318] Human CD38-His antigens were used (Cambridge Biologics, Cambridge, MA) for full kinetic analysis. Kinetic characterization of purified antibodies was performed using SPR technology on a BIACORE 3000 (GE Healthcare). A capture assay using human IgG1 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 tagged antigen, anti-His antibody 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 μ L/min with an adjusted RU value that would result in maximal analyte binding signal of typically 30 RU. Binding kinetics were measured against the trispecific antibodies. 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 μ L/min. Chip surfaces were regenerated with the regeneration solution of the respective capture kit. Kinetic parameters were analyzed and calculated in the BIA evaluation program package v4.1 using a flow cell without captured antibody as reference and the 1:1 Langmuir binding model with mass transfer.

Daratumumab competition binding assay

[0319] For Daratumumab competition binding assay, Daratumumab was amine coupled to the active surface of CM5 chip. Reference surface was left blank and used to subtract any non-specific binding of injected molecules. Recombinant CD38-His (Sino Biological, Part# 10818-H08H) was injected over the Daratumumab surface followed by injection of test antibodies. If a monospecific anti-CD38 antibody recognized an epitope on CD38 which was different from that of Daratumumab, injection of the antibody resulted in an increased SPR signal. If an antibody recognized an overlapping epitope as Daratumumab, injection of the antibody did not increase SPR signal.

Results

[0320] The binding affinities of selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains for human CD38 were determined by SPR. The association rate constant (K_{on}), dissociation rate constant (K_{off}), and the K_D of the selected trispecific antibodies are provided in **Table A**. The selected trispecific antibodies showed various degrees of affinities against human CD38 antigen.

Table A. Binding characteristics of selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains for human CD38 determined by SPR.

Anti-CD38 binding domain	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)
CD38VH1	5.55E+05	1.58E-03	2.85E-09
CD38hhy992	1.35E+06	1.75E-04	1.29E-10
CD38hyb6284	7.85E+05	5.12E-04	6.52E-10
CD38hyb5739	9.80E+05	5.46E-03	5.57E-09
CD38hhy1195	1.27E+06	1.80E-02	1.42E-08
CD38hhy1370	3.76E+05	3.29E-04	8.76E-10

[0321] The binding affinities of selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains for human CD3, human CD28, human CD38 and cynomolgus monkey CD38 were then determined by ELISA as described above. As shown in **FIGS. 2B-2E**, the selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains showed various affinities to human (**FIG. 2B**) and cynomolgus monkey CD38 (**FIG. 2C**), but similar affinity to human CD3 (**FIG. 2D**) and CD28 (**FIG. 2E**). EC50 values were then calculated by GraphPad Prism 7.02 using variable slope model with four-parameter logistic curve. The EC50 values of the selected trispecific antibodies for human CD3, human CD28, human CD38 and cynomolgus monkey CD38 are provided in **Table B**. Control antibody was a human IgG4 isotype control.

Table B. EC50 values of selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains for human CD3, human CD28, human CD38 and cynomolgus monkey CD38.

Anti-CD38 binding domain	EC50 (pM)			
	hCD38	Cyno CD38	hCD3	hCD28
CD38VH1	7244	2128	6742	725

CD38hhy992	229	912	33593	809
CD38hyb6284	253	290	8222	711
CD38hyb5739	984	1628	10791	825
CD38hhy1195	102537	37701	7631	697
CD38hhy1370	587	553	24968	1257

[0322] An SPR competition assay was carried out to determine whether anti-CD38 antibodies hhy6284, hhy992, hhy5379, or hhy1195 (tested in monospecific antibody format) compete with Daratumumab for binding to CD38. Following CD38 injection over Daratumumab (immobilized on SPR sensor chip), the test antibodies (or Daratumumab) were injected over the Daratumumab/CD38 complex. As shown in **FIG. 3**, injection of Hyb6264, hhy992, Hyb5379, and Hhy1195 increased SPR signal, indicating that these antibodies recognized the epitopes on CD38 which are different from the epitope which Daratumumab recognizes. As expected, injection of free Daratumumab (a competitive binding control) did not increase the SPR signal.

[0323] Binding of anti-CD38 antibodies to human or cynomolgus CD38 polypeptides is summarized in Table B2.

Table B2. Summary of anti-CD38 binding characteristics to human or cynomolgus CD38.

Name	ELISA huCD38 EC50 nM	ELISA cynoCD38 EC50 nM	FACS huCD38 EC50 nM	FACS cynoCD38 EC50 nM	SPR huCD38 KD M	SPR cynoCD38 KD M
AntiCD38_hyb_5739	0.12	0.09	0.3	0.5		
AntiCD38_hyb_6284	0.11	0.13	0.4	0.7		
AntiCD38_hhy_992	0.09	0.08	100	288	3.65E-10	6.12E-09
AntiCD38_hhy_1195	1.4	0.86	38	15	4.00E-08	2.60E-08

[0324] Anti-CD38 antibodies were also tested for competitive binding to daratumumab in SPR assay. For daratumumab competition binding assay, daratumumab was amine coupled to the active surface of CM5 chip. Reference surface was left blank and used to subtract any non-specific binding of injected molecules. Recombinant CD38-His (Sino Biological, Part# 10818-H08H) was injected over the daratumumab surface followed by injection of test antibodies. If an antibody recognizes an epitope on CD38 which is different from that of daratumumab, injection of the antibody will result in an increased SPR signal. If an antibody recognizes an overlapping epitope as daratumumab, injection of the antibody will not

increase SPR signal. According to the results of these assays the tested antibodies hhy992, hyb6284, hhy1195 and hhy1370 did not compete with daratumumab.

Example 3: Trispecific CD38/CD3xCD28 antibodies promote lysis of human multiple myeloma and lymphoma tumor cells.

[0325] An *in vitro* cell lysis assay was used to determine whether trispecific CD38/CD3xCD28 antibodies had anti-tumor cell activity using human multiple myeloma and lymphoma cells.

Materials and Methods

In vitro killing assay against tumor cells using human T cells

[0326] Target tumor cells were labeled with the membrane dye PKH-26 (Sigma) and co-cultured for 24 hours with human PBMC or enriched CD8 T cells as effector cells at E:T ratio of 10:1 (E:T=3:1 using enriched CD8 T cells) in the presence of indicated concentrations of tri-specific or relevant control antibodies. Peripheral blood mononuclear cells were isolated from normal human donors by Ficoll separation, and autologous CD8⁺ or pan-T cells were enriched using kits from Miltenyi Biotec (San Diego, CA). The extent of cell lysis in the target cells was determined by staining with a LIVE/DEAD™ Fixable Violet Dead Cell Stain Kit (Life Technologies) and measured by the number of dead cells in the labelled target cell population by running the samples on an LSRFortessa instrument (BD Biosciences) followed by analysis using the Flowjo software (Treestar).

In vitro killing assay against tumor cells using human T cells in the presence of Daratumumab

[0327] 5 nM Daratumumab or isotype control antibodies were pre-incubated with PKH-26 labeled target tumor cells (10⁵ cells/well) for 30 minutes, followed by addition of trispecific TCEs at indicated concentrations, and human PBMCs (E:T=10:1). 24 hours later, the extent of cell lysis in the target cells was determined by staining with a LIVE/DEAD™ Fixable Violet Dead Cell Stain Kit (Life Technologies) and measured by the number of dead cells in the labelled target cell population by running the samples on an LSRFortessa instrument (BD Biosciences) followed by analysis using the Flowjo software (Treestar).

