

adverse effects, such as cytokine release syndrome and evidence of liver damage. These toxicities limit the dose of CD40 agonist that can be delivered, and thus may result in insufficient activation of the CD40 pathway in tumor-associated APC population, negatively impacting the efficacy of this therapeutic approach. Therapeutics capable of localizing activation of CD40 signaling in tumor tissue may improve anti-tumor effects while limiting systemic toxicities.

[0005] In order to achieve tumor localization, an agonistic multispecific antibody construct that binds both CD40 and a tumor-associated antigen (TAA), mesothelin (MSLN), was designed. Robust agonist activity of this multispecific antibody construct on CD40-expressing APCs is entirely dependent on the presence of neighboring MSLN-expressing cells. The multispecific antibody construct was specifically engineered to lack CD40 agonist activity upon binding to CD40 in the absence of MSLN-expressing cells. In addition, introduction of mutations into the IgG Fc domain limits binding to Fc receptors, thus preventing Fc receptor-mediated CD40 agonist activity. Thus, the MSLN-dependent CD40 agonist multispecific antibody construct described herein has the potential to drive robust CD40-mediated activation of APCs in a manner that is confined primarily to tumor tissue, thus minimizing induction of systemic toxicities.

SUMMARY OF THE INVENTION

[0006] The present ~~invention~~disclosure is directed to a multispecific antibody construct comprising:

[0007] (i) a first antibody comprising two light chains and two heavy chains, wherein

[0008] the light chains comprise a first variable region (VL1) and a light chain constant region (CL);

[0009] the heavy chains comprise a first heavy variable region (VH1) and CH1, hinge, CH2, and CH3 regions;

[0010] the heavy chains comprise at least one amino acid substitution that results in a reduced binding affinity of the heavy chain for human Fc gamma RI receptor as compared with an unsubstituted heavy chain; and

[0011] (ii) a scFv comprising a second light chain variable region (VL2) and a second heavy chain variable region (VH2) of a second antibody, wherein the VL2 and the VH2 are connected via a first peptide linker,

[0012] wherein the scFv is fused at its amino terminus to the carboxyl terminus of each of the heavy chains through a second peptide linker such that a heavy chain fusion protein is formed; and

[0013] wherein the first antibody specifically binds to and agonizes human CD40 (SEQ ID NO: 1) and the scFv specifically binds to human mesothelin (MSLN) (SEQ ID NO: 2).

[0014] In one ~~embodiment~~example, the multispecific antibody construct specifically agonizes CD40 in a MSLN-dependent fashion.

[0015] In one ~~embodiment~~example, the multispecific antibody construct comprises mutations limiting Fc receptor binding and thus decreases Fc receptor-dependent CD40 agonism.

[0016] In one embodimentexample, the two light chains are identical and the two heavy chain fusion proteins are identical.

[0017] In one embodimentexample, the heavy chain comprises an amino acid substitution selected from the group consisting of:

[0018] (i) N297G or N297A;

[0019] (ii) L234A and L235A; and

[0020] (iii) R292C and V302C;

[0021] wherein the amino acid numbering is EU numbering according to Kabat.

[0022] In one embodimentexample, the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

[0023] In one embodimentexample, the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0024] SEQ ID NOs: 58, 59, and 60, respectively;

[0025] SEQ ID NOs: 64, 65, and 66, respectively;

[0026] SEQ ID NOs: 70, 71, and 72, respectively;

[0027] SEQ ID NOs: 76, 77, and 78, respectively;

[0028] SEQ ID NOs: 82, 83, and 84, respectively;

[0029] SEQ ID NOs: 88, 89, and 90, respectively;

[0030] SEQ ID NOs: 94, 95, and 96, respectively;

[0031] SEQ ID NOs: 100, 101, and 102, respectively;

[0032] SEQ ID NOs: 106, 107, and 108, respectively;

[0033] SEQ ID NOs: 112, 113, and 114, respectively;

[0034] SEQ ID NOs: 118, 119, and 120, respectively;

[0035] SEQ ID NOs: 124, 125, and 126, respectively; and

[0036] SEQ ID NOs: 130, 131, and 132, respectively;

[0037] the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0038] SEQ ID NOs: 136, 137, and 138, respectively;

[0039] SEQ ID NOs: 142, 143, and 144, respectively;

[0040] SEQ ID NOs: 148, 149, and 150, respectively;

[0041] SEQ ID NOs: 154, 155, and 156, respectively;

[0042] SEQ ID NOs: 160, 161, and 162, respectively;

[0043] SEQ ID NOs: 166, 167, and 168, respectively;

[0044] SEQ ID NOs: 172, 173, and 174, respectively;

[0045] SEQ ID NOs: 178, 179, and 180, respectively;

[0046] SEQ ID NOs: 184, 185, and 186, respectively;

[0047] SEQ ID NOs: 190, 191, and 192, respectively;

[0048] SEQ ID NOs: 196, 197, and 198, respectively;

[0049] SEQ ID NOs: 202, 203, and 204, respectively; and

[0050] SEQ ID NOs: 208, 209, and 210, respectively;

[0051] the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0052] SEQ ID NOs: 230, 231, and 232, respectively;

[0053] SEQ ID NOs: 236, 237, and 238, respectively;

[0054] SEQ ID NOs: 242, 243, and 244, respectively; and

[0055] SEQ ID NOs: 248, 249, and 250, respectively;

[0056] and the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0057] SEQ ID NOs: 254, 255, and 256, respectively;

[0058] SEQ ID NOs: 260, 261, and 262, respectively;

[0059] SEQ ID NOs: 266, 267, and 268, respectively; and

[0060] SEQ ID NOs: 272, 273, and 274, respectively.

[0061] In one ~~embodiment~~example, 1) the VL1 and VH1 are selected from the group consisting of:

[0062] a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[0063] b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[0064] c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

[0065] d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

[0066] e) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

[0067] f) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

[0068] g) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

[0069] h) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

[0070] i) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

[0071] j) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

[0072] k) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

[0073] l) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

[0074] m) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively;

[0075] and

[0076] 2) the VL2 and VH2 are selected from the group consisting of:

[0077] a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

[0078] b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

[0079] c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

[0080] d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively.

[0081] In one embodimentexample, the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53;

[0082] the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54;

[0083] the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;

[0084] the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226.

[0085] In one embodimentexample,

[0086] 1) the VL1 and VH1 are selected from the group consisting of:

[0087] a) a VL1 comprising SEQ ID NO: 5 and a VH1 comprising SEQ ID NO: 6;

[0088] b) a VL1 comprising SEQ ID NO: 9 and a VH1 comprising SEQ ID NO: 10;

[0089] c) a VL1 comprising SEQ ID NO: 13 and a VH1 comprising SEQ ID NO: 14;

[0090] d) a VL1 comprising SEQ ID NO: 17 and a VH1 comprising SEQ ID NO: 18;

[0091] e) a VL1 comprising SEQ ID NO: 21 and a VH1 comprising SEQ ID NO: 22;

[0092] f) a VL1 comprising SEQ ID NO: 25 and a VH1 comprising SEQ ID NO: 26;

[0093] g) a VL1 comprising SEQ ID NO: 29 and a VH1 comprising SEQ ID NO: 30;

[0094] h) a VL1 comprising SEQ ID NO: 33 and a VH1 comprising SEQ ID NO: 34;

[0095] i) a VL1 comprising SEQ ID NO: 37 and a VH1 comprising SEQ ID NO: 38;

[0096] j) a VL1 comprising SEQ ID NO: 41 and a VH1 comprising SEQ ID NO: 42;

[0097] k) a VL1 comprising SEQ ID NO: 45 and a VH1 comprising SEQ ID NO: 46;

[0098] l) a VL1 comprising SEQ ID NO: 49 and a VH1 comprising SEQ ID NO: 50; and

[0099] m) a VL1 comprising SEQ ID NO: 53 and a VH1 comprising SEQ ID NO: 54;

[0100] and

[0101] 2) the VL2 and VH2 are selected from the group consisting of:

[0102] a) a VL2 comprising SEQ ID NO: 213 and a VH2 comprising SEQ ID NO: 214;

[0103] b) a VL2 comprising SEQ ID NO: 217 and a VH2 comprising SEQ ID NO: 218;

[0104] c) a VL2 comprising SEQ ID NO: 221 and a VH2 comprising SEQ ID NO: 222; and

[0105] d) a VL2 comprising SEQ ID NO: 225 and a VH2 comprising SEQ ID NO: 226.

[0106] In one embodimentexample, the CL of the light chain is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.

[0107] In one embodimentexample, the CH1-hinge-CH2-CH3 of the heavy chain is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.

[0108] In one embodimentexample, the first peptide linker is selected from the group consisting of SEQ ID NOs: 888-893.

[0109] In one embodimentexample, the second peptide linker is selected from the group consisting of SEQ ID NOs: 887-893.

[0110]

[0111] In one embodimentexample, the first peptide linker comprises SEQ ID NO: 889 and the second peptide linker comprises SEQ ID NO: 887.

[0112] In one embodimentexample,

[0113] the light chain comprises a sequence selected from the group consisting of SEQ ID NOs: 286, 290, 294, 298, 302, 306, 310, 314, 318, 322, 326, 330, 336, 342, 346, 350, 354, 358, 362, 366, 370, 374, and 378; and

[0114] the heavy chain fusion protein comprises a sequence selected from the group consisting of SEQ ID Nos: 285, 289, 293, 297, 301, 305, 309, 313, 317, 321, 325, 329, 333, 337, 341, 345, 349, 353, 357, 361, 365, 369, 373, and 377.

