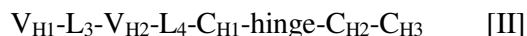


CLAIMS

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



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;

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); and wherein optionally the V_{H1} domain comprises the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWIGSIYPG NVNTNYAQKFQGRATLTVDTSISTAYMELSRLRSDDTAVYYCTRSHYGLDWNFD VWGKGTTVTVSS (SEQ ID NO:91), and/or the V_{L1} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCQASQNIYVWLNWYQQKPGKAPKLLIYKASNLH TGVPSRFSGSGSGTDFTLTISLQPEDATYYCQQGQTYPYTFGQGTKLEIK (SEQ ID NO:92).

4. The binding protein of any one of claims 1-3, 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); and wherein optionally the V_{H2} domain comprises the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWVRQAPGKQLEWVAQIK DKSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALS PFDYWGQGTLVTVSS (SEQ ID NO:93) or

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

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKV SNRFSGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK

(SEQ ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKV
SNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK

(SEQ ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK

(SEQ ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRTYLSWYLQKPGQSPQSLIYKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK

(SEQ ID NO:98).

5. The binding protein of any one of claims 1-4, wherein the third antigen binding site binds a tumor target protein.

6. The binding protein of any one of claims 1-4, wherein the third antigen binding site binds a human CD38 polypeptide.

7. The binding protein of claim 6, 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);

(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);

(g) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCASGYTFTSYAMHWVKEAPGQRLEWIGYIYP GQGGTNYNQKFQGRATLTADTSASTAYMELSSLRSED TAVYFCARTGGLRRAYF TYWGQGT LVT VSS (SEQ ID NO:79), and/or the V_{L3} domain comprises the amino acid sequence of DIVLTQSPATLSLSPGERATISCRASQSVSSYGQGMHWYQQKPGQPPRLLIYGAS SRATGIPARFSGSGSGTDFTLTISP LEPEDFAVYYCQQNKEDPWTFGGGGTKLEIK (SEQ ID NO:80);

(h) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEFSIHWVRQAPGQGLEWMGGFDP EDGETIYAQKFQGRVIMTEDTSTD TAYMEMNSLRSEDTAIYYCTTGRFFDWFWG QGTLVTVSS (SEQ ID NO:81), and/or the V_{L3} domain comprises the amino acid sequence of EIILTQSPAILSLSPGERATLSCRASQSVISRFLSWYQVKPGLAPRLLIYGASTRATGI PVRFSGSGSGTDFSLTISSLQPEDCAVYYCQQDSNLPITFGQGTRLEIK (SEQ ID NO:82);

(i) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYAFTTYLVEWIRQRPGQGLEWMGVINP GSGSTNYAQKFQGRVTMTVDRSSTTAYMELSRLRSDDTAVYYCARYAYGYWG QGTLVTVSS (SEQ ID NO:83), and/or the V_{L3} domain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRY TGVPSRFSGSGSGTDFTLTISSLQPEDLATYYCQQYSTYPFTFGQGTKLEIK (SEQ ID NO:84);

(j) the V_{H3} domain comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYSFTNYAVHWVRQAPGQGLEWMGVISP YYGDTTYAQKFQGRVTMTVDKSSSTAYMELSRLRSDDTAVYYCARRFEGFYYS MDYWGQGTLVTVSS (SEQ ID NO:85), and/or the V_{L3} domain comprises the amino acid sequence of DVVMTQSPLSLPVTLGQPASISCRPSQSLVHSNGNTYLNWYQQRPGQSPKLLIYK VSKRFSGVPRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGTKVEI K (SEQ ID NO:86);

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

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMYWVRQAPGKGLEWVAVIWY
DGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDG
GMDVWGQGT TVTVSS (SEQ ID NO:87), and/or the V_{L3} domain comprises the amino
acid sequence of

DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSG
VPSRFGSGSGTEFTLTISLQPEDFATYYCQQLNSFPYTFGQGTKLEIK (SEQ ID
NO:88); or

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

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWY
DGSNKYYADSVKGRFTISGDNSKNTLYLQMNSLRAEDTAVYYCARMFRGAFDY
WGQGT LVTVSS (SEQ ID NO:89), and/or the V_{L3} domain comprises the amino acid
sequence of

AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQS
GVPSRFGSGSGTDFTLTISGLQPEDSATYYCLQDYIYYPTFGQGTKVEIK (SEQ ID
NO:90).