Results

[0328] The *in vitro* cell killing activity of CD38/CD28sup x CD3mid_ENLQ DKHTT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains was determined using a human multiple myeloma cell line NCI-H929 that expresses both CD38

and CD28. The assay was carried out in the presence of 5nM Daratumumab or isotype control antibodies (present during the assay period). As shown in **FIGS. 4A-4B**, all tested trispecific antibodies led to cell lysis in a concentration-dependent manner in the presence and absence of Daratumumab. The EC50 values were then calculated in the presence and absence of Daratumumab (**Table C**). The cell killing activities of trispecific antibodies CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA with the CD38VH1 or CD38hhy1370 anti-CD38 binding domains were reduced by Daratumumab, while trispecific antibodies with the CD38hyb5739, CD38hyb6284, or CD38hhy1195 anti-CD38 binding domains exhibited between 3-8 fold reductions in cell killing activity in the presence of Daratumumab (**Table C**).

Table C. *In vitro* killing activity against human multiple myeloma cell line NCI-H929 (CD38+/CD28+) by CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains in the presence of Daratumumab.

	Anti-CD38 binding domains					
EC50 (pM)	CD38VH1	CD38hhy99	CD38hyb573	CD38hyb628	CD38hhy119	CD38hhy1370
With Dara	29.82	125.8	9.115	33.65	89.27	255.4
With human IgG1	1.063	13.43	2.736	4.37	16.97	9.599

[0329] In addition, an *in vitro* cell lysis assay was used to measure the cell killing activity of selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains using a human lymphoma cell line OCI-LY19 that expresses CD38 but not CD28. The assay was carried out in the presence of 5nM Daratumumab or isotype control antibodies which were present in the assay period. As shown in **FIGS. 5A-5B**, all tested trispecific led to cell lysis in a concentration-dependent manner in the presence and absence of Daratumumab. The EC50 values were then calculated in the presence and absence of Daratumumab (**Table D**). The cell killing activity of

CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with CD38VH1 anti-CD38 binding domain was reduced by about 24 fold by Daratumumab, while trispecific antibodies with the CD38hhy992, CD38hyb5739, CD38hyb6284, CD38hhy1195, or CD38hhy1370 anti-CD38 binding domains also exhibited reductions in cell killing activity in the presence of Daratumumab (**Table D**).

Table D. *In vitro* killing activity against human lymphoma cell line OCI-LY19 (CD38+/CD28-) by selected CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains in the presence of Daratumumab.

	Anti-CD38 binding domains					
EC50 (pM)	CD38V H1	CD38hhy9 92	CD38hyb57 39	CD38hyb62 84	CD38hhy11 95	CD38hhy13 70
With Dara	135.9	133.3	219.1	81.05	715.2	209.8
With huma n IgG1	5.662	57.32	60.97	42.07	296.4	58.54

Example 4: CD38/CD28xCD3 trispecific antibodies promote CMV-specific immune response

[0330] As part of adaptive immunity, T cell immunity plays a crucial role in controlling viral infection and cancer, possibly eliminating infected cells and malignant cells which result in clearance of viral infection or cure of cancer. In chronic infectious diseases such as Herpes viral infection (HSV, CMV, EBV, etc.), HIV, and HBV viruses establish their persistence in humans by various mechanisms including immune suppression, T cell exhaustion, and latency establishment. Nevertheless, viral infection generally induces viral antigen specific immunity including antigen specific CD8 T cells that can readily recognize infected cells for controlling or killing through cytokine release or cytotoxic T cell (CTL) mediated killing

processes. Thus, viral antigen specific T cell activation and/or amplification *in vivo* and/or *ex vivo* provide therapeutic strategies against chronic viral infections.

[0331] Anti-CD38/CD28xCD3 trispecific antibodies were developed and evaluated for their potential in activating T cells, and promoting proliferation and/or amplification of antigen specific T cells. These trispecific Abs can effectively expand CD4 and CD8 effector and memory populations, including antigen specific CD8 T central memory and effector memory cells *in vitro*. Specifically, *in vitro* expansion of CMV and EBV specific CD8 central memory and effector memory cells were demonstrated. The anti-CD38/CD28xCD3 trispecific antibodies described herein exhibited novel properties by engaging CD3/CD28/CD38, providing signaling pathways to stimulate and expand T cells, which may offer an effective strategy treating chronic infectious diseases such as HSV, CMV, EBV, HIV-1, and HBV infections.

[0332] In this Example, the ability of CD38/CD28xCD3 trispecific antibodies to promote activation and expansion of CMV-specific T cells was determined.

Materials and Methods

In vitro T cell proliferation measurement

[0333] T cells were isolated from human PBMC donors by negative selection using a magnetic Pan T Cell Isolation Kit (Miltenyi Biotec GmbH, Germany). Antibodies were coated onto 96-well cell culture plates by preparing the antibodies in sterile PBS and dispensing 50 μ L into each well (350 ng/well). The plates were then incubated at 37°C for at least 2 hours and then washed with sterile PBS. The untouched T cells were added to the antibody-coated plates (5×10^5 cells/mL) and incubated at 37°C for multiple days. The cells were passaged with new cell culture media onto fresh antibody-coated plates on Day 4. In certain experiments with 7 days incubation, only fresh medium was added without changing to fresh antibody-coated plate. The cells were collected at specific time points and cell numbers calculated using CountBright™ counting beads.

In vitro T cell proliferation assay and T cell subset determination

[0334] Peripheral blood mononuclear cells were isolated from blood of healthy human donors collected by Research Blood Components, LLC (Boston, MA). The PBMCs were added to antibody-coated plates (350 ng/well) (5×10^5 cells/mL), as previously described above, and incubated at 37°C for 3 and 7 days. The cells were collected at specific time points and analyzed by flow cytometry for T cell subsets: naïve (CCR7+ CD45RO-), Tcm (CCR7+

CD45RO+), Tem (CCR7- CD45RO+), Tregs (CD4+ Foxp3+ CD25hi). CMV pp65-specific and EBV BMLF-specific CD8+ T cells were detected using fluorescent-conjugated pentamer restricted to the PBMC donors' HLA/viral peptide (A*02:01/NLVPMVATV, SEQ ID NO:284), (A*02:01/GLCTLVAML, SEQ ID NO:285), respectively (ProImmune, Oxford, UK). PBMC was obtained from HemaCare (Van Nuys, CA) for donors with known CMV or EBV infection. PMBC from donors negative for the restricting HLA type was used as negative control. Staining was done as per manufacturer's protocol.

Quantification of CMV-specific T-Cells

[0335] As indicated above Peripheral blood mononuclear cells (PBMCs) were isolated from blood of known CMV-infected human donors and added to plates containing the trispecific antibody or control antibody. The plates were incubated at 37°C. The cells were collected at specific time points and analyzed by flow cytometry.

Results

[0336] CD38/CD28sup x CD3mid_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains ΔVH1CD38 (control), CD38VH1, CD38hhy992, CD38hyb5739, CD38hyb6284, CD38hhy1195, and CD38hhy1370 were tested as described above using PBMCs isolated from CMV-infected human donor D (**FIGS. 6A-6J**) and CMV-infected human donor E (**FIGS. 7A-7J**). All tested CD38 trispecific Abs activated and promoted the proliferation of CMV-specific T cells, leading to increases in CMV-specific CD8+ T cells (cells/well) with different potency and kinetics in a dose response manner over the 7 day experiment (CMV Donor D, **FIGS. 6A-6B**; CMV Donor E, **FIGS. 7A-7B**). In addition, all tested CD38 trispecific Abs promoted the amplification (cells/well) of CMV-specific central memory (T_{cm}) (CMV Donor D, **FIGS. 6C-6D**; CMV Donor E, **FIGS. 7C-7D**) and effector memory (T_{em}) CD8+ T cells (CMV Donor D, **FIGS. 6E-6F**; CMV Donor E, **FIGS. 7E-7F**), which were both amplified dramatically in 7 days. **FIGS. 6G-6J** (CMV Donor D) and **FIGS. 7G-7J** (CMV Donor E) provide time courses showing the percent of CMV-specific T_{cm} and T_{em} cells at days 0, 3, and 7 of the 7-day experiments described above.