[0115] In one embodimentexample, the light chain and the heavy chain fusion protein comprise polypeptides comprising amino acid sequences selected from the group consisting of:

[0116] SEQ ID NO: 286 and SEQ ID NO: 285, respectively;

[0117] SEQ ID NO: 290 and SEQ ID NO: 289, respectively;

[0118] SEQ ID NO: 294 and SEQ ID NO: 293, respectively;

[0119] SEQ ID NO: 298 and SEQ ID NO: 297, respectively;

[0120] SEQ ID NO: 302 and SEQ ID NO: 301, respectively;

[0121] SEQ ID NO: 306 and SEQ ID NO: 305, respectively;

[0122] SEQ ID NO: 310 and SEQ ID NO: 309, respectively;

[0123] SEQ ID NO: 314 and SEQ ID NO: 313, respectively;

[0124] SEQ ID NO: 318 and SEQ ID NO: 317, respectively;

[0125] SEQ ID NO: 322 and SEQ ID NO: 321, respectively;

[0126] SEQ ID NO: 326 and SEQ ID NO: 325, respectively;

[0127] SEQ ID NO: 330 and SEQ ID NO: 329, respectively;

[0128] SEQ ID NO: 334 and SEQ ID NO: 333, respectively;

[0129] SEQ ID NO: 338 and SEQ ID NO: 337, respectively;

[0130] SEQ ID NO: 342 and SEQ ID NO: 341, respectively;

[0131] SEQ ID NO: 346 and SEQ ID NO: 345, respectively;

[0132] SEQ ID NO: 350 and SEQ ID NO: 349, respectively;

[0133] SEQ ID NO: 354 and SEQ ID NO: 353, respectively;

[0134] SEQ ID NO: 358 and SEQ ID NO: 357, respectively;

[0135] SEQ ID NO: 362 and SEQ ID NO: 361, respectively;

[0136] SEQ ID NO: 366 and SEQ ID NO: 365, respectively;

[0137] SEQ ID NO: 370 and SEQ ID NO: 369, respectively;

[0138] SEQ ID NO: 374 and SEQ ID NO: 373, respectively; and

[0139] SEQ ID NO: 378 and SEQ ID NO: 377, respectively.

[0140] In one aspectexample, the present inventiondisclosure is directed to a polynucleotide encoding the light chain of the antibody construct of the present inventiondisclosure.

[0141] In one aspectexample, the present inventiondisclosure is directed to a polynucleotide encoding the heavy chain fusion protein of the antibody construct of the present inventiondisclosure.

[0142] In one aspectexample, the present inventiondisclosure is directed to a vector comprising the polynucleotide encoding the light chain of the antibody construct, the polynucleotide encoding the heavy chain of the antibody construct, or both.

[0143] In one aspectexample, the present inventiondisclosure is directed to a host cell transformed or transfected with the vector or the polynucleotide encoding the light chain of the antibody construct and the polynucleotide encoding the heavy chain of the antibody construct.

[0144] In one aspectexample, the present inventiondisclosure is directed to a process for producing the antibody construct of the present inventiondisclosure, the process comprising culturing a host cell comprising a polynucleotide encoding the light chain and also comprising a polynucleotide encoding the heavy chain fusion protein under conditions allowing the expression of the antibody construct, and recovering the produced antibody construct from the culture.

[0145] In one aspectexample, the present inventiondisclosure is directed to a pharmaceutical composition comprising the antibody construct according to the present inventiondisclosure and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative or adjuvant.

[0146] In one aspectexample, the present inventiondisclosure is directed to a method for treating or ameliorating a solid tumor disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof an effective amount of the antibody construct according to the present inventiondisclosure.

[0147] In one embodimentexample, the solid tumor disease is selected from the group consisting of: ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer disease or a metastatic cancer disease derived from any of the foregoing.

[0148] In one aspectexample, the present inventiondisclosure is directed to a kit comprising the antibody construct according to the present inventiondisclosure and, optionally, directions for use.

[0149] In one aspectexample, the present inventiondisclosure is directed to a multispecific antibody construct comprising:

[0150] (i) a first antibody comprising two light chains and two heavy chains, wherein

[0151] the light chains comprise a first variable region (VL1) and a light chain constant region (CL);

[0152] the heavy chains comprise a first heavy variable region (VH1) and CH1, hinge, CH2, and CH3 regions;

[0153] the heavy chains comprise at least one amino acid substitution that results in a reduced binding affinity of the heavy chain for human Fc gamma RI receptor as compared with an unsubstituted heavy chain; and

[0154] (ii) a scFv comprising a second light chain variable region (VL2) and a second heavy chain variable region (VH2) of a second antibody, wherein the VL2 and the VH2 are connected via a first peptide linker,

[0155] wherein the scFv is fused at its amino terminus to the carboxyl terminus of each of the heavy chains through a second peptide linker such that a heavy chain fusion protein is formed; and

[0156] wherein the first antibody specifically binds to human mesothelin (MSLN) (SEQ ID NO: 2) and the scFv specifically binds to and agonizes human CD40 (SEQ ID NO: 1).

[0157] In one [embodimentexample](#), the multispecific antibody construct specifically agonizes CD40 in a MSLN-dependent fashion.

[0158] In one [embodimentexample](#), the multispecific antibody construct comprises mutations limiting Fc receptor binding and thus decreases Fc receptor-dependent CD40 agonism.

[0159] In one [embodimentexample](#), the two light chains are identical and the two heavy chain fusion proteins are identical.

[0160] In one [embodimentexample](#), the heavy chain comprises an amino acid substitution selected from the group consisting of:

[0161] (i) N297G or N297A;

[0162] (ii) L234A and L235A; and

[0163] (iii) R292C and V302C;

[0164] wherein the amino acid numbering is EU numbering according to Kabat.

[0165] In one [embodimentexample](#), the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

[0166] In one [embodimentexample](#):

[0167] the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0168] SEQ ID NOs: 230, 231, and 232, respectively;

[0169] SEQ ID NOs: 236, 237, and 238, respectively;

[0170] SEQ ID NOs: 242, 243, and 244, respectively; and

[0171] SEQ ID NOs: 248, 249, and 250, respectively;

[0172] the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0173] SEQ ID NOs: 254, 255, and 256, respectively;

[0174] SEQ ID NOs: 260, 261, and 262, respectively;

[0175] SEQ ID NOs: 266, 267, and 268, respectively; and

[0176] SEQ ID NOs: 272, 273, and 274, respectively;

[0177] the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0178] SEQ ID NOs: 58, 59, and 60, respectively;

[0179] SEQ ID NOs: 64, 65, and 66, respectively;

[0180] SEQ ID NOs: 70, 71, and 72, respectively;

[0181] SEQ ID NOs: 76, 77, and 78, respectively;

[0182] SEQ ID NOs: 82, 83, and 84, respectively;

[0183] SEQ ID NOs: 88, 89, and 90, respectively;

[0184] SEQ ID NOs: 94, 95, and 96, respectively;

[0185] SEQ ID NOs: 100, 101, and 102, respectively;

[0186] SEQ ID NOs: 106, 107, and 108, respectively;

[0187] SEQ ID NOs: 112, 113, and 114, respectively;

[0188] SEQ ID NOs: 118, 119, and 120, respectively;

[0189] SEQ ID NOs: 124, 125, and 126, respectively; and

[0190] SEQ ID NOs: 130, 131, and 132, respectively;

[0191] and

[0192] the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0193] SEQ ID NOs: 136, 137, and 138, respectively;

[0194] SEQ ID NOs: 142, 143, and 144, respectively;

[0195] SEQ ID NOs: 148, 149, and 150, respectively;

[0196] SEQ ID NOs: 154, 155, and 156, respectively;

[0197] SEQ ID NOs: 160, 161, and 162, respectively;

[0198] SEQ ID NOs: 166, 167, and 168, respectively;

[0199] SEQ ID NOs: 172, 173, and 174, respectively;

[0200] SEQ ID NOs: 178, 179, and 180, respectively;

[0201] SEQ ID NOs: 184, 185, and 186, respectively;

[0202] SEQ ID NOs: 190, 191, and 192, respectively;

[0203] SEQ ID NOs: 196, 197, and 198, respectively;

[0204] SEQ ID NOs: 202, 203, and 204, respectively; and

[0205] SEQ ID NOs: 208, 209, and 210, respectively.

[0206] In one ~~embodiment~~example,

[0207] 1) the VL1 and VH1 are selected from the group consisting of:

[0208] a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

[0209] b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

[0210] c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

[0211] d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively;

[0212] and

[0213] 2) the VL2 and VH2 are selected from the group consisting of:

[0214] a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[0215] b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[0216] c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

[0217] d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

[0218] e) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

[0219] f) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

[0220] g) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

[0221] h) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

[0222] i) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

[0223] j) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

[0224] k) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

[0225] l) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

[0226] m) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.

[0227] In one [embodimentexample](#):

[0228] the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;

[0229] the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226;

[0230] the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and

[0231] the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.

[0232] In one [embodimentexample](#):

[0233] 1) the VL1 and VH1 are selected from the group consisting of:

[0234] a) a VL1 comprising SEQ ID NO: 213 and a VH1 comprising SEQ ID NO: 214;

[0235] b) a VL1 comprising SEQ ID NO: 217 and a VH1 comprising SEQ ID NO: 218;

[0236] c) a VL1 comprising SEQ ID NO: 221 and a VH1 comprising SEQ ID NO: 222; and

[0237] d) a VL1 comprising SEQ ID NO: 225 and a VH1 comprising SEQ ID NO: 226;

[0238] and

[0239] 2) the VL2 and VH2 are selected from the group consisting of:

[0240] a) a VL2 comprising SEQ ID NO: 5 and a VH2 comprising SEQ ID NO: 6;