8. The binding protein of claim 6, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:156;
the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:157; the
third polypeptide chain comprises the amino acid sequence of SEQ ID NO:158; and the
fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:159;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID
NO:160; the second polypeptide chain comprises the amino acid sequence of SEQ ID

NO:161; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:162; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:163;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:164; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:165; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:166; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:167;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:168; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:169; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:170; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:171;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:172; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:173; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:174; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:175;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:176; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:177; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:178; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:179;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:181; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:182; the third polypeptide chain comprises 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

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:185; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:186; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:187; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:188.

9. The binding protein of any one of claims 1-5, wherein the third antigen binding site binds a human HER2 polypeptide.

10. The binding protein of claim 9, wherein:

(a) 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);

(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 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 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 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 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 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);

(g) 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);

(h) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAM
DYWGQGTLVTVSS (SEQ ID NO:72),
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMD
YWGQGTLVTVSS (SEQ ID NO:73),
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMD
YWGQGTLVTVSS (SEQ ID NO:74),

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTN
AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMD
YWGQGTLVTVSS (SEQ ID NO:75), or

EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTN
AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMD
YWGQGTLVTVSS (SEQ ID NO:76), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:77) or

DIQMTQSPSSLSASVGDRVTITCRASQDVQTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:78);

(i) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAM
DYWGQGTLVTVSS (SEQ ID NO:72), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:77);

(j) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDYIHWVRQAPGKGLEWVARIYPTQ
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEFGFYAMD

YWGQGTLVTVSS (SEQ ID NO:73), and/or the V_{L3} domain comprises the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:77);

(k) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHWRQAPGKGLEWVARIYPTN
AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMD
YWGQGTLVTVSS (SEQ ID NO:75), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:77);

(l) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHWRQAPGKGLEWVARIYPTQ
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGSGFYAMD
YWGQGTLVTVSS (SEQ ID NO:74), and/or the V_{L3} domain comprises the amino acid
sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:77);

(m) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIRDITYIHWRQAPGKGLEWVARIYPTN

AYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGEGFYAMD
YWGQGTLVTVSS (SEQ ID NO:76), and/or the V_{L3} domain comprises the amino acid
sequence of
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:77); or

(n) the V_{H3} domain comprises the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAM
DYWGQGTLVTVSS (SEQ ID NO:72), and/or the V_{L3} domain comprises the amino acid
sequence of
DIQMTQSPSSLSASVGDRVTITCRASQDVQTA VAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ
ID NO:78).

11. The binding protein of claim 9, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:100;
the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:101; the
third polypeptide chain comprises the amino acid sequence of SEQ ID NO:102; and the
fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:103;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID
NO:104; the second polypeptide chain comprises the amino acid sequence of SEQ ID
NO:105; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:106;
and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:107;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:112; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:113; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:114; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:115;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:116; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:117; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:118; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:119;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:120; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:121; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:122; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:123;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:124; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:125; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:126; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:127;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:128; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:129; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:130; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:131;

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:132; the second polypeptide chain comprises the amino acid sequence of SEQ ID

NO:133; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:134; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:135;

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:136; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:137 ; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:138; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:139;

(j) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:140; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:141 ; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:142; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:143;

(k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:144; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:145; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:146; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:147;

(l) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:148; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:149; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:150; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:151;

(m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:152; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:153; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:154; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:155;

(n) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:286; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:287; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:288; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:289;

(o) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:290; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:291 ; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:292; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:293;

(p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:294; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:295 ; the third polypeptide chain comprises 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

(q) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:298; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:299; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:300; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:301.