[0337] Taken together, these data indicate that CD38/CD28xCD3 trispecific antibodies promote activation and expansion of CMV-specific T cells, such as CMV-specific CD8+ T cells, CMV-specific effector memory (T_{em}) CD8+ T cells, and CMV-specific central memory (T_{cm}) CD8+ T cells.

Example 5: CD38/CD28xCD3 trispecific antibodies promote EBV-specific immune response

[0338] Next, the ability of CD38/CD28xCD3 trispecific antibodies to promote activation and expansion of Epstein-Barr virus (EBV)-specific T cells was determined.

Materials and Methods

Quantification of EBV-specific T-Cells

[0339] As indicated above, peripheral blood mononuclear cells (PBMCs) were isolated from blood of known EBV-infected human donors and added to plates containing the trispecific antibody or control antibody. The plates were incubated at 37°C for up to 11 days. The cells were collected at specific time points and analyzed by flow cytometry.

Results

[0340] CD38/CD28^{sup} x CD3^{mid}_ENLQ DKTHT IgG4 FALA trispecific antibodies with alternative anti-CD38 binding domains ΔVH1CD38 (control), CD38VH1, CD38hhy992, CD38hyb5739, CD38hyb6284, CD38hhy1195, and CD38hhy1370 were also tested as described above using PBMCs isolated from EBV-infected donor C (**FIGS. 8A-8J**) and EBV-infected donor D (**FIGS. 9A-12**). All tested CD38 trispecific Abs activated T cells and promoted the proliferation of EBV-specific T cells, leading to increases in EBV-specific CD8⁺ T cells (cells/well) with different potency and kinetics in a dose response manner over the 7 day experiment (EBV Donor C, **FIGS. 8A-8B**; EBV Donor D, **FIGS. 9A-9B**). In addition, all tested CD38 trispecific Abs promoted the amplification (cells/well) of EBV-specific central memory (T_{cm}) (EBV Donor C, **FIGS. 8C-8D**; EBV Donor D, **FIGS. 9C-9D**) and effector memory (T_{em}) CD8⁺ T cells (EBV Donor C, **FIGS. 8E-8F**; EBV Donor D, **FIGS. 9E-9F**), which were both amplified dramatically in 7 days. **FIGS. 8G-8J** (EBV Donor C) and **FIGS. 9G-12** (EBV Donor D) provide time courses showing the percent of EBV-specific T_{cm} and T_{em} cells at days 0, 3, and 7 of the 7-day experiments described above.

[0341] Taken together, these data indicate that CD38/CD28xCD3 trispecific antibodies promote activation and expansion of EBV-specific T cells, such as EBV-specific CD8⁺ T cells, EBV-specific effector memory (T_{em}) CD8⁺ T cells, and EBV-specific central memory (T_{cm}) CD8⁺ T cells.

Example 6: Anti-tumor effects of Her2/CD28 x CD3 trispecific antibody in tumor-bearing mice

[0342] In this Example, the Her2/CD28 x CD3 trispecific antibody was tested for anti-tumor effects in a ZR-75-1 tumor bearing Nod scid gamma (NSG) mouse model engrafted with *in vitro* expanded T cells.

Materials and Methods

[0343] NSG mice were divided into 5 groups of 10 mice each. On Day 0, ZR-75-1 human breast cancer cells were implanted into the mammary fat pad with 50% matrigel into each mouse at 5 million cells/mouse. On Days 17/18, expansion of human CD3+ T cells was begun. Randomization of mice occurred on Day 24 when tumors were approximately 150mm³. On Day 25, all mice were engrafted with *in vitro* expanded human CD3+ T cells at 10 million cells in 300μL/mouse (1QW, 1 IP injection).

[0344] Starting on Day 25, one group of mice received doses of vehicle alone (8% w/v sucrose, 0.05% w/v polysorbate 80, 10mM histidine, pH 5.5), while the other 4 groups received Her2/CD28 x CD3 trispecific antibody, both at 10mL/kg. Groups receiving trispecific antibody were dosed at 100, 10, 1, or 0.1 μg/kg. Antibody or vehicle was administered 1QW intravenously in 2 doses (*e.g.*, Days 25 and 32). Blood and tumor tissue was collected on Day 38 or 39.

Results

[0345] Her2/CD28 x CD3 trispecific antibody (binding protein #2 from Table 1, corresponding to SEQ ID Nos:104-107) was compared to vehicle control for its effects on human breast tumor growth in the NSG mouse model engrafted with *in vitro* expanded human T cells described above. Treatment with Her2/CD28 x CD3 trispecific antibody at the highest dose (100ug/kg) led to the most significant inhibition of tumor growth and regression, although the 10ug/kg dose also showed anti-tumor effects (**FIGS. 13A & 13D**). No significant body weight loss was observed (**FIG. 13B**). Individual tumor volumes over time from each trispecific antibody treatment group are provided in **FIG. 13C**.

[0346] Next, the effect of trispecific antibody treatment on individual immune cell subsets was examined. Human CD45+, human CD8+, and human CD4+ cell populations were measured by flow cytometry, as well as mouse CD45+ cells (**FIGS. 14A-14C**). Highest dose (100ug/kg) of trispecific antibody led to depletion of human CD4+ cells, and this effect was dose dependent (**FIGS. 14B & 14C**). Counts of human CD8+ cells were largely unaffected by trispecific antibody administration.

[0347] The effect of trispecific antibody treatment on tumor infiltrating lymphocytes (TILs) was also assessed by immunohistochemical (IHC) staining for human CD45, CD4, and CD8. Using H&E staining, tumors from the low dose groups (1ug/kg or 0.1ug/kg trispecific antibody) were generally of comparable size as the vehicle control group. As shown in **FIGS. 15A-15C**, human TILs were increased in the group receiving the low dose of Her2/CD28 x CD3 trispecific antibody, but human TILs were sparse in the high dose group. IHC images were also examined quantitatively (**FIGS. 16A-16C**). These results indicated significant reductions in CD45+ and CD8+ cells in the higher trispecific antibody dose groups (100ug/kg and 10ug/kg).

[0348] Compared to vehicle control, tumors from the high dose trispecific antibody treatment groups (100ug/kg or 10ug/kg) were characterized by sparse TILs. Moderate to large numbers of CD45+, CD4+, or CD8+ human TILs were observed in the 1ug/kg and 0.1ug/kg trispecific antibody treatment groups. These TILs were mostly present at the tumor edges but occasionally extended deeper into the tumor core.

[0349] In conclusion, these results demonstrate that treatment of ZR-75-1 breast tumor bearing NSG mice engrafted with *in vitro* activated T cells using 2 intravenous doses of HER2-targeting, T cell-engaging trispecific antibody at 100ug/kg or 10ug/kg resulted in significant reductions in tumor volume and, concomitantly, a significant decrease in TILs. At the 1ug/kg trispecific antibody dose, there was a marginal and inconsistent trend for increased TILs as compared to vehicle control.

Example 7: Effect of anti-HER2 and anti-CD3 antigen binding domain sequences in Her2/CD28 x CD3 trispecific antibody on cancer cell killing

[0350] This Example describes the effect of anti-Her2 and anti-CD3 variable domain sequences on target cell killing. In this Example, a Her2/CD28 x CD3 trispecific antibody (“control”) with wild-type trastuzumab antigen binding domain and an anti-CD3 antigen binding domain without 32/35 QQ mutations in the VL domain (*see* Example 1) was compared with Her2/CD28 x CD3 trispecific antibodies #1-6 from Table 1, corresponding to SEQ ID Nos:100-103, 104-107, 286-289, 290-293, 294-297, and 298-301, respectively.