- [0241] b) a VL2 comprising SEQ ID NO: 9 and a VH2 comprising SEQ ID NO: 10;
- [0242] c) a VL2 comprising SEQ ID NO: 13 and a VH2 comprising SEQ ID NO: 14;
- [0243] d) a VL2 comprising SEQ ID NO: 17 and a VH2 comprising SEQ ID NO: 18;
- [0244] e) a VL2 comprising SEQ ID NO: 21 and a VH2 comprising SEQ ID NO: 22;
- [0245] f) a VL2 comprising SEQ ID NO: 25 and a VH2 comprising SEQ ID NO: 26;
- [0246] g) a VL2 comprising SEQ ID NO: 29 and a VH2 comprising SEQ ID NO: 30;
- [0247] h) a VL2 comprising SEQ ID NO: 33 and a VH2 comprising SEQ ID NO: 34;
- [0248] i) a VL2 comprising SEQ ID NO: 37 and a VH2 comprising SEQ ID NO: 38;
- [0249] j) a VL2 comprising SEQ ID NO: 41 and a VH2 comprising SEQ ID NO: 42;
- [0250] k) a VL2 comprising SEQ ID NO: 45 and a VH2 comprising SEQ ID NO: 46;
- [0251] l) a VL2 comprising SEQ ID NO: 49 and a VH2 comprising SEQ ID NO: 50; and
- [0252] m) a VL2 comprising SEQ ID NO: 53 and a VH2 comprising SEQ ID NO: 54.
- [0253] In one embodimentexample, the CL of the light chain is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.
- [0254] In one embodimentexample, the CH1-hinge-CH2-CH3 of the heavy chain is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.
- [0255] In one embodimentexample, the first peptide linker is selected from the group consisting of SEQ ID NOs: 888-893.
- [0256] In one embodimentexample, the second peptide linker is selected from the group consisting of SEQ ID NOs: 887-893.
- [0257] In one embodimentexample, the first peptide linker comprises SEQ ID NO: 889 and the second peptide linker comprises SEQ ID NO: 887.
- [0258] In one embodimentexample,
- [0259] the light chain comprises a sequence selected from the group consisting of SEQ ID NOs: 382, 386, 390, 394, 398, 402, 406, 410, 414, 418, 422, 426, 430, 434, 438, 442, 446, and 450; and
- [0260] the heavy chain fusion protein comprises a sequence selected from the group consisting of SEQ ID NOs: 381, 385, 389, 393, 397, 401, 405, 409, 413, 417, 421, 425, 429, 433, 437, 441, 445, and 449.
- [0261] In one embodimentexample, the light chain and the heavy chain fusion protein comprise polypeptides comprising amino acid sequences selected from the group consisting of:
- [0262] SEQ ID NO: 382 and SEQ ID NO: 381, respectively;
- [0263] SEQ ID NO: 386 and SEQ ID NO: 385, respectively;
- [0264] SEQ ID NO: 390 and SEQ ID NO: 389, respectively;
- [0265] SEQ ID NO: 394 and SEQ ID NO: 393, respectively;
- [0266] SEQ ID NO: 398 and SEQ ID NO: 397, respectively;

[0267] SEQ ID NO: 402 and SEQ ID NO: 401, respectively;
[0268] SEQ ID NO: 406 and SEQ ID NO: 405, respectively;
[0269] SEQ ID NO: 410 and SEQ ID NO: 409, respectively;
[0270] SEQ ID NO: 414 and SEQ ID NO: 413, respectively;
[0271] SEQ ID NO: 418 and SEQ ID NO: 417, respectively;
[0272] SEQ ID NO: 422 and SEQ ID NO: 421, respectively;
[0273] SEQ ID NO: 426 and SEQ ID NO: 425, respectively;
[0274] SEQ ID NO: 430 and SEQ ID NO: 429, respectively;
[0275] SEQ ID NO: 434 and SEQ ID NO: 433, respectively;
[0276] SEQ ID NO: 438 and SEQ ID NO: 437, respectively;
[0277] SEQ ID NO: 442 and SEQ ID NO: 441, respectively;
[0278] SEQ ID NO: 446 and SEQ ID NO: 445, respectively; and
[0279] SEQ ID NO: 450 and SEQ ID NO: 449, respectively.

[0280] In one aspect example, the present invention disclosure is directed to a multispecific antibody construct comprising:

[0281] a) two identical heavy chain fusion proteins each comprising a first heavy chain variable region (VH1) and a first CH1 domain, wherein the first CH1 domain is linked to a hinge-CH2-CH3 polypeptide, and wherein the hinge-CH2-CH3 polypeptide is linked to a second heavy chain variable region (VH2), wherein the VH2 is linked to a second CH1 domain; wherein

[0282] i) the VH1 or first CH1 domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of positions 39, 44, and 183 using EU numbering; and

[0283] ii) the VH2 or second CH1 domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of a residue that corresponds to positions 39, 44, and 183 using EU numbering; and

[0284] b) a second polypeptide comprising a first light chain, wherein the first light chain comprises a first light chain variable region (VL1) and a first CL region; and wherein the VL1 or first CL domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering; and

[0285] c) a third polypeptide comprising a second light chain, wherein the second light chain comprises a second light chain variable region (VL2) and a second CL region;. and wherein the VL2 or second CL domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering;

[0286] wherein the VH1 and VL1 interact to bind a first antigen and wherein the VH2 and VL2 interact to bind a second antigen;

[0287] wherein:

[0288] the first antigen is human CD40 (SEQ ID NO: 1) and the second antigen is human mesothelin (“MSLN”; SEQ ID NO: 2); or

[0289] the first antigen is human MSLN (SEQ ID NO: 2) and the second antigen is human CD40 (SEQ ID NO: 1).

[0290] In one ~~aspect~~example, the present ~~invention~~disclosure is directed to a multispecific antibody construct comprising:

[0291] a) two identical heavy chain fusion proteins each comprising a first heavy chain variable region (VH1) and a first CH1 domain, wherein the first CH1 domain is linked to a hinge-CH2-CH3 polypeptide, and wherein the hinge-CH2-CH3 polypeptide is linked to a second heavy chain variable region (VH2), wherein the VH2 is linked to a second CH1 domain; wherein

[0292] i) the VH1 or first CH1 domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of positions 39, 44, and 183 using EU numbering; and

[0293] ii) the VH2 or second CH1 domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of a residue that corresponds to positions 39, 44, and 183 using EU numbering; and

[0294] b) a second polypeptide comprising a first light chain, wherein the first light chain comprises a first light chain variable region (VL1) and a first CL region; and wherein the VL1 or first CL domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering; and

[0295] c) a third polypeptide comprising a second light chain, wherein the second light chain comprises a second light chain variable region (VL2) and a second CL region; and wherein the VL2 or second CL domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering;

[0296] wherein the VH1 and VL1 interact to bind a first antigen and wherein the VH2 and VL2 interact to bind a second antigen;

[0297] wherein:

[0298] the first antigen is human CD40 (SEQ ID NO: 1) and the second antigen is human mesothelin (“MSLN”; SEQ ID NO: 2); or

[0299] the first antigen is human MSLN (SEQ ID NO: 2) and the second antigen is human CD40 (SEQ ID NO: 1).

[0300] In one ~~embodiment~~example, the hinge-CH2-CH3 polypeptide is linked to the VH2 via a peptide linker.

[0301] In one [embodimentexample](#), the peptide linker comprises a sequence selected from the group consisting of (Gly₃Ser)₂ (SEQ ID NO: 916), (Gly₄Ser)₂ (SEQ ID NO: 888), (Gly₃Ser)₃ (SEQ ID NO: 917), (Gly₄Ser)₃ (SEQ ID NO: 889), (Gly₃Ser)₄ (SEQ ID NO: 918), (Gly₄Ser)₄ (SEQ ID NO: 890), (Gly₃Ser)₅ (SEQ ID NO: 919), (Gly₄Ser)₅ (SEQ ID NO: 920), (Gly₃Ser)₆ (SEQ ID NO: 921), and (Gly₄Ser)₆ (SEQ ID NO: 922).

[0302] In one [embodimentexample](#),

[0303] a) the VH1 or first CH1 domain comprises a mutation selected from the group consisting of Q39K, G44K, and S183K using EU numbering;

[0304] b) the VH2 or second CH1 domain comprises a mutation selected from the group consisting of Q39E, G44E, and S183E using EU numbering;

[0305] c) the VL1 or first CL domain comprises a mutation selected from the group consisting of Q38E, G100E, and S176E using EU numbering; and

[0306] d) the VL2 or second CL domain comprises a mutation selected from the group consisting of Q38K, G100K, and S176K using EU numbering.

[0307] In one [embodimentexample](#),

[0308] a) the first CH1 domain comprises a S183K mutation using EU numbering;

[0309] b) the second CH1 domain comprises a S183E mutation using EU numbering;

[0310] c) the first CL domain comprises a S176E mutation using EU numbering; and

[0311] d) the second CL domain comprises a S176K mutation using EU numbering.

[0312] In one [embodimentexample](#),

[0313] a) the VH1 comprises a Q39K mutation and the first CH1 domain comprises a S183K mutation using EU numbering;

[0314] b) the VH2 comprises a Q39E mutation and the second CH1 domain comprises a S183E mutation using EU numbering;

[0315] c) the VL1 comprises a Q38E mutation and the first CL domain comprises a S176E mutation using EU numbering; and

[0316] d) the VL2 comprises a Q38K mutation and the second CL domain comprises a S176K mutation using EU numbering.

[0317] In one [embodimentexample](#),

[0318] a) the first CH1 domain comprises G44K and S183K mutations using EU numbering;

[0319] b) the second CH1 domain comprises G44E and S183E mutations using EU numbering;

[0320] c) the first CL domain comprises G100E and S176E mutations using EU numbering; and

[0321] d) the second CL domain comprises G100K and S176K mutations using EU numbering.

[0322] In one [embodimentexample](#),

[0323] a) the VH1 or first CH1 domain comprises a mutation selected from the group consisting of Q39E, G44E, and S183E using EU numbering;

[0324] b) the VH2 or second CH1 domain comprises a mutation selected from the group consisting of Q39K, G44K, and S183K using EU numbering;

[0325] c) the VL1 or first CL domain comprises a mutation selected from the group consisting of Q38K, G100K, and S176K using EU numbering; and

[0326] d) the VL2 or second CL domain comprises a mutation selected from the group consisting of Q38E, G100E, and S176E using EU numbering.

[0327] In one [embodimentexample](#),

[0328] a) the first CH1 domain comprises a S183E mutation using EU numbering;

[0329] b) the second CH1 domain comprises a S183K mutation using EU numbering;

[0330] c) the first CL domain comprises a S176K mutation using EU numbering; and

[0331] d) the second CL domain comprises a S176E mutation using EU numbering.

[0332] In one [embodimentexample](#),

[0333] a) the VH1 comprises a Q39E mutation and the first CH1 domain comprises a S183E mutation using EU numbering;

[0334] b) the VH2 comprises a Q39K mutation and the second CH1 domain comprises a S183K mutation using EU numbering;

[0335] c) the VL1 comprises a Q38K mutation and the first CL domain comprises a S176K mutation using EU numbering; and

[0336] d) the VL2 comprises a Q38E mutation and the second CL domain comprises a S176E mutation using EU numbering.