12. The binding protein of any one of claims 1-11, wherein:

(a) 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);

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

(c) 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; or

(d) at least one of L₁, L₂, L₃ or L₄ comprises the sequence DKTHT (SEQ ID NO:66), wherein optionally L₁, L₂, L₃ and L₄ comprise the sequence DKTHT (SEQ ID NO:66).

13. The binding protein of any one of claims 1-7, 9, 10, and 12, wherein:

(a) the hinge-C_{H2}-C_{H3} domains of the second and the third polypeptide chains are human IgG4 hinge-C_{H2}-C_{H3} domains, and wherein the hinge-C_{H2}-C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 234 and 235 of human IgG4 according to EU Index, wherein the amino acid substitutions are F234A and L235A;

(b) the hinge-C_{H2}-C_{H3} domains of the second and the third polypeptide chains are human IgG4 hinge-C_{H2}-C_{H3} domains, and wherein the hinge-C_{H2}-C_{H3} 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;

(c) the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG1 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} 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; or

(d) the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG1 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} 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.

14. The binding protein of any one of claims 1-7, 9, 10, 12, and 13, wherein the hinge- C_{H2} - C_{H3} domains of the second and the third polypeptide chains are human IgG4 hinge- C_{H2} - C_{H3} domains, and wherein the hinge- C_{H2} - C_{H3} domains each comprise amino acid substitutions at positions corresponding to positions 228 and 409 of human IgG4 according to EU Index, wherein the amino acid substitutions are S228P and R409K.

15. The binding protein of any one of claims 1-7, 9, 10, and 12-14, wherein:

(a) the hinge- C_{H2} - C_{H3} domain of the second polypeptide chain comprises amino acid substitutions at positions corresponding to positions 349, 366, 368, and 407 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are Y349C, T366S, L368A, and Y407V; and wherein the hinge- C_{H2} - C_{H3} domain of the third polypeptide chain comprises amino acid substitutions at positions corresponding to positions 354 and 366 of human IgG1 or IgG4 according to EU Index, wherein the amino acid substitutions are S354C and T366W; or

(b) 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.

16. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the binding protein of any one of claims 1-15.

17. An expression vector comprising the nucleic acid molecule of claim 16.

18. An isolated host cell comprising the nucleic acid molecule of claim 16 or the expression vector of claim 17; wherein optionally the host cell is a mammalian or insect cell.

19. A pharmaceutical composition comprising the binding protein of any one of claims 1-15 and a pharmaceutically acceptable carrier.

20. The binding protein of any one of claims 1-15 or the pharmaceutical composition of claim 19 for use in treating cancer in a patient.

21. The binding protein for use or the composition for use of claim 20, wherein the at least one binding protein is to be co-administered with a chemotherapeutic agent.

22. The binding protein for use or the composition for use of claim 20 or claim 21, wherein the patient is a human.

23. The binding protein for use or the composition for use of any one of claims 20-22, wherein the third antigen binding site binds a human CD38 polypeptide, and wherein cancer cells from the patient express CD38; wherein optionally the cancer is multiple myeloma, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or a B cell lymphoma.

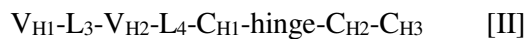
24. The binding protein for use or the composition for use of claim 23, wherein, prior to administration of the binding protein, the patient has been treated with daratumumab without a wash-out period.

25. The binding protein for use or the composition for use of any one of claims 20-22, wherein the third antigen binding site binds a human HER2 polypeptide, and wherein cancer cells from the patient express HER2; wherein optionally the cancer is breast cancer, colorectal cancer, gastric cancer, or non-small cell lung cancer (NSCLC).

26. 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 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

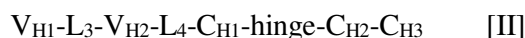
wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

27. The binding protein for use of claim 26, wherein the T cell expresses a chimeric antigen receptor (CAR) on its cell surface or comprises a polynucleotide encoding a CAR; and/or wherein the T cell is a memory T cell or an effector T cell.