Materials and Methods

[0351] CD8+ T cells were isolated from human PBMCs from healthy donor using a magnetic bead isolation kit (Miltenyi Biotec). The T cells were used as effector cells against breast cancer cell lines expressing various levels of HER2 at 3:1 (Effector:Target) ratio. The

cells were incubated with experimental or control trispecific antibody for 2 days before flow cytometry acquisition using viability dye (Invitrogen) and PKH26 target cell staining (Sigma). Mean EC50 for target cell lysis was calculated from 2-3 PBMC donors for each trispecific Ab.

Results

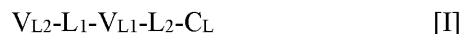
[0352] All trispecific antibodies were characterized for *in vitro* cell lysis of three HER2+ breast cancer target cell lines: HCC1954, BT20, and MDA-MB-231. HCC1954 breast cancer cells were found to express high levels of HER2, as assessed by flow cytometry (up to ~150,000 receptors/cell), IHC (3+), or the HercepTest HER2 expression assay (3+) (**FIG. 17A**). BT20 breast cancer cells were found to express intermediate levels of HER2, as assessed by flow cytometry (~60,000 receptors/cell), IHC (1+), or the HercepTest HER2 expression assay (1+) (**FIG. 17C**). MDA-MB-231 breast cancer cells were found to express low levels of HER2, as assessed by flow cytometry (~9,000 receptors/cell), IHC (0+), or the HercepTest HER2 expression assay (0) (**FIG. 17E**). Results of the cell killing assays targeting HCC1954, BT20, or MDA-MB-231 are shown in **FIGS. 17B, 17D, and 17F**, respectively, comparing binding protein #2 vs. control or binding proteins #1 and #5 vs. control. The results demonstrated that the Her2/CD28 x CD3 trispecific antibodies having 30R/55Q/102E mutations in the anti-HER2 arm and 32/35 QQ mutations in the VL domain of the anti-CD3 arm showed improved target cell killing against all three cell lines, particularly at lower antibody concentrations.

[0353] Mean EC50 (pM) for *in vitro* cell killing was determined for all trispecific antibodies targeting the three breast cancer cell lines noted above (HCC1954, BT20, and MDA-MB-231) as well as the gastric cancer cell lines OE19 (high HER2 expression) and GSU (intermediate HER2 expression). Generally, the Her2/CD28 x CD3 trispecific antibodies having mutations in the anti-HER2 arm and in the VL domain of the anti-CD3 arm showed a lower EC50 (and thus superior cell killing) against all three breast cancer cell lines (**FIG. 18A**) and both gastric cancer cell lines (**FIG. 18B**). These results demonstrate that, while all trispecific antibodies are able to induce cell killing of HER2+ cells, the mutated trispecific antibodies consistently displayed improved cell killing efficacy against multiple target cell types.

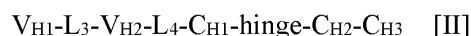
CLAIMS

What is claimed is:

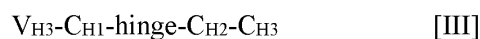
1. A binding protein comprising four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of

IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site.

2. The binding protein of claim 1, wherein the first binding site binds a CD28 polypeptide.

3. The binding protein of claim 2, wherein the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYY (SEQ ID NO:49), a CDR-H2 sequence comprising the amino acid sequence of IYPGNVNT (SEQ ID NO:50), and a CDR-H3 sequence comprising the amino acid sequence of TRSHYGLDWNFDV (SEQ ID NO:51), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QNIYVW (SEQ ID NO:52), a CDR-L2 sequence comprising the amino acid sequence of KAS (SEQ ID NO:53), and a CDR-L3 sequence comprising the amino acid sequence of QQGQTYPY (SEQ ID NO:54).

4. The binding protein of claim 3, wherein the V_{H1} domain comprises the amino acid sequence of
 of
 QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYYIHWVRQAPGQGLEWIGSIYPGNV
 NTNYAQKFQGRATLTVDTSISTAYMELSRLSDDTAVYYCTRSHYGLDWNFDVWG
 KGTTVTVSS (SEQ ID NO:91), and/or the V_{L1} domain comprises the amino acid sequence of
 DIQMTQSPSSLSASVGDRVTITCQASQNIYVWLNWYQQKPGKAPKLLIYKASNLHTG
 VPSRFSGSGSGTDFTLTISLQPEDIATYYCQQGQTPYPTFGQGTKLEIK (SEQ ID
 NO:92).

5. The binding protein of any one of claims 1-4, wherein the CDR-L1 sequence of the V_{L2} domain comprises an amino acid sequence selected from the group consisting of QSLVHQNAQTY (SEQ ID NO:59), QSLVHENLQTY (SEQ ID NO:60), QSLVHENLFTY (SEQ ID NO:61), and QSLVHENLRITY (SEQ ID NO:62).

6. The binding protein of claim 5, wherein the V_{H2} domain comprises the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
 NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY
 WGQGTLLTVSS (SEQ ID NO:93) or

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIKDKS
 NSYATYYASSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDYW
 GQGTLLTVSS (SEQ ID NO:302), and/or the V_{L2} domain comprises an amino acid

sequence selected from the group consisting of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS
 N RFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
 ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVS
 N RFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
 ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVS
 NR FSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
 ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWYLQKPGQSPQSLIYKVS
 N RFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
 ID NO:98).

7. The binding protein of any one of claims 1-6, wherein the third antigen binding site binds a tumor target protein.

8. The binding protein of any one of claims 1-6, wherein the third antigen binding site binds a human CD38 polypeptide.

9. The binding protein of claim 8, wherein:

(a) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:13), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:14), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:15), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:16), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:17), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:18);

(b) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTLTEFS (SEQ ID NO:19), a CDR-H2 sequence comprising the amino acid sequence of FDPEDGET (SEQ ID NO:20), and a CDR-H3 sequence comprising the amino acid sequence of TTGRFFDWF (SEQ ID NO:21), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVISRF (SEQ ID NO:22), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:23), and a CDR-L3 sequence comprising the amino acid sequence of QQDSNLPIT (SEQ ID NO:24);

(c) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYAFTTYL (SEQ ID NO:25), a CDR-H2 sequence comprising the amino acid sequence of INPGSGST (SEQ ID NO:26), and a CDR-H3 sequence comprising the amino acid sequence of ARYAYGY (SEQ ID NO:27), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QNVGTA (SEQ ID NO:28), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:29), and a CDR-L3 sequence comprising the amino acid sequence of QQYSTYPFT (SEQ ID NO:30);

(d) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYSFTNYA (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of ISPYYGDT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARRFEGFYYSMDY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHSNGNTY (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of SQSTHVPLT (SEQ ID NO:36);

(e) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARDPGLRYFDGGMDV (SEQ ID NO:39), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGISSY (SEQ ID NO:40), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:41), and a CDR-L3 sequence comprising the amino acid sequence of QQLNSFPYT (SEQ ID NO:42); or

(f) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:43), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:44), and a CDR-H3 sequence comprising the amino acid sequence

of ARMFRGAFDY (SEQ ID NO:45), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:46), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:47), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:48).