[0337] In one [embodimentexample](#),

[0338] a) the first CH1 domain comprises G44E and S183E mutations using EU numbering;

[0339] b) the second CH1 domain comprises G44K and S183K mutations using EU numbering;

[0340] c) the first CL domain comprises G100K and S176K mutations using EU numbering; and

[0341] d) the second CL domain comprises G100E and S176E mutations using EU numbering.

[0342] In one [embodimentexample](#), the hinge-CH2-CH3 polypeptide comprises an amino acid substitution selected from the group consisting of:

[0343] (i) N297G or N297A;

[0344] (ii) L234A and L235A; and

[0345] (iii) R292C and V302C;

[0346] wherein the amino acid numbering is EU numbering according to Kabat.

[0347] In one [embodimentexample](#), the hinge-CH2-CH3 polypeptide comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

[0348] In one ~~embodiment~~example, the first antigen is human CD40 (SEQ ID NO: 1) and the second antigen is human MSLN (SEQ ID NO: 2); and

[0349] the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0350] SEQ ID NOs: 58, 59, and 60, respectively;

[0351] SEQ ID NOs: 64, 65, and 66, respectively;

[0352] SEQ ID NOs: 70, 71, and 72, respectively;

[0353] SEQ ID NOs: 76, 77, and 78, respectively;

[0354] SEQ ID NOs: 82, 83, and 84, respectively;

[0355] SEQ ID NOs: 88, 89, and 90, respectively;

[0356] SEQ ID NOs: 94, 95, and 96, respectively;

[0357] SEQ ID NOs: 100, 101, and 102, respectively;

[0358] SEQ ID NOs: 106, 107, and 108, respectively;

[0359] SEQ ID NOs: 112, 113, and 114, respectively;

[0360] SEQ ID NOs: 118, 119, and 120, respectively;

[0361] SEQ ID NOs: 124, 125, and 126, respectively; and

[0362] SEQ ID NOs: 130, 131, and 132, respectively;

[0363] the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0364] SEQ ID NOs: 136, 137, and 138, respectively;

[0365] SEQ ID NOs: 142, 143, and 144, respectively;

[0366] SEQ ID NOs: 148, 149, and 150, respectively;

[0367] SEQ ID NOs: 154, 155, and 156, respectively;

[0368] SEQ ID NOs: 160, 161, and 162, respectively;

[0369] SEQ ID NOs: 166, 167, and 168, respectively;

[0370] SEQ ID NOs: 172, 173, and 174, respectively;

[0371] SEQ ID NOs: 178, 179, and 180, respectively;

[0372] SEQ ID NOs: 184, 185, and 186, respectively;

[0373] SEQ ID NOs: 190, 191, and 192, respectively;

[0374] SEQ ID NOs: 196, 197, and 198, respectively;

[0375] SEQ ID NOs: 202, 203, and 204, respectively; and

[0376] SEQ ID NOs: 208, 209, and 210, respectively;

[0377] the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0378] SEQ ID NOs: 230, 231, and 232, respectively;

[0379] SEQ ID NOs: 236, 237, and 238, respectively;

[0380] SEQ ID NOs: 242, 243, and 244, respectively; and

[0381] SEQ ID NOs: 248, 249, and 250, respectively;

[0382] and the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0383] SEQ ID NOs: 254, 255, and 256, respectively;

[0384] SEQ ID NOs: 260, 261, and 262, respectively;

[0385] SEQ ID NOs: 266, 267, and 268, respectively; and

[0386] SEQ ID NOs: 272, 273, and 274, respectively.

[0387]

[0388] ~~64. The antibody construct of claim 63, wherein~~ In one embodiment example,

[0389] 1) the VL1 and VH1 are selected from the group consisting of:

[0390] a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[0391] b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[0392] c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

[0393] d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

[0394] e) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

[0395] f) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

[0396] g) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

[0397] h) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

[0398] i) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

[0399] j) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

[0400] k) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

[0401] l) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

[0402] m) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively;

[0403] and

[0404] 2) the VL2 and VH2 are selected from the group consisting of:

[0405] a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

[0406] b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

[0407] c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

[0408] d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively.

[0409] In one **embodiment** example:

[0410] the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53;

[0411] the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54;

[0412] the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;

[0413] the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226.

[0414] In one embodimentexample:

[0415] 1) the VL1 and VH1 are selected from the group consisting of:

[0416] a) a VL1 comprising SEQ ID NO: 5 and a VH1 comprising SEQ ID NO: 6;

[0417] b) a VL1 comprising SEQ ID NO: 9 and a VH1 comprising SEQ ID NO: 10;

[0418] c) a VL1 comprising SEQ ID NO: 13 and a VH1 comprising SEQ ID NO: 14;

[0419] d) a VL1 comprising SEQ ID NO: 17 and a VH1 comprising SEQ ID NO: 18;

[0420] e) a VL1 comprising SEQ ID NO: 21 and a VH1 comprising SEQ ID NO: 22;

[0421] f) a VL1 comprising SEQ ID NO: 25 and a VH1 comprising SEQ ID NO: 26;

[0422] g) a VL1 comprising SEQ ID NO: 29 and a VH1 comprising SEQ ID NO: 30;

[0423] h) a VL1 comprising SEQ ID NO: 33 and a VH1 comprising SEQ ID NO: 34;

[0424] i) a VL1 comprising SEQ ID NO: 37 and a VH1 comprising SEQ ID NO: 38;

[0425] j) a VL1 comprising SEQ ID NO: 41 and a VH1 comprising SEQ ID NO: 42;

[0426] k) a VL1 comprising SEQ ID NO: 45 and a VH1 comprising SEQ ID NO: 46;

[0427] l) a VL1 comprising SEQ ID NO: 49 and a VH1 comprising SEQ ID NO: 50; and

[0428] m) a VL1 comprising SEQ ID NO: 53 and a VH1 comprising SEQ ID NO: 54;

[0429] and

[0430] 2) the VL2 and VH2 are selected from the group consisting of:

[0431] a) a VL2 comprising SEQ ID NO: 213 and a VH2 comprising SEQ ID NO: 214;

[0432] b) a VL2 comprising SEQ ID NO: 217 and a VH2 comprising SEQ ID NO: 218;

[0433] c) a VL2 comprising SEQ ID NO: 221 and a VH2 comprising SEQ ID NO: 222; and

[0434] d) a VL2 comprising SEQ ID NO: 225 and a VH2 comprising SEQ ID NO: 226.

[0435] In one aspectexample, the present inventiondisclosure is directed to a polynucleotide encoding the first light chain of the antibody construct.

[0436] In one aspectexample, the present inventiondisclosure is directed to a polynucleotide encoding the second light chain of the antibody construct.

[0437] In one aspectexample, the present inventiondisclosure is directed to a polynucleotide encoding the heavy chain fusion protein of the antibody construct.

[0438] In one aspectexample, the present inventiondisclosure is directed to a vector comprising:

[0439] a) the polynucleotide encoding the first light chain of the antibody construct,

[0440] b) the polynucleotide encoding the second light chain of the antibody construct,

[0441] c) the polynucleotide encoding the heavy chain fusion protein of the antibody construct, or

[0442] d) any combination of a), b), and c).

[0443] In one aspectexample, the present inventiondisclosure is directed to a host cell transformed or transfected with the vector or polynucleotide according to the present inventiondisclosure.

[0444] In one aspectexample, the present inventiondisclosure is directed to a process for producing the antibody construct according to the present inventiondisclosure, the process comprising culturing a host cell comprising a polynucleotide encoding the first light chain, a polynucleotide encoding the second light chain and a polynucleotide encoding the heavy chain fusion protein under conditions allowing the expression of the antibody construct, and recovering the produced antibody construct from the culture.

[0445] In one aspectexample, the present inventiondisclosure is directed to a pharmaceutical composition comprising the antibody construct according to the present inventiondisclosure and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative or adjuvant.

[0446] In one aspectexample, the present inventiondisclosure is directed to a method for treating or ameliorating a solid tumor disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof an effective amount of the antibody construct according to the present inventiondisclosure.

[0447] In one embodimentexample, the solid tumor disease is selected from the group consisting of: ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer disease or a metastatic cancer disease derived from any of the foregoing.

[0448] In one aspectexample, the present inventiondisclosure is directed to a kit comprising the antibody construct according to the present inventiondisclosure and, optionally, directions for use.

[0449] In one embodimentexample, the first antigen is human MSLN (SEQ ID NO: 2) and the second antigen is human CD40 (SEQ ID NO: 1); wherein:

[0450] the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0451] SEQ ID NOs: 230, 231, and 232, respectively;

[0452] SEQ ID NOs: 236, 237, and 238, respectively;

[0453] SEQ ID NOs: 242, 243, and 244, respectively; and

[0454] SEQ ID NOs: 248, 249, and 250, respectively;

[0455] the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0456] SEQ ID NOs: 254, 255, and 256, respectively;

[0457] SEQ ID NOs: 260, 261, and 262, respectively;

[0458] SEQ ID NOs: 266, 267, and 268, respectively; and

[0459] SEQ ID NOs: 272, 273, and 274, respectively;

[0460] the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0461] SEQ ID NOs: 58, 59, and 60, respectively;

[0462] SEQ ID NOs: 64, 65, and 66, respectively;

[0463] SEQ ID NOs: 70, 71, and 72, respectively;

[0464] SEQ ID NOs: 76, 77, and 78, respectively;

[0465] SEQ ID NOs: 82, 83, and 84, respectively;

[0466] SEQ ID NOs: 88, 89, and 90, respectively;

[0467] SEQ ID NOs: 94, 95, and 96, respectively;

[0468] SEQ ID NOs: 100, 101, and 102, respectively;

[0469] SEQ ID NOs: 106, 107, and 108, respectively;

[0470] SEQ ID NOs: 112, 113, and 114, respectively;

[0471] SEQ ID NOs: 118, 119, and 120, respectively;

[0472] SEQ ID NOs: 124, 125, and 126, respectively; and

[0473] SEQ ID NOs: 130, 131, and 132, respectively;

[0474] and

[0475] the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0476] SEQ ID NOs: 136, 137, and 138, respectively;

[0477] SEQ ID NOs: 142, 143, and 144, respectively;

[0478] SEQ ID NOs: 148, 149, and 150, respectively;

[0479] SEQ ID NOs: 154, 155, and 156, respectively;

[0480] SEQ ID NOs: 160, 161, and 162, respectively;

[0481] SEQ ID NOs: 166, 167, and 168, respectively;

[0482] SEQ ID NOs: 172, 173, and 174, respectively;

[0483] SEQ ID NOs: 178, 179, and 180, respectively;

[0484] SEQ ID NOs: 184, 185, and 186, respectively;

[0485] SEQ ID NOs: 190, 191, and 192, respectively;

[0486] SEQ ID NOs: 196, 197, and 198, respectively;

[0487] SEQ ID NOs: 202, 203, and 204, respectively; and

[0488] SEQ ID NOs: 208, 209, and 210, respectively.