28. 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 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

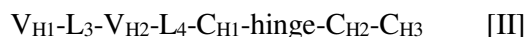
wherein V_{H3} and V_{L3} form a third antigen binding site that binds a CD38 polypeptide.

29. The binding protein for use of claim 28, wherein the virus-specific memory T cell is to be contacted with the binding protein *in vitro* or *ex vivo*; and/or wherein contacting the virus-specific memory T cell with the trispecific binding protein causes activation and/or proliferation of virus-specific memory T cells.

30. 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 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.

31. The binding protein for use of claim 30, wherein the patient is a human.

32. The binding protein for use of claim 30 or claim 31, wherein the binding protein is to be administered to the patient in pharmaceutical formulation comprising the binding protein and a pharmaceutically acceptable carrier; and/or wherein administration of the binding

protein results in activation and/or proliferation of virus-specific memory T cells in the patient.

33. The binding protein for use of any one of claims 27-29 and 32, wherein the memory T cells are CD8+ or CD4+ memory T cells; wherein optionally the memory T cells are central memory T cells (T_{CM}) or effector memory T cells (T_{EM}).

34. The binding protein for use of any one of claims 28-33, 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).

35. The binding protein for use of any one of claims 26-34, 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.

36. The binding protein for use of any one of claims 26-35, 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 QQQQTYPY (SEQ ID NO:54); wherein optionally the V_{H1} domain comprises the amino acid sequence of QVQLVQSGAEVVKPGASVKVSCASGYTFTSYYIHWVRQAPGQGLEWIGSIYPG NVNTNYAQKFQGRATLTVDTSISTAYMELSRRLRSDDTAVYYCTRSHYGLDWNFD

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

DIQMTQSPSSLSASVGDRVTITCQASQNIYVWLNWYQQKPGKAPKLLIYKASNLH
TGVPSRFSGSGSGTDFTLTISLQPEDATYYCQQGQTYPTYTFGQGTKLEIK (SEQ
ID NO:92).

37. The binding protein for use of any one of claims 26-36, 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); wherein
optionally the V_{H2} domain comprises the amino acid sequence of

QVQLVESGGGVVQPGRSLRLSCAASGFTFTKAWMHWRQAPGKQLEWVAQIK
DKSNSYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCRGVYYALS
PFDYWGQGTLVTVSS (SEQ ID NO:93) or

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

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHQNAQTYLSWYLQKPGQSPQSLIYKV
SNRFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:95),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLQTYLSWYLQKPGQSPQSLIYKV
SNRFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK
(SEQ ID NO:96),

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLFTYLSWYLQKPGQSPQSLIYKVS

NRFSGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK

(SEQ ID NO:97), and

DIVMTQTPLSLSVTPGQPASISCKSSQSLVHENLRITYLSWYLQKPGQSPQSLIYKVS

NRFSGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCGQGTQYPFTFGSGTKVEIK

(SEQ ID NO:98).

38. The binding protein for use of any one of claims 26-37, 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);

(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);

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

QVQLVQSGAEVVKPGASVKVSCKASGYTFTSYAMHWVKEAPGQRLEWIGYIYP
GQGGTNYNQKFQGRATLTADTSASTAYMELSSLRSEDTAVYFCARTGGLRRAYF
TYWGQGTLLTVSS (SEQ ID NO:79), and/or the V_{L3} domain comprises the amino acid sequence of

DIVLTQSPATLSLSPGERATISCRASQSVSSYGQGMHWYQQKPGQPPRLLIYGAS
SRATGIPARFSGSGSGTDFTLTISPLEDFAVYYCQQNKEDPWTFGGGGTKLEIK
(SEQ ID NO:80);

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

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEFSIHWVRQAPGQGLEWMGGFDP
EDGETIYAQKFQGRVIMTEDTSTDATYMEMNSLRSEDTAIYYCTTGRFFDWFVG
QGTLLTVSS (SEQ ID NO:81), and/or the V_{L3} domain comprises the amino acid sequence of