10. The binding protein of claim 9, wherein:

(a) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYAMHWVKEAPGQRLEWIGYIYPGQGGTNYNQKFQGRATLTADTSASTAYMELSSLRSEDNAVYFCARTGGLRRAYFTYWGQGTLLTVSS (SEQ ID NO:79), and/or the V_{L3} domain comprises the amino acid sequence of DIVLTQSPATLSLSPGERATISCRASQSVSSYGQGMHWYQQKPGQPPRLIYGASSRATGIPARFSGSGSGTDFTLTISPLEDFAVYYCQQNKEDPWTFGGGKLEIK (SEQ ID NO:80);

(b) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEFSIHWVRQAPGQGLEWMGGFDPEDGETIYAQKFQGRVIMTEDTSTDATYMEMNSLRSEDTAIYYCTTGRFFDWFVGQGTLLTVSS (SEQ ID NO:81), and/or the V_{L3} domain comprises the amino acid sequence of EIILTQSPAILSLSPGERATLSCRASQSVISRFLSWYQVKPGLAPRLIYGASTRATGIPVRFSGSGSGTDFTSLTISSLQPEDCAVYYCQQDSNLPITFGQGTRLEIK (SEQ ID NO:82);

(c) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYAFTTYLVEWIRQRPQGQGLEWMGVINPGSGSTNYAQKFQGRVTMTVDRSSTTAYMELSRLRSDDTAVYYCARYAYGYWGQGTLLTVSS (SEQ ID NO:83), and/or the V_{L3} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRYTGVPSPRFSGSGSGTDFTLTISLQPEDLATYYCQQYSTYPFTFGQGTKLEIK (SEQ ID NO:84);

(d) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYSTNYAVHWVRQAPGQGLEWMGVISPY YGDTTYAQKFQGRVTMTVDKSSSTAYMELSRLRSDDTAVYYCARRFEGFYYSMDYWGQGTLLTVSS (SEQ ID NO:85), and/or the V_{L3} domain comprises the amino acid sequence of DVVMTQSPLSLPVTLGQPASISCRPSQSLVHSNGNTYLNWYQQRPGQSPKLLIYKVS

KRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGKVEIK
(SEQ ID NO:86);

(e) the V_{H3} domain comprises the amino acid sequence of
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMWVRQAPGKGLEWVAVIWYDG
SNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDGGMD
VWGQGTITVTVSS (SEQ ID NO:87), and/or the V_{L3} domain comprises the amino acid
sequence of
DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSGVP
SRFSGSGSGTEFTLTISLQPEDFATYYCQQLNSFPYTFGQGTKLEIK (SEQ ID NO:88);
or

(f) the V_{H3} domain comprises the amino acid sequence of
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDG
SNKYYADSVKGRFTISGDNSKNTLYLQMNSLRAEDTAVYYCARMFRGAFDYWGQG
TLTVTVSS (SEQ ID NO:89), and/or the V_{L3} domain comprises the amino acid sequence of
AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQSG
VPSRFSGSGSGTDFTLTISGLQPEDSATYYCLQDYIYYPTFGQGTKVEIK (SEQ ID
NO:90).

11. The binding protein of claim 8, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:156
or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID
NO:156; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:157
or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID
NO:157; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:158 or
an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID
NO:158; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID
NO:159 or an amino acid sequence that is at least 95% identical to the amino acid sequence of
SEQ ID NO:159;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:160
or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID
NO:160; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:161
or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID

NO:161; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:162 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:162; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:163 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:163;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:164 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:164; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:165 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:165; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:166 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:166; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:167 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:167;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:168 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:168; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:169 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:169; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:170 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:170; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:171 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:171;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:172 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:172; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:173 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:173; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:174 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:174; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:175 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:175;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:176 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:176; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:177 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:177; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:178 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:178; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:179 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:179;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:181 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:181; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:182 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:182; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:183 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:183; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:184 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:184; or

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:185 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:185; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:186 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:186; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:187 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:187; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:188 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:188.

12. The binding protein of any one of claims 1-7, wherein the third antigen binding site binds a human HER2 polypeptide.

13. The binding protein of claim 12, wherein:

(a) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1) or GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), IYPTQGYT (SEQ ID NO:4), or IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), SRWGGEFGFYAMDY (SEQ ID NO:7), or SRWGGSGFYAMDY (SEQ ID NO:8), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9) or QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12);

(b) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIKDTY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12);

(c) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEFGFYAMDY (SEQ ID NO:7), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12);

(d) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDTY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12);

(e) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTQGYT (SEQ ID NO:4), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGSGFYAMDY (SEQ ID NO:8), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12);

(f) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIRDY (SEQ ID NO:2), a CDR-H2 sequence comprising the amino acid sequence of IYPTNAYT (SEQ ID NO:5), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGEFGFYAMDY (SEQ ID NO:7), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVNTA (SEQ ID NO:9), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12); or

(g) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFNIKDY (SEQ ID NO:1), a CDR-H2 sequence comprising the amino acid sequence of IYPTNGYT (SEQ ID NO:3), and a CDR-H3 sequence comprising the amino acid sequence of SRWGGDGFYAMDY (SEQ ID NO:6), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVQTA (SEQ ID NO:10), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:11), and a CDR-L3 sequence comprising the amino acid sequence of QQHYTTP (SEQ ID NO:12).

14. The binding protein of claim 13, wherein:

(a) the V_{H3} domain comprises the amino acid sequence of
 EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
 GQGTLVTVSS (SEQ ID NO:72),
 EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMDYW
 GQGTLVTVSS (SEQ ID NO:73),
 EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYW

GQGTLVTVSS (SEQ ID NO:74),
 EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTNA
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYW
 GQGTLVTVSS (SEQ ID NO:75), or
 EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTNA
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYW
 GQGTLVTVSS (SEQ ID NO:76), and/or the V_{L3} domain comprises the amino acid sequence
 of
 DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
 VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
 NO:77) or
 DIQMTQSPSSLSASVGDRVTITCRASQDVQTAFAWYQQKPGKAPKLLIYSASFLYSG
 VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
 NO:78);

(b) the V_{H3} domain comprises the amino acid sequence of
 EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
 GQGTLVTVSS (SEQ ID NO:72), and/or the V_{L3} domain comprises the amino acid sequence
 of
 DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
 VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
 NO:77);

(c) the V_{H3} domain comprises the amino acid sequence of
 EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
 YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYW
 GQGTLVTVSS (SEQ ID NO:73), and/or the V_{L3} domain comprises the amino acid sequence
 of
 DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
 VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
 NO:77);

(d) the V_{H3} domain comprises the amino acid sequence of
 EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTNA

YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYW
GQGLTVTVSS (SEQ ID NO:75), and/or the V_{L3} domain comprises the amino acid sequence
of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77);

(e) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMDYW
GQGLTVTVSS (SEQ ID NO:74), and/or the V_{L3} domain comprises the amino acid sequence
of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77);

(f) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTNA
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMDYW
GQGLTVTVSS (SEQ ID NO:76), and/or the V_{L3} domain comprises the amino acid sequence
of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:77); or

(g) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGLTVTVSS (SEQ ID NO:72), and/or the V_{L3} domain comprises the amino acid sequence
of

DIQMTQSPSSLSASVGDRVTITCRASQDVQTA VAWYQQKPGKAPKLLIYSASFLYSG
VPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID
NO:78).

15. The binding protein of claim 12, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:100 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:100; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:101 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:101; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:102 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:102; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:103 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:103;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:104 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:104; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:105 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:105; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:106 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:106; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:107 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:107;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:112 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:112; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:113 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:113; 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;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:116 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:116; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:117 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:117; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:118 or

an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:118; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:119 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:119;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:120 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:120; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:121 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:121; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:122 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:122; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:123 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:123;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:124 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:124; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:125 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:125; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:126 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:126; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:127 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:127;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:128 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:128; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:129 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:129; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:130 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:130; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:131 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:131;

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:132 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:132; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:133 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:133; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:134 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:134; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:135 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:135;

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:136 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:136; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:137 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:137; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:138 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:138; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:139 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:139;

(j) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:140 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:140; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:141 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:141; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:142 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:142; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:143 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:143;

(k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:144 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:144; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:145 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:145; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:146 or

an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:146; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:147 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:147;

(l) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:148 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:148; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:149 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:149; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:150 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:150; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:151 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:151;

(m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:152 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:152; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:153 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:153; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:154 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:154; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:155 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:155;

(n) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:286 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:286; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:287 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:287; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:288 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:288; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:289 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:289;

(o) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:290 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:290; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:291 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:291; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:292 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:292; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:293 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:293;

(p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:294 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:294; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:295 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:295; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:296 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:296; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:297 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:297; or

(q) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:298 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:298; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:299 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:299; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:300 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:300; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:301 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:301.