[0489] In one embodiment example,

[0490] 1) the VL1 and VH1 are selected from the group consisting of:

[0491] a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

[0492] b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

[0493] c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

[0494] d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively;

[0495] and

[0496] 2) the VL2 and VH2 are selected from the group consisting of:

[0497] a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[0498] b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[0499] c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

[0500] d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

[0501] e) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

[0502] f) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

[0503] g) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

[0504] h) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

[0505] i) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

[0506] j) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

[0507] k) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

[0508] l) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

[0509] m) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.

[0510] In one embodimentexample,

[0511] the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;

[0512] the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226;

[0513] the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and

[0514] the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.

[0515] In one embodimentexample,

[0516] 1) the VL1 and VH1 are selected from the group consisting of:

[0517] a) a VL1 comprising SEQ ID NO: 213 and a VH1 comprising SEQ ID NO: 214;

[0518] b) a VL1 comprising SEQ ID NO: 217 and a VH1 comprising SEQ ID NO: 218;

[0519] c) a VL1 comprising SEQ ID NO: 221 and a VH1 comprising SEQ ID NO: 222; and

[0520] d) a VL1 comprising SEQ ID NO: 225 and a VH1 comprising SEQ ID NO: 226;

[0521] and

[0522] 2) the VL2 and VH2 are selected from the group consisting of:

[0523] a) a VL2 comprising SEQ ID NO: 5 and a VH2 comprising SEQ ID NO: 6;

[0524] b) a VL2 comprising SEQ ID NO: 9 and a VH2 comprising SEQ ID NO: 10;

[0525] c) a VL2 comprising SEQ ID NO: 13 and a VH2 comprising SEQ ID NO: 14;

[0526] d) a VL2 comprising SEQ ID NO: 17 and a VH2 comprising SEQ ID NO: 18;

[0527] e) a VL2 comprising SEQ ID NO: 21 and a VH2 comprising SEQ ID NO: 22;

[0528] f) a VL2 comprising SEQ ID NO: 25 and a VH2 comprising SEQ ID NO: 26;

[0529] g) a VL2 comprising SEQ ID NO: 29 and a VH2 comprising SEQ ID NO: 30;
 [0530] h) a VL2 comprising SEQ ID NO: 33 and a VH2 comprising SEQ ID NO: 34;
 [0531] i) a VL2 comprising SEQ ID NO: 37 and a VH2 comprising SEQ ID NO: 38;
 [0532] j) a VL2 comprising SEQ ID NO: 41 and a VH2 comprising SEQ ID NO: 42;
 [0533] k) a VL2 comprising SEQ ID NO: 45 and a VH2 comprising SEQ ID NO: 46;
 [0534] l) a VL2 comprising SEQ ID NO: 49 and a VH2 comprising SEQ ID NO: 50; and
 [0535] m) a VL2 comprising SEQ ID NO: 53 and a VH2 comprising SEQ ID NO: 54.

[0536] In one aspect, the present invention is directed to an antigen binding protein that specifically binds and agonizes human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

[0537] the VL comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0538] SEQ ID NOs: 58, 59, and 60, respectively;
 [0539] SEQ ID NOs: 64, 65, and 66, respectively;
 [0540] SEQ ID NOs: 70, 71, and 72, respectively;
 [0541] SEQ ID NOs: 76, 77, and 78, respectively;
 [0542] SEQ ID NOs: 82, 83, and 84, respectively;
 [0543] SEQ ID NOs: 88, 89, and 90, respectively;
 [0544] SEQ ID NOs: 94, 95, and 96, respectively;
 [0545] SEQ ID NOs: 100, 101, and 102, respectively;
 [0546] SEQ ID NOs: 106, 107, and 108, respectively;
 [0547] SEQ ID NOs: 112, 113, and 114, respectively;
 [0548] SEQ ID NOs: 118, 119, and 120, respectively;
 [0549] SEQ ID NOs: 124, 125, and 126, respectively; and
 [0550] SEQ ID NOs: 130, 131, and 132, respectively;
 [0551] and

[0552] the VH comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0553] SEQ ID NOs: 136, 137, and 138, respectively;
 [0554] SEQ ID NOs: 142, 143, and 144, respectively;
 [0555] SEQ ID NOs: 148, 149, and 150, respectively;
 [0556] SEQ ID NOs: 154, 155, and 156, respectively;
 [0557] SEQ ID NOs: 160, 161, and 162, respectively;
 [0558] SEQ ID NOs: 166, 167, and 168, respectively;
 [0559] SEQ ID NOs: 172, 173, and 174, respectively;
 [0560] SEQ ID NOs: 178, 179, and 180, respectively;
 [0561] SEQ ID NOs: 184, 185, and 186, respectively;

[0562] SEQ ID NOs: 190, 191, and 192, respectively;

[0563] SEQ ID NOs: 196, 197, and 198, respectively;

[0564] SEQ ID NOs: 202, 203, and 204, respectively; and

[0565] SEQ ID NOs: 208, 209, and 210, respectively.

[0566] In one ~~embodiment~~example, the multispecific antibody construct comprises mutations limiting Fc receptor binding and thus decreases Fc receptor-dependent CD40 agonism.

[0567] In one ~~embodiment~~example,

[0568] the VL and VH are selected from the group consisting of:

[0569] a) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[0570] b) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[0571] c) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

[0572] d) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

[0573] e) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

[0574] f) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

[0575] g) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

[0576] h) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

[0577] i) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

[0578] j) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

[0579] k) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

[0580] l) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

[0581] m) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.

[0582] In one [embodimentexample](#),

[0583] the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and

[0584] the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.

[0585] In one [embodimentexample](#),

[0586] the VL and VH are selected from the group consisting of:

[0587] a) a VL comprising SEQ ID NO: 5 and a VH comprising SEQ ID NO: 6;

[0588] b) a VL comprising SEQ ID NO: 9 and a VH comprising SEQ ID NO: 10;

[0589] c) a VL comprising SEQ ID NO: 13 and a VH comprising SEQ ID NO: 14;

[0590] d) a VL comprising SEQ ID NO: 17 and a VH comprising SEQ ID NO: 18;

[0591] e) a VL comprising SEQ ID NO: 21 and a VH comprising SEQ ID NO: 22;

[0592] f) a VL comprising SEQ ID NO: 25 and a VH comprising SEQ ID NO: 26;

[0593] g) a VL comprising SEQ ID NO: 29 and a VH comprising SEQ ID NO: 30;

[0594] h) a VL comprising SEQ ID NO: 33 and a VH comprising SEQ ID NO: 34;

[0595] i) a VL comprising SEQ ID NO: 37 and a VH comprising SEQ ID NO: 38;

[0596] j) a VL comprising SEQ ID NO: 41 and a VH comprising SEQ ID NO: 42;

[0597] k) a VL comprising SEQ ID NO: 45 and a VH comprising SEQ ID NO: 46;

[0598] l) a VL comprising SEQ ID NO: 49 and a VH comprising SEQ ID NO: 50; and

[0599] m) a VL comprising SEQ ID NO: 53 and a VH comprising SEQ ID NO: 54.

[0600] In one [embodimentexample](#), the heavy chain comprises an amino acid substitution selected from the group consisting of:

[0601] (i) N297G or N297A;

[0602] (ii) L234A and L235A; and

[0603] (iii) R292C and V302C;

[0604] wherein the amino acid numbering is EU numbering according to Kabat.

[0605] In one [embodimentexample](#), the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

[0606] In one [embodimentexample](#), the antigen binding protein further comprises a light chain CL polypeptide linked to the VL, wherein the CL polypeptide is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.

[0607] In one [embodimentexample](#), the antigen binding protein further comprises a heavy chain CH1-hinge-CH2-CH3 polypeptide wherein the CH1-hinge-CH2-CH3 polypeptide is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.

[0608] In one [embodimentexample](#), the antigen binding protein further comprises a second antigen binding portion that specifically binds a second antigen.

[0609] In one [embodimentexample](#), the second antigen is a tumor associated antigen (TAA).

BRIEF DESCRIPTION OF THE DRAWINGS

[0610] Figure 1 depicts on cell binding of anti-MSLN antibodies to CHO cells expressing human MSLN.

[0611] Figure 2 depicts Activity of anti-CD40 antibodies with and without crosslinking in human B cell assay.

[0612] Figure 3 depicts Bivalent bispecific antibody formats.

[0613] Figure 4 depicts Generation of cell lines expressing varying levels of MSLN.

[0614] Figure 5 depicts Pharmacokinetic properties and stability of anti-CD40xMSLN bispecific molecules in mouse.

[0615] Figure 6 depicts Generation of MC38-human EPCAM and B16F10-human EPCAM expressing cell line.

[0616] Figure 7 depicts Activity of mouse surrogate anti-CD40xhuman EPCAM bispecific molecule.

[0617] Figure 8 depicts Mouse surrogate anti-CD40xhuman EPCAM bispecific molecule has tumor-localized, TAA-mediated X-linking-dependent activity in vivo.

[0618] Figure 9 depicts Mouse surrogate anti-CD40xhuman EPCAM bispecific molecule enhances CD8+ T cell anti-tumor responses.