EIILTQSPAILSLSPGERATLSCRASQSVISRFLSWYQVKPGLAPRLLIYGASTRATGI
PVRFSGSGSGTDFSLTISSLQPEDCAVYYCQQDSNLPITFGQGTRLEIK (SEQ ID
NO:82);

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

QVQLVQSGAEVKKPGASVKVSCKASGYAFTTYLVEWIRQRPGQGLEWMGVINP

GSGSTNYAQKFQGRVTMTVDRSSTAYMELSRLRSDDTAVYYCARYAYGYWG
QGTLLTVSS (SEQ ID NO:83), and/or the V_{L3} domain comprises the amino acid sequence
of

DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWYQQKPGKSPKQLIYSASNRY
TGVPSRFSGSGSGTDFTLTISSLQPEDLATYYCQQYSTYPFTFGQGTKLEIK (SEQ
ID NO:84);

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

QVQLVQSGAEVKKPGASVKVSCKASGYSFTNYAVHWVRQAPGQGLEWMGVISP
YYGDTTYAQKFQGRVTMTVDKSSSTAYMELSRLRSDDTAVYYCARRFEGFYYS
MDYWGQGTLLTVSS (SEQ ID NO:85), and/or the V_{L3} domain comprises the amino
acid sequence of

DVVMTQSPSLPVTLGQPASISCRPSQSLVHSNGNTYLNWYQRPQGSPKLLIYK
VSKRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGKVEI
K (SEQ ID NO:86);

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

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMYWVRQAPGKGLEWVAVIWY
DGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYHCARDPGLRYFDG
GMDVWGQGTLLTVSS (SEQ ID NO:87), and/or the V_{L3} domain comprises the amino
acid sequence of

DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIFAASTLHSG
VPSRFSGSGSGTEFTLTISLQPEDFATYYCQQLNSFPYTFGQGTKLEIK (SEQ ID
NO:88); or

(l) the V_{H3} domain comprises the amino acid sequence of
 QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWY
 DGSNKYYADSVKGRFTISGDNSKNTLYLQMNSLRAEDTAVYYCARMFRGAFDY
 WGQGTLLTVSS (SEQ ID NO:89), and/or the V_{L3} domain comprises the amino acid
 sequence of
 AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQS
 GVPSRFGSGSGTDFLTISGLQPEDSATYYCLQDYIYYPTFGQGTKVEIK (SEQ ID
 NO:90).

39. The binding protein for use of any one of claims 26-37, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:156
 ; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:157; the
 third polypeptide chain comprises the amino acid sequence of SEQ ID NO:158; and the
 fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:159;

(b) the first polypeptide chain comprises the amino acid sequence of SEQ ID
 NO:160; the second polypeptide chain comprises the amino acid sequence of SEQ ID
 NO:161; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:162;
 and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:163;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:164;
 the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:165 ; the
 third polypeptide chain comprises the amino acid sequence of SEQ ID NO:166; and the
 fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:167;

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID
 NO:168; the second polypeptide chain comprises the amino acid sequence of SEQ ID

NO:169; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:170; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:171;

(e) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:172 ; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:173; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:174; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:175;

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:176; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:177; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:178; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:179;

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:181 ; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:182; the third polypeptide chain comprises 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

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:185 ; the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:186 ; the third polypeptide chain comprises the amino acid sequence of SEQ ID NO:187; and the fourth polypeptide chain comprises the amino acid sequence of SEQ ID NO:188.

40. 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 1-15; wherein optionally 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.

41. 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;

wherein optionally the first, second, third, and fourth polynucleotides are present on one or more expression vectors.

42. An isolated host cell comprising the vector system of claim 40 or the kit of polynucleotides of claim 41; wherein optionally the host cell is a mammalian or insect cell.

43. A method of producing the binding protein of any one of claims 1-15, the method comprising culturing the isolated host cell of claim 18 or 42 under conditions such that the host cell expresses the binding protein.