16. The binding protein of any one of claims 1-15, wherein at least one of L₁, L₂, L₃ or L₄ is independently 0 amino acids in length.

17. The binding protein of any one of claims 1-15, wherein (a) L₁, L₂, L₃ and L₄ each independently are zero amino acids in length or comprise a sequence selected from the group

consisting of GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO: 70), S, RT, TKGPS (SEQ ID NO: 68), GQPKAAP (SEQ ID NO: 67), and GGSGSSGSGG (SEQ ID NO: 71); or (b) L₁, L₂, L₃ and L₄ each independently comprise a sequence selected from the group consisting of GGGGSGGGGS (SEQ ID NO:69), GGGGSGGGSGGGGS (SEQ ID NO:70), S, RT, TKGPS (SEQ ID NO:68), GQPKAAP (SEQ ID NO: 67), and GGSGSSGSGG (SEQ ID NO:71).

18. The binding protein of any one of claims 1-15, wherein L₁ comprises the sequence GQPKAAP (SEQ ID NO: 67), L₂ comprises the sequence TKGPS (SEQ ID NO:68), L₃ comprises the sequence S, and L₄ comprises the sequence RT.

19. The binding protein of any one of claims 1-15, wherein at least one of L₁, L₂, L₃ or L₄ comprises the sequence DKTHT (SEQ ID NO:66).

20. The binding protein of claim 19, wherein L₁, L₂, L₃ and L₄ comprise the sequence DKTHT (SEQ ID NO:66).

21. The binding protein of any one of claims 1-20, wherein the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG4 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ 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.

22. The binding protein of any one of claims 1-20, wherein the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG4 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ domains each comprise amino acid substitutions at positions corresponding to positions 233-236 of human IgG4 according to EU Index, wherein the amino acid substitutions are E233P, F234V, L235A, and a deletion at 236.

23. The binding protein of any one of claims 1-22, wherein the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG4 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ 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.

24. The binding protein of any one of claims 1-20, wherein the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG1 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ domains 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.
25. The binding protein of any one of claims 1-20, wherein the hinge-CH₂-CH₃ domains of the second and the third polypeptide chains are human IgG1 hinge-CH₂-CH₃ domains, and wherein the hinge-CH₂-CH₃ domains each comprise amino acid substitutions at positions corresponding to positions 298, 299, and 300 of human IgG1 according to EU Index, wherein the amino acid substitutions are S298N, T299A, and Y300S.
26. The binding protein of any one of claims 1-25, wherein the hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ 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.
27. The binding protein of any one of claims 1-25, wherein the hinge-CH₂-CH₃ 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 hinge-CH₂-CH₃ 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.
28. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the binding protein of any one of claims 1-27.
29. An expression vector comprising the nucleic acid molecule of claim 28.
30. An isolated host cell comprising the nucleic acid molecule of claim 28 or the expression vector of claim 29.

31. The isolated host cell of claim 30, wherein the host cell is a mammalian or insect cell.
32. A pharmaceutical composition comprising the binding protein of any one of claims 1-27 and a pharmaceutically acceptable carrier.
33. 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 claims 1-27 or the pharmaceutical composition of claim 32.
34. The method of claim 33, wherein the at least one binding protein is co-administered with a chemotherapeutic agent.
35. The method of claim 33 or claim 34, wherein the patient is a human.
36. The method of any one of claims 33-35, wherein the third antigen binding site binds a human CD38 polypeptide, and wherein cancer cells from the patient express CD38.
37. The method of claim 36, wherein the cancer is multiple myeloma.
38. The method of claim 36, wherein the cancer is acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or a B cell lymphoma.
39. The method of any one of claims 36-38, wherein, prior to administration of the binding protein, the patient has been treated with daratumumab without a wash-out period.
40. The method of any one of claims 33-35, wherein the third antigen binding site binds a human HER2 polypeptide, and wherein cancer cells from the patient express HER2.
41. The method of claim 40, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, or non-small cell lung cancer (NSCLC).
42. The binding protein of any one of claims 7-27 or the pharmaceutical composition of claim 32 for use in preventing and/or treating cancer in a patient.
43. The binding protein for use or the composition for use of claim 42, wherein the at least one binding protein is to be co-administered with a chemotherapeutic agent.
44. The binding protein for use or the composition for use of claim 42 or claim 43, wherein the patient is a human.

45. The binding protein for use or the composition for use of any one of claims 42-44, wherein the third antigen binding site binds a human CD38 polypeptide, and wherein cancer cells from the patient express CD38.

46. The binding protein for use or the composition for use of claim 45, wherein the cancer is multiple myeloma.

47. The binding protein for use or the composition for use of claim 45, wherein the cancer is acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or a B cell lymphoma.

48. The binding protein for use or the composition for use of any one of claims 45-47, wherein, prior to administration of the binding protein, the patient has been treated with daratumumab without a wash-out period.

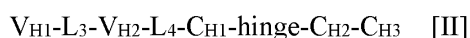
49. The binding protein for use or the composition for use of any one of claims 42-44, wherein the third antigen binding site binds a human HER2 polypeptide, and wherein cancer cells from the patient express HER2.

50. The binding protein for use or the composition for use of claim 49, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, or non-small cell lung cancer (NSCLC).

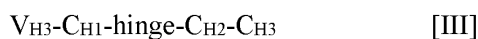
51. A method for expanding T cells, comprising contacting a T cell with a binding protein comprising four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

52. The method of claim 51, wherein the T cell expresses a chimeric antigen receptor (CAR) on its cell surface or comprises a polynucleotide encoding a CAR.

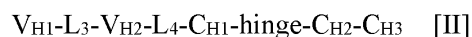
53. The method of claim 51 or claim 52, wherein the T cell is a memory T cell or an effector T cell.

54. A method for expanding virus-specific memory T cells, comprising contacting a virus-specific memory T cell with a binding protein comprising four polypeptide chains that form

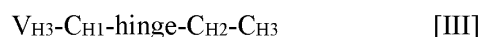
the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino

acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

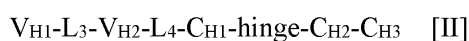
55. The method of claim 54, wherein the virus-specific memory T cell is contacted with the binding protein *in vitro* or *ex vivo*.

56. The method of claim 54 or claim 55, wherein contacting the virus-specific memory T cell with the binding protein causes activation and/or proliferation of virus-specific memory T cells.

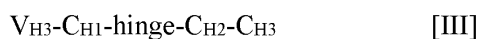
57. A method for treating chronic viral infection, comprising administering to a patient in need thereof an effective amount of a binding protein comprising four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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

L₁, L₂, L₃ and L₄ 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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

58. The method of claim 57, wherein the patient is a human.

59. The method of claim 57 or claim 58, wherein the binding protein is administered to the patient in pharmaceutical formulation comprising the binding protein and a pharmaceutically acceptable carrier.

60. The method of any one of claims 57-59, wherein administration of the binding protein results in activation and/or proliferation of virus-specific memory T cells in the patient.

61. The method of any one of claims 53-56 and 60, wherein the memory T cells are CD8⁺ or CD4⁺ memory T cells.

62. The method of any one of claims 53-56, 60, and 61, wherein the memory T cells are central memory T cells (T_{CM}) or effector memory T cells (T_{EM}).