[0619] Figure 10 depicts Mouse surrogate anti-CD40xhuman EPCAM bispecific molecule has tumor-localized, TAA-mediated X-linking-dependent activity in vivo.

[0620] Figure 11 depicts Mouse surrogate anti-CD40xhuman EPCAM bispecific molecule does not increase levels of systemic cytokines or increase liver inflammation.

[1130] SEQ ID NOs: 236, 237, and 238, respectively;
[1131] SEQ ID NOs: 242, 243, and 244, respectively; and
[1132] SEQ ID NOs: 248, 249, and 250, respectively;
[1133] and the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[1134] SEQ ID NOs: 254, 255, and 256, respectively;
[1135] SEQ ID NOs: 260, 261, and 262, respectively;
[1136] SEQ ID NOs: 266, 267, and 268, respectively; and
[1137] SEQ ID NOs: 272, 273, and 274, respectively.

[1138]

[1139] ~~64. The antibody construct of claim 63, wherein~~ In one embodiment,

[1140] 1) the VL1 and VH1 are selected from the group consisting of:

[1141] a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[1142] b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[1143] c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

[1144] d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

[1145] e) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

[1146] f) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

[1147] g) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

[1148] h) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

CLAIMS

We claim:

~~1. A multispecific antibody construct comprising:~~

~~(i) a first antibody comprising two light chains and two heavy chains, wherein~~

~~the light chains comprise a first variable region (VL1) and a light chain constant region (CL);~~

~~the heavy chains comprise a first heavy variable region (VH1) and CH1, hinge, CH2, and~~

~~CH3 regions;~~

~~the heavy chains comprise at least one amino acid substitution that results in a reduced binding affinity of the heavy chain for human Fc gamma RI receptor as compared with an unsubstituted heavy chain; and~~

~~(ii) a scFv comprising a second light chain variable region (VL2) and a second heavy chain variable region (VH2) of a second antibody, wherein the VL2 and the VH2 are connected via a first peptide linker,~~

~~wherein the scFv is fused at its amino terminus to the carboxyl terminus of each of the heavy chains through a second peptide linker such that a heavy chain fusion protein is formed; and~~

~~wherein the first antibody specifically binds to and agonizes human CD40 (SEQ ID NO: 1) and the scFv specifically binds to human mesothelin (MSLN) (SEQ ID NO: 2).~~

~~2. The antibody construct of claim 1, wherein the two light chains are identical and the two heavy chain fusion proteins are identical.~~

~~3. The antibody construct according to any preceding claim, wherein the heavy chain comprises an amino acid substitution selected from the group consisting of:~~

~~(i) N297G or N297A;~~

~~(ii) L234A and L235A; and~~

~~(iii) R292C and V302C;~~

~~wherein the amino acid numbering is EU numbering according to Kabat.~~

~~4. The antibody construct according to claim 3, wherein the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.~~

~~5. The antibody construct of any preceding claim, wherein:~~

~~the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of: SEQ ID NOs: 58, 59, and 60, respectively;~~

~~SEQ ID NOs: 64, 65, and 66, respectively;~~
~~SEQ ID NOs: 70, 71, and 72, respectively;~~
~~SEQ ID NOs: 76, 77, and 78, respectively;~~
~~SEQ ID NOs: 82, 83, and 84, respectively;~~
~~SEQ ID NOs: 88, 89, and 90, respectively;~~
~~SEQ ID NOs: 94, 95, and 96, respectively;~~
~~SEQ ID NOs: 100, 101, and 102, respectively;~~
~~SEQ ID NOs: 106, 107, and 108, respectively;~~
~~SEQ ID NOs: 112, 113, and 114, respectively;~~
~~SEQ ID NOs: 118, 119, and 120, respectively;~~
~~SEQ ID NOs: 124, 125, and 126, respectively; and~~
~~SEQ ID NOs: 130, 131, and 132, respectively;~~

~~the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:~~

~~SEQ ID NOs: 136, 137, and 138, respectively;~~
~~SEQ ID NOs: 142, 143, and 144, respectively;~~
~~SEQ ID NOs: 148, 149, and 150, respectively;~~
~~SEQ ID NOs: 154, 155, and 156, respectively;~~
~~SEQ ID NOs: 160, 161, and 162, respectively;~~
~~SEQ ID NOs: 166, 167, and 168, respectively;~~
~~SEQ ID NOs: 172, 173, and 174, respectively;~~
~~SEQ ID NOs: 178, 179, and 180, respectively;~~
~~SEQ ID NOs: 184, 185, and 186, respectively;~~
~~SEQ ID NOs: 190, 191, and 192, respectively;~~
~~SEQ ID NOs: 196, 197, and 198, respectively;~~
~~SEQ ID NOs: 202, 203, and 204, respectively; and~~
~~SEQ ID NOs: 208, 209, and 210, respectively;~~

~~the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:~~

~~SEQ ID NOs: 230, 231, and 232, respectively;~~
~~SEQ ID NOs: 236, 237, and 238, respectively;~~
~~SEQ ID NOs: 242, 243, and 244, respectively; and~~
~~SEQ ID NOs: 248, 249, and 250, respectively;~~

~~and the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:~~

~~SEQ ID NOs: 254, 255, and 256, respectively;~~
~~SEQ ID NOs: 260, 261, and 262, respectively;~~
~~SEQ ID NOs: 266, 267, and 268, respectively; and~~

SEQ ID NOs: 272, 273, and 274, respectively.

6. The antibody construct of any preceding claim, wherein

1) the VL1 and VH1 are selected from the group consisting of:

a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

e) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

f) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

g) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

h) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

i) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

j) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

k) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

l) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

m) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively;

and

2) the VL2 and VH2 are selected from the group consisting of:

a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH2 comprising a

~~CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively.~~

~~7. The antibody construct of any preceding claim, wherein:~~

~~the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53;~~

~~the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54;~~

~~the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;~~

~~the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226.~~

~~8. The antibody construct of any preceding claim, wherein:~~

~~1) the VL1 and VH1 are selected from the group consisting of:~~

~~a) a VL1 comprising SEQ ID NO: 5 and a VH1 comprising SEQ ID NO: 6;~~

~~b) a VL1 comprising SEQ ID NO: 9 and a VH1 comprising SEQ ID NO: 10;~~

~~c) a VL1 comprising SEQ ID NO: 13 and a VH1 comprising SEQ ID NO: 14;~~

~~d) a VL1 comprising SEQ ID NO: 17 and a VH1 comprising SEQ ID NO: 18;~~

~~e) a VL1 comprising SEQ ID NO: 21 and a VH1 comprising SEQ ID NO: 22;~~

~~f) a VL1 comprising SEQ ID NO: 25 and a VH1 comprising SEQ ID NO: 26;~~

~~g) a VL1 comprising SEQ ID NO: 29 and a VH1 comprising SEQ ID NO: 30;~~

~~h) a VL1 comprising SEQ ID NO: 33 and a VH1 comprising SEQ ID NO: 34;~~

~~i) a VL1 comprising SEQ ID NO: 37 and a VH1 comprising SEQ ID NO: 38;~~

~~j) a VL1 comprising SEQ ID NO: 41 and a VH1 comprising SEQ ID NO: 42;~~

~~k) a VL1 comprising SEQ ID NO: 45 and a VH1 comprising SEQ ID NO: 46;~~

~~l) a VL1 comprising SEQ ID NO: 49 and a VH1 comprising SEQ ID NO: 50; and~~

~~m) a VL1 comprising SEQ ID NO: 53 and a VH1 comprising SEQ ID NO: 54;~~

~~and~~

~~2) the VL2 and VH2 are selected from the group consisting of:~~

~~a) a VL2 comprising SEQ ID NO: 213 and a VH2 comprising SEQ ID NO: 214;~~

~~b) a VL2 comprising SEQ ID NO: 217 and a VH2 comprising SEQ ID NO: 218;~~

~~c) a VL2 comprising SEQ ID NO: 221 and a VH2 comprising SEQ ID NO: 222; and~~

~~d) a VL2 comprising SEQ ID NO: 225 and a VH2 comprising SEQ ID NO: 226.~~

9. The antibody construct according to any preceding claim, wherein the CL of the light chain is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.

10. The antibody construct according to any preceding claim, wherein the CH1 hinge-CH2-CH3 of the heavy chain is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.

11. The antibody construct according to any preceding claim, wherein the first peptide linker is selected from the group consisting of SEQ ID NOs: 888-893.

12. The antibody construct according to any preceding claim, wherein the second peptide linker is selected from the group consisting of SEQ ID NOs: 887-893.

13. The antibody construct according to any preceding claim, wherein the first peptide linker comprises SEQ ID NO: 889 and the second peptide linker comprises SEQ ID NO: 887.

14. The antibody construct according to any preceding claim, wherein
the light chain comprises a sequence selected from the group consisting of SEQ ID NOs: 286, 290, 294, 298, 302, 306, 310, 314, 318, 322, 326, 330, 336, 342, 346, 350, 354, 358, 362, 366, 370, 374, and 378; and
the heavy chain fusion protein comprises a sequence selected from the group consisting of SEQ ID Nos: 285, 289, 293, 297, 301, 305, 309, 313, 317, 321, 325, 329, 333, 337, 341, 345, 349, 353, 357, 361, 365, 369, 373, and 377.

15. The antibody construct according to any preceding claim, wherein the light chain and the heavy chain fusion protein comprise polypeptides comprising amino acid sequences selected from the group consisting of:

SEQ ID NO: 286 and SEQ ID NO: 285, respectively;
SEQ ID NO: 290 and SEQ ID NO: 289, respectively;
SEQ ID NO: 294 and SEQ ID NO: 293, respectively;
SEQ ID NO: 298 and SEQ ID NO: 297, respectively;
SEQ ID NO: 302 and SEQ ID NO: 301, respectively;
SEQ ID NO: 306 and SEQ ID NO: 305, respectively;
SEQ ID NO: 310 and SEQ ID NO: 309, respectively;
SEQ ID NO: 314 and SEQ ID NO: 313, respectively;
SEQ ID NO: 318 and SEQ ID NO: 317, respectively;
SEQ ID NO: 322 and SEQ ID NO: 321, respectively;
SEQ ID NO: 326 and SEQ ID NO: 325, respectively;

~~SEQ ID NO: 330 and SEQ ID NO: 329, respectively;
SEQ ID NO: 334 and SEQ ID NO: 333, respectively;
SEQ ID NO: 338 and SEQ ID NO: 337, respectively;
SEQ ID NO: 342 and SEQ ID NO: 341, respectively;
SEQ ID NO: 346 and SEQ ID NO: 345, respectively;
SEQ ID NO: 350 and SEQ ID NO: 349, respectively;
SEQ ID NO: 354 and SEQ ID NO: 353, respectively;
SEQ ID NO: 358 and SEQ ID NO: 357, respectively;
SEQ ID NO: 362 and SEQ ID NO: 361, respectively;
SEQ ID NO: 366 and SEQ ID NO: 365, respectively;
SEQ ID NO: 370 and SEQ ID NO: 369, respectively;
SEQ ID NO: 374 and SEQ ID NO: 373, respectively; and
SEQ ID NO: 378 and SEQ ID NO: 377, respectively.~~

~~16. A polynucleotide encoding the light chain of the antibody construct according to any preceding claim.~~

~~17. A polynucleotide encoding the heavy chain fusion protein of the antibody construct according to any preceding claim.~~

~~18. A vector comprising the polynucleotide according to claim 16, the polynucleotide according to claim 17, or both.~~

~~19. A host cell transformed or transfected with the polynucleotide according to claim 16 and the polynucleotide according to claim 17.~~

~~20. A process for producing the antibody construct according to any one of claims 1-15, said process comprising culturing a host cell comprising a polynucleotide encoding the light chain and also comprising a polynucleotide encoding the heavy chain fusion protein under conditions allowing the expression of the antibody construct, and recovering the produced antibody construct from the culture.~~

~~21. A pharmaceutical composition comprising the antibody construct according to any one of claims 1-15 and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative or adjuvant.~~

22. A method for treating or ameliorating a solid tumor disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof an effective amount of the antibody construct according to any one of claims 1-15.

23. The method according to claim 22, wherein the solid tumor disease is selected from the group consisting of: ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer disease or a metastatic cancer disease derived from any of the foregoing.

24. A kit comprising the antibody construct according to any one of claims 1-15 and, optionally, directions for use.

25. A multispecific antibody construct comprising:

(i) a first antibody comprising two light chains and two heavy chains, wherein

the light chains comprise a first variable region (VL1) and a light chain constant region (CL);

the heavy chains comprise a first heavy variable region (VH1) and CH1, hinge, CH2, and

CH3 regions;

the heavy chains comprise at least one amino acid substitution that results in a reduced binding affinity of the heavy chain for human Fc gamma RI receptor as compared with an unsubstituted heavy chain; and

(ii) a scFv comprising a second light chain variable region (VL2) and a second heavy chain variable region (VH2) of a second antibody, wherein the VL2 and the VH2 are connected via a first peptide linker,

wherein the scFv is fused at its amino terminus to the carboxyl terminus of each of the heavy chains through a second peptide linker such that a heavy chain fusion protein is formed; and

wherein the first antibody specifically binds to human mesothelin (MSLN) (SEQ ID NO: 2) and the scFv specifically binds to and agonizes human CD40 (SEQ ID NO: 1).

26. The antibody construct of claim 25, wherein the two light chains are identical and the two heavy chain fusion proteins are identical.

27. The antibody construct according to any one of claims 25-26, wherein the heavy chain comprises an amino acid substitution selected from the group consisting of:

(i) N297G or N297A;

(ii) L234A and L235A; and

(iii) R292C and V302C;

wherein the amino acid numbering is EU numbering according to Kabat.

~~28. The antibody construct according to claim 27, wherein the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.~~

~~29. The antibody construct of any one of claims 25-28, wherein:~~

~~the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:~~

~~SEQ ID NOs: 230, 231, and 232, respectively;~~

~~SEQ ID NOs: 236, 237, and 238, respectively;~~

~~SEQ ID NOs: 242, 243, and 244, respectively; and~~

~~SEQ ID NOs: 248, 249, and 250, respectively;~~

~~the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting~~

~~of:~~

~~SEQ ID NOs: 254, 255, and 256, respectively;~~

~~SEQ ID NOs: 260, 261, and 262, respectively;~~

~~SEQ ID NOs: 266, 267, and 268, respectively; and~~

~~SEQ ID NOs: 272, 273, and 274, respectively;~~

~~the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:~~

~~SEQ ID NOs: 58, 59, and 60, respectively;~~

~~SEQ ID NOs: 64, 65, and 66, respectively;~~

~~SEQ ID NOs: 70, 71, and 72, respectively;~~

~~SEQ ID NOs: 76, 77, and 78, respectively;~~

~~SEQ ID NOs: 82, 83, and 84, respectively;~~

~~SEQ ID NOs: 88, 89, and 90, respectively;~~

~~SEQ ID NOs: 94, 95, and 96, respectively;~~

~~SEQ ID NOs: 100, 101, and 102, respectively;~~

~~SEQ ID NOs: 106, 107, and 108, respectively;~~

~~SEQ ID NOs: 112, 113, and 114, respectively;~~

~~SEQ ID NOs: 118, 119, and 120, respectively;~~

~~SEQ ID NOs: 124, 125, and 126, respectively; and~~

~~SEQ ID NOs: 130, 131, and 132, respectively;~~

~~and~~

~~the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting~~

~~of:~~

~~SEQ ID NOs: 136, 137, and 138, respectively;~~

~~SEQ ID NOs: 142, 143, and 144, respectively;~~

~~SEQ ID NOs: 148, 149, and 150, respectively;~~

~~SEQ ID NOs: 154, 155, and 156, respectively;~~

~~SEQ ID NOs: 160, 161, and 162, respectively;~~

SEQ ID NOs: 166, 167, and 168, respectively;
SEQ ID NOs: 172, 173, and 174, respectively;
SEQ ID NOs: 178, 179, and 180, respectively;
SEQ ID NOs: 184, 185, and 186, respectively;
SEQ ID NOs: 190, 191, and 192, respectively;
SEQ ID NOs: 196, 197, and 198, respectively;
SEQ ID NOs: 202, 203, and 204, respectively; and
SEQ ID NOs: 208, 209, and 210, respectively.

30. The antibody construct of any one of claims 25-29, wherein

1) the VL1 and VH1 are selected from the group consisting of:

a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively;

and

2) the VL2 and VH2 are selected from the group consisting of:

a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

e) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

f) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

g) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

h) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

i) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

j) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

k) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

~~l) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and~~

~~m) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.~~

31. The antibody construct of any one of claims 25-30, wherein:

~~the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;~~

~~the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226;~~

~~the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and~~

~~the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.~~

32. The antibody construct of any one of claims 25-31, wherein:

~~1) the VL1 and VH1 are selected from the group consisting of:~~

~~a) a VL1 comprising SEQ ID NO: 213 and a VH1 comprising SEQ ID NO: 214;~~

~~b) a VL1 comprising SEQ ID NO: 217 and a VH1 comprising SEQ ID NO: 218;~~

~~c) a VL1 comprising SEQ ID NO: 221 and a VH1 comprising SEQ ID NO: 222; and~~

~~d) a VL1 comprising SEQ ID NO: 225 and a VH1 comprising SEQ ID NO: 226;~~

~~and~~

~~2) the VL2 and VH2 are selected from the group consisting of:~~

~~a) a VL2 comprising SEQ ID NO: 5 and a VH2 comprising SEQ ID NO: 6;~~

~~b) a VL2 comprising SEQ ID NO: 9 and a VH2 comprising SEQ ID NO: 10;~~

~~c) a VL2 comprising SEQ ID NO: 13 and a VH2 comprising SEQ ID NO: 14;~~

~~d) a VL2 comprising SEQ ID NO: 17 and a VH2 comprising SEQ ID NO: 18;~~

~~e) a VL2 comprising SEQ ID NO: 21 and a VH2 comprising SEQ ID NO: 22;~~

~~f) a VL2 comprising SEQ ID NO: 25 and a VH2 comprising SEQ ID NO: 26;~~

~~g) a VL2 comprising SEQ ID NO: 29 and a VH2 comprising SEQ ID NO: 30;~~

~~h) a VL2 comprising SEQ ID NO: 33 and a VH2 comprising SEQ ID NO: 34;~~

~~i) a VL2 comprising SEQ ID NO: 37 and a VH2 comprising SEQ ID NO: 38;~~

~~j) a VL2 comprising SEQ ID NO: 41 and a VH2 comprising SEQ ID NO: 42;~~

- k) a VL2 comprising SEQ ID NO: 45 and a VH2 comprising SEQ ID NO: 46;
- l) a VL2 comprising SEQ ID NO: 49 and a VH2 comprising SEQ ID NO: 50; and
- m) a VL2 comprising SEQ ID NO: 53 and a VH2 comprising SEQ ID NO: 54.

33. The antibody construct according to any one of claims 25-32, wherein the CL of the light chain is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.

34. The antibody construct according to any one of claims 25-33, wherein the CH1 hinge-CH2-CH3 of the heavy chain is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.

35. The antibody construct according to any one of claims 25-34, wherein the first peptide linker is selected from the group consisting of SEQ ID NOs: 888-893.

36. The antibody construct according to any one of claims 25-35, wherein the second peptide linker is selected from the group consisting of SEQ ID NOs: 887-893.

37. The antibody construct according to any one of claims 25-36, wherein the first peptide linker comprises SEQ ID NO: 889 and the second peptide linker comprises SEQ ID NO: 887.

38. The antibody construct according to any one of claims 25-37, wherein
the light chain comprises a sequence selected from the group consisting of SEQ ID NOs: 382, 386, 390, 394, 398, 402, 406, 410, 414, 418, 422, 426, 430, 434, 438, 442, 446, and 450; and
the heavy chain fusion protein comprises a sequence selected from the group consisting of SEQ ID NOs: 381, 385, 389, 393, 397, 401, 405, 409, 413, 417, 421, 425, 429, 433, 437, 441, 445, and 449.