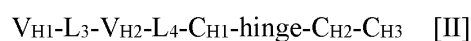
63. The method of any one of claims 54-62, wherein the virus is a human immunodeficiency virus (HIV), influenza virus, cytomegalovirus (CMV), hepatitis B virus (HBV), human papillomavirus (HPV), Epstein-barr virus (EBV), human foamy virus (HFV), herpes simplex virus 1 (HSV-1), or herpes simplex virus 1 (HSV-2).

64. The method of any one of claims 51-63, wherein the CD28 polypeptide is a human CD28 polypeptide, wherein the CD3 polypeptide is a human CD3 polypeptide, and wherein the CD38 polypeptide is a human CD38 polypeptide.

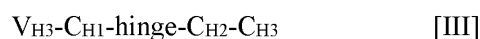
65. A binding protein for use in expanding T cells, wherein the binding protein is to be contacted with a T cell, wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X_1 is E or Q, X_2 is A or L, and X_3 is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

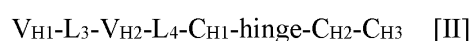
66. The binding protein for use of claim 65, wherein the T cell expresses a chimeric antigen receptor (CAR) on its cell surface or comprises a polynucleotide encoding a CAR.

67. The binding protein for use of claim 65 or claim 66, wherein the T cell is a memory T cell or an effector T cell.

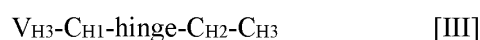
68. A binding protein for use in expanding virus-specific memory T cells, wherein the binding protein is to be contacted with a virus-specific memory T cell, wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X_1 is E or Q, X_2 is A or L, and X_3 is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

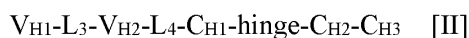
69. The binding protein for use of claim 68, wherein the virus-specific memory T cell is to be contacted with the binding protein *in vitro* or *ex vivo*.

70. The binding protein for use of claim 68 or claim 69, wherein contacting the virus-specific memory T cell with the trispecific binding protein causes activation and/or proliferation of virus-specific memory T cells.

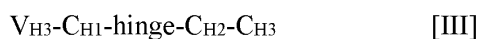
71. A binding protein for use in treating chronic viral infection, wherein the binding protein is to be administered to a patient in need thereof, wherein the binding protein comprises four polypeptide chains that form the three antigen binding sites, wherein a first polypeptide chain comprises a structure represented by the formula:



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



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



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



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; and

wherein V_{H1} and V_{L1} form a first antigen binding site that binds a CD28 polypeptide;

wherein V_{H2} and V_{L2} form a second antigen binding site that binds a CD3 polypeptide, wherein the V_{H2} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFTKAW (SEQ ID NO:55), a CDR-H2 sequence comprising the amino acid sequence of IKDKSNSYAT (SEQ ID NO:56), and a CDR-H3 sequence comprising the amino acid sequence of RGVYYALSPFDY (SEQ ID NO:57), and the V_{L2} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHX₁NX₂X₃TY, wherein X₁ is E or Q, X₂ is A or L, and X₃ is Q, R, or F (SEQ ID NO:180), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:64), and a CDR-L3 sequence comprising the amino acid sequence of GQGTQYPFT (SEQ ID NO:65); and

wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

72. The binding protein for use of claim 71, wherein the patient is a human.

73. The binding protein for use of claim 71 or claim 72, wherein the binding protein is to be administered to the patient in pharmaceutical formulation comprising the binding protein and a pharmaceutically acceptable carrier.

74. The binding protein for use of any one of claims 71-73, wherein administration of the binding protein results in activation and/or proliferation of virus-specific memory T cells in the patient.

75. The binding protein for use of any one of claims 67-70 and 74, wherein the memory T cells are CD8⁺ or CD4⁺ memory T cells.

76. The binding protein for use of any one of claims 67-70, 74, and 75, wherein the memory T cells are central memory T cells (T_{CM}) or effector memory T cells (T_{EM}).

77. The binding protein for use of any one of claims 68-76, wherein the virus is a human immunodeficiency virus (HIV), influenza virus, cytomegalovirus (CMV), hepatitis B virus (HBV), human papillomavirus (HPV), Epstein-barr virus (EBV), human foamy virus (HFV), herpes simplex virus 1 (HSV-1), or herpes simplex virus 2 (HSV-2).

78. The binding protein for use of any one of claims 65-77, wherein the CD28 polypeptide is a human CD28 polypeptide, wherein the CD3 polypeptide is a human CD3 polypeptide, and wherein the CD38 polypeptide is a human CD38 polypeptide.

79. The method or binding protein for use of any one of claims 51-78, wherein the V_{H1} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYY (SEQ ID NO:49), a CDR-H2 sequence comprising the amino acid sequence of IYPGNVNT (SEQ ID NO:50), and a CDR-H3 sequence comprising the amino acid sequence of TRSHYGLDWNFDV (SEQ ID NO:51), and the V_{L1} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QNIYVW (SEQ ID NO:52), a CDR-L2 sequence comprising the amino acid sequence of KAS (SEQ ID NO:53), and a CDR-L3 sequence comprising the amino acid sequence of QQGQTYPY (SEQ ID NO:54).

80. The method or binding protein for use of claim 79, wherein the V_{H1} domain comprises the amino acid sequence of

QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPGNV
NTNYAQKFQGRATLTVDTSISTAYMELSRLRSDDTAVYYCTRSHYGLDWNFDVWG
KGTTVTVSS (SEQ ID NO:91), and/or the V_{L1} domain comprises the amino acid sequence of
DIQMTQSPSSLSASVGDRVTITCQASQNIYVWLNWYQQKPGKAPKLLIYKASNLHTG
VPSRFSGSGSGTDFTLTISLQPEDIATYYCQQGQTYPTYTFGQGTKLEIK (SEQ ID
NO:92).

81. The method or binding protein for use of any one of claims 51-80, wherein the CDR-L1 sequence of the V_{L2} domain comprises an amino acid sequence selected from the group consisting of QSLVHQNAQTY (SEQ ID NO:59), QSLVHENLQTY (SEQ ID NO:60), QSLVHENLFTY (SEQ ID NO:61), and QSLVHENLRTY (SEQ ID NO:62).

82. The method or binding protein for use of claim 81, wherein the V_{H2} domain comprises the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKS
NSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDY
WGQGLTVTVSS (SEQ ID NO:93) or

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIKDKS
NSYATYYASSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALSPFDYW
GQGLTVTVSS (SEQ ID NO:302), and/or the V_{L2} domain comprises an amino acid

sequence selected from the group consisting of

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ
ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWYLQKPGQSPQSLIYKVS

RFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK (SEQ ID NO:98).

83. The method or binding protein for use of any one of claims 51-82, wherein:

(a) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTSYA (SEQ ID NO:13), a CDR-H2 sequence comprising the amino acid sequence of IYPGQGGT (SEQ ID NO:14), and a CDR-H3 sequence comprising the amino acid sequence of ARTGGLRRAYFTY (SEQ ID NO:15), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVSSYGQGF (SEQ ID NO:16), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:17), and a CDR-L3 sequence comprising the amino acid sequence of QQNKEDPWT (SEQ ID NO:18);

(b) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTLTEFS (SEQ ID NO:19), a CDR-H2 sequence comprising the amino acid sequence of FDPEDGET (SEQ ID NO:20), and a CDR-H3 sequence comprising the amino acid sequence of TTGRFFDWF (SEQ ID NO:21), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVISRF (SEQ ID NO:22), a CDR-L2 sequence comprising the amino acid sequence of GAS (SEQ ID NO:23), and a CDR-L3 sequence comprising the amino acid sequence of QQDSNLPIT (SEQ ID NO:24);

(c) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYAFTTYL (SEQ ID NO:25), a CDR-H2 sequence comprising the amino acid sequence of INPGSGST (SEQ ID NO:26), and a CDR-H3 sequence comprising the amino acid sequence of ARYAYGY (SEQ ID NO:27), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QNVGTA (SEQ ID NO:28), a CDR-L2 sequence comprising the amino acid sequence of SAS (SEQ ID NO:29), and a CDR-L3 sequence comprising the amino acid sequence of QQYSTYPFT (SEQ ID NO:30);

(d) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYSFTNYA (SEQ ID NO:31), a CDR-H2 sequence comprising the amino acid sequence of ISPYYGDT (SEQ ID NO:32), and a CDR-H3 sequence comprising the amino acid sequence of ARRFEGFYYSMDY (SEQ ID NO:33), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLVHSNGNTY (SEQ ID NO:34), a CDR-L2 sequence comprising the amino acid sequence of KVS (SEQ ID NO:35), and a CDR-L3 sequence comprising the amino acid sequence of SQSTHVPLT (SEQ ID NO:36);

(e) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:37), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:38), and a CDR-H3 sequence comprising the amino acid sequence of ARDPGLRYFDGGMDV (SEQ ID NO:39), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGISSY (SEQ ID NO:40), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:41), and a CDR-L3 sequence comprising the amino acid sequence of QQLNSFPYT (SEQ ID NO:42); or

(f) the V_{H3} domain comprises a CDR-H1 sequence comprising the amino acid sequence of GFTFSSYG (SEQ ID NO:43), a CDR-H2 sequence comprising the amino acid sequence of IWYDGSNK (SEQ ID NO:44), and a CDR-H3 sequence comprising the amino acid sequence of ARMFRGAFDY (SEQ ID NO:45), and the V_{L3} domain comprises a CDR-L1 sequence comprising the amino acid sequence of QGIRND (SEQ ID NO:46), a CDR-L2 sequence comprising the amino acid sequence of AAS (SEQ ID NO:47), and a CDR-L3 sequence comprising the amino acid sequence of LQDYIYYPT (SEQ ID NO:48).

84. The method or binding protein for use of claim 83, wherein:

(a) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYAMHWVKEAPGQRLEWIGYIYPGQGGTNYNQKFQGRATLTADTSASTAYMELSSLRSEDTAVYFCARTGGLRRAYFTYWGQGTLLTVSS (SEQ ID NO:79), and/or the V_{L3} domain comprises the amino acid sequence of DIVLTQSPATLSLSPGERATISCRASQSVSSYGQGMHWYQKPGQPPRLLIYGASSRATGIPARFSGSGSGTDFTLTISPLEPEDFAVYYCQQNKEDPWTFGGGKLEIK (SEQ ID NO:80);

(b) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEFSIHWVRQAPGQGLEWMGGFDPEDGETIYAQKFQGRVIMTEDTSTDYAYMEMNSLRSEDTAIYYCTTGRFFDWFVGQGTLLTVSS (SEQ ID NO:81), and/or the V_{L3} domain comprises the amino acid sequence of EIILTQSPAILSLSPGERATLSRASQSVISRFLSWYQVKPGLAPRLLIYGASTRATGIPVRFSGSGSGTDFSLTISSLQPEDCAVYYCQQDSNLPITFGQGTRLEIK (SEQ ID NO:82);

(c) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYAFTTYLVEWIRQRPGQGLEWMGVINPGSGSTNYAQKFQGRVTMTVDRSSTTAYMELSRSLRSDDTAVYYCARYAYGYWGQGTLL

VTVSS (SEQ ID NO:83), and/or the V_{L3} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRYTG VPSRFSGSGSGTDFTLTISLQPEDLATYYCQQYSTYPFTFGQGTKLEIK (SEQ ID NO:84);

(d) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYSFTNYAVHWVRQAPGQGLEWMGVISPY YGDTTYAQKFQGRVTMTVDKSSSTAYMELSRLSDDTAVYYCARRFEGFYYSMDY WGQGTLLTVSS (SEQ ID NO:85), and/or the V_{L3} domain comprises the amino acid sequence of DVVMTQSPSLPVTLLGQPASISCRPSQSLVHSNGNTYLNWYQQRPGQSPKLLIYKVS KRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGTKVEIK (SEQ ID NO:86);

(e) the V_{H3} domain comprises the amino acid sequence of QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMVWRQAPGKGLEWVAVIWDG SNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDGGMD VWGQGTTLTVSS (SEQ ID NO:87), and/or the V_{L3} domain comprises the amino acid sequence of DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSGVP SRFSGSGSGTEFTLTISLQPEDFATYYCQQLNSFPYTFGQGTKLEIK (SEQ ID NO:88); or

(f) the V_{H3} domain comprises the amino acid sequence of QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWDG SNKYYADSVKGRFTISGDNSKNTLYLQMNSLRAEDTAVYYCARMFRGAFDYWGQGTLLTVSS (SEQ ID NO:89), and/or the V_{L3} domain comprises the amino acid sequence of AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISGLQPEDSATYYCLQDYIYYPTFGQGTKVEIK (SEQ ID NO:90).

85. The method or binding protein for use of any one of claims 51-82, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:156 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:156; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:157

or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:157; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:158 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:158; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:159 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:159;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:160 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:160; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:161 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:161; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:162 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:162; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:163 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:163;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:164 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:164; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:165 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:165; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:166 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:166; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:167 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:167;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:168 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:168; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:169 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:169; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:170 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:170; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID

NO:171 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:171;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:172 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:172; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:173 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:173; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:174 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:174; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:175 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:175;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:176 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:176; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:177 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:177; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:178 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:178; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:179 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:179;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:181 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:181; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:182 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:182; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:183 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:183; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:184 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:184; or

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:185 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ

ID NO:185; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:186 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:186; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:187 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:187; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:188 or an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:188.

86. A vector system comprising one or more vectors encoding a first, second, third, and fourth polypeptide chain of a binding protein of any one of claims 1-27.

87. The vector system of claim 86, wherein 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.

88. A kit of polynucleotides, comprising:

(a) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:189, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:190, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:191, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:192;

(b) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:193, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:194, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:195, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:196;

(c) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:197, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:198, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:199, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:200;

(d) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:201, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:202, a third

polynucleotide comprising the polynucleotide sequence of SEQ ID NO:203, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:204;

(e) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:205, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:206, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:207, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:208;

(f) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:209, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:210, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:211, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:212;

(g) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:213, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:214, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:215, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:216;

(h) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:217, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:218, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:219, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:220;

(i) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:221, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:222, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:223, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:224;

(j) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:225, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:226, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:227, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:228;

(k) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:229, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:230, a third

polynucleotide comprising the polynucleotide sequence of SEQ ID NO:231, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:232;

(l) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:233, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:234, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:235, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:236;

(m) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:237, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:238, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:239, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:240;

(n) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:241, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:242, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:243, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:244;

(o) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:245, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:246, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:247, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:248;

(p) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:249, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:250, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:251, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:252;

(q) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:253, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:254, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:255, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:256;

(r) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:257, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:258, a third

polynucleotide comprising the polynucleotide sequence of SEQ ID NO:259, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:260;

(s) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:261, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:262, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:263, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:264;

(t) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:265, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:266, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:267, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:268;

(u) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:269, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:270, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:271, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:272; or

(v) a first polynucleotide comprising the polynucleotide sequence of SEQ ID NO:273, a second polynucleotide comprising the polynucleotide sequence of SEQ ID NO:274, a third polynucleotide comprising the polynucleotide sequence of SEQ ID NO:275, and a fourth polynucleotide comprising the polynucleotide sequence of SEQ ID NO:276.

89. The kit of claim 88, wherein the first, second, third, and fourth polynucleotides are present on one or more expression vectors.