39. The antibody construct according to any one of claims 25-38, wherein the light chain and the heavy chain fusion protein comprise polypeptides comprising amino acid sequences selected from the group consisting of:

- SEQ ID NO: 382 and SEQ ID NO: 381, respectively;
- SEQ ID NO: 386 and SEQ ID NO: 385, respectively;
- SEQ ID NO: 390 and SEQ ID NO: 389, respectively;
- SEQ ID NO: 394 and SEQ ID NO: 393, respectively;
- SEQ ID NO: 398 and SEQ ID NO: 397, respectively;
- SEQ ID NO: 402 and SEQ ID NO: 401, respectively;
- SEQ ID NO: 406 and SEQ ID NO: 405, respectively;
- SEQ ID NO: 410 and SEQ ID NO: 409, respectively;

~~SEQ ID NO: 414 and SEQ ID NO: 413, respectively;
SEQ ID NO: 418 and SEQ ID NO: 417, respectively;
SEQ ID NO: 422 and SEQ ID NO: 421, respectively;
SEQ ID NO: 426 and SEQ ID NO: 425, respectively;
SEQ ID NO: 430 and SEQ ID NO: 429, respectively;
SEQ ID NO: 434 and SEQ ID NO: 433, respectively;
SEQ ID NO: 438 and SEQ ID NO: 437, respectively;
SEQ ID NO: 442 and SEQ ID NO: 441, respectively;
SEQ ID NO: 446 and SEQ ID NO: 445, respectively; and
SEQ ID NO: 450 and SEQ ID NO: 449, respectively.~~

~~40. A polynucleotide encoding the light chain of the antibody construct according to any one of claims 25-39.~~

~~41. A polynucleotide encoding the heavy chain fusion protein of the antibody construct according to any one of claims 25-39.~~

~~42. A vector comprising the polynucleotide according to claim 40, the polynucleotide according to claim 41, or both.~~

~~43. A host cell transformed or transfected with the polynucleotide according to claim 40 and the polynucleotide according to claim 42.~~

~~44. A process for producing the antibody construct according to any one of claims 25-39, said process comprising culturing a host cell comprising a polynucleotide encoding the light chain and also comprising a polynucleotide encoding the heavy chain fusion protein under conditions allowing the expression of the antibody construct, and recovering the produced antibody construct from the culture.~~

~~45. A pharmaceutical composition comprising the antibody construct according to any one of claims 25-39 and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative or adjuvant.~~

~~46. A method for treating or ameliorating a solid tumor disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof an effective amount of the antibody construct according to any one of claims 25-39.~~

~~47. The method according to claim 46, wherein the solid tumor disease is selected from the group consisting of: ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer disease or a metastatic cancer disease derived from any of the foregoing.~~

~~48. A kit comprising the antibody construct according to any one of claims 25-39 and, optionally, directions for use.~~

~~49. A multispecific antibody construct comprising:~~

~~a) two identical heavy chain fusion proteins each comprising a first heavy chain variable region (VH1) and a first CH1 domain, wherein the first CH1 domain is linked to a hinge-CH2-CH3 polypeptide, and wherein the hinge-CH2-CH3 polypeptide is linked to a second heavy chain variable region (VH2), wherein the VH2 is linked to a second CH1 domain; wherein~~

~~i) the VH1 or first CH1 domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of positions 39, 44, and 183 using EU numbering; and~~

~~ii) the VH2 or second CH1 domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of a residue that corresponds to positions 39, 44, and 183 using EU numbering; and~~

~~b) a second polypeptide comprising a first light chain, wherein the first light chain comprises a first light chain variable region (VL1) and a first CL region; and wherein the VL1 or first CL domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering; and~~

~~c) a third polypeptide comprising a second light chain, wherein the second light chain comprises a second light chain variable region (VL2) and a second CL region; and wherein the VL2 or second CL domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering;~~

~~wherein the VH1 and VL1 interact to bind a first antigen and wherein the VH2 and VL2 interact to bind a second antigen;~~

~~wherein:~~

~~the first antigen is human CD40 (SEQ ID NO: 1) and the second antigen is human mesothelin ("MSLN"; SEQ ID NO: 2); or~~

~~the first antigen is human MSLN (SEQ ID NO: 2) and the second antigen is human CD40 (SEQ ID NO: 1).~~

~~50. A multispecific antibody construct comprising:~~

a) two identical heavy chain fusion proteins each comprising a first heavy chain variable region (VH1) and a first CH1 domain, wherein the first CH1 domain is linked to a hinge-CH2-CH3 polypeptide, and wherein the hinge-CH2-CH3 polypeptide is linked to a second heavy chain variable region (VH2), wherein the VH2 is linked to a second CH1 domain; wherein

i) the VH1 or first CH1 domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of positions 39, 44, and 183 using EU numbering; and

ii) the VH2 or second CH1 domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of a residue that corresponds to positions 39, 44, and 183 using EU numbering; and

b) a second polypeptide comprising a first light chain, wherein the first light chain comprises a first light chain variable region (VL1) and a first CL region; and wherein the VL1 or first CL domain comprises at least one amino acid substitution to introduce a positively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering; and

c) a third polypeptide comprising a second light chain, wherein the second light chain comprises a second light chain variable region (VL2) and a second CL region; and wherein the VL2 or second CL domain comprises at least one amino acid substitution to introduce a negatively charged amino acid at a residue selected from the group consisting of positions 38, 100, and 176 using EU numbering;

wherein the VH1 and VL1 interact to bind a first antigen and wherein the VH2 and VL2 interact to bind a second antigen;

wherein:

the first antigen is human CD40 (SEQ ID NO: 1) and the second antigen is human mesothelin ("MSLN"; SEQ ID NO: 2); or

the first antigen is human MSLN (SEQ ID NO: 2) and the second antigen is human CD40 (SEQ ID NO: 1).

51. The antibody construct according to any one of claims 49 or 50, wherein the hinge-CH2-CH3 polypeptide is linked to the VH2 via a peptide linker.

52. The antibody construct according to 51, wherein the peptide linker comprises a sequence selected from the group consisting of (Gly₃Ser)₂ (SEQ ID NO: 916), (Gly₄Ser)₂ (SEQ ID NO: 888), (Gly₃Ser)₃ (SEQ ID NO: 917), (Gly₄Ser)₃ (SEQ ID NO: 889), (Gly₃Ser)₄ (SEQ ID NO: 918), (Gly₄Ser)₄ (SEQ ID NO: 890), (Gly₃Ser)₅ (SEQ ID NO: 919), (Gly₄Ser)₅ (SEQ ID NO: 920), (Gly₃Ser)₆ (SEQ ID NO: 921), and (Gly₄Ser)₆ (SEQ ID NO: 922).

53. The antigen binding protein according to claim 49, wherein

- a) the VH1 or first CH1 domain comprises a mutation selected from the group consisting of Q39K, G44K, and S183K using EU numbering;
- b) the VH2 or second CH1 domain comprises a mutation selected from the group consisting of Q39E, G44E, and S183E using EU numbering;
- c) the VL1 or first CL domain comprises a mutation selected from the group consisting of Q38E, G100E, and S176E using EU numbering; and
- d) the VL2 or second CL domain comprises a mutation selected from the group consisting of Q38K, G100K, and S176K using EU numbering.

54. The antigen binding protein according to claim 53, wherein

- a) the first CH1 domain comprises a S183K mutation using EU numbering;
- b) the second CH1 domain comprises a S183E mutation using EU numbering;
- c) the first CL domain comprises a S176E mutation using EU numbering; and
- d) the second CL domain comprises a S176K mutation using EU numbering.

55. The antigen binding protein according to claim 53, wherein

- a) the VH1 comprises a Q39K mutation and the first CH1 domain comprises a S183K mutation using EU numbering;
- b) the VH2 comprises a Q39E mutation and the second CH1 domain comprises a S183E mutation using EU numbering;
- c) the VL1 comprises a Q38E mutation and the first CL domain comprises a S176E mutation using EU numbering; and
- d) the VL2 comprises a Q38K mutation and the second CL domain comprises a S176K mutation using EU numbering.

56. The antigen binding protein according to claim 53, wherein

- a) the first CH1 domain comprises G44K and S183K mutations using EU numbering;
- b) the second CH1 domain comprises G44E and S183E mutations using EU numbering;
- c) the first CL domain comprises G100E and S176E mutations using EU numbering; and
- d) the second CL domain comprises G100K and S176K mutations using EU numbering.

57. The antigen binding protein according to claim 50, wherein

- a) the VH1 or first CH1 domain comprises a mutation selected from the group consisting of Q39E, G44E, and S183E using EU numbering;
- b) the VH2 or second CH1 domain comprises a mutation selected from the group consisting of Q39K, G44K, and S183K using EU numbering;

- e) the VL1 or first CL domain comprises a mutation selected from the group consisting of Q38K, G100K, and S176K using EU numbering; and
- d) the VL2 or second CL domain comprises a mutation selected from the group consisting of Q38E, G100E, and S176E using EU numbering.

58. The antigen binding protein according to claim 57, wherein

- a) the first CH1 domain comprises a S183E mutation using EU numbering;
- b) the second CH1 domain comprises a S183K mutation using EU numbering;
- c) the first CL domain comprises a S176K mutation using EU numbering; and
- d) the second CL domain comprises a S176E mutation using EU numbering.

59. The antigen binding protein according to claim 57, wherein

- a) the VH1 comprises a Q39E mutation and the first CH1 domain comprises a S183E mutation using EU numbering;
- b) the VH2 comprises a Q39K mutation and the second CH1 domain comprises a S183K mutation using EU numbering;
- c) the VL1 comprises a Q38K mutation and the first CL domain comprises a S176K mutation using EU numbering; and
- d) the VL2 comprises a Q38E mutation and the second CL domain comprises a S176E mutation using EU numbering.

60. The antigen binding protein according to claim 57, wherein

- a) the first CH1 domain comprises G44E and S183E mutations using EU numbering;
- b) the second CH1 domain comprises G44K and S183K mutations using EU numbering;
- c) the first CL domain comprises G100K and S176K mutations using EU numbering; and
- d) the second CL domain comprises G100E and S176E mutations using EU numbering.

61. The antibody construct according to any one of claims 49-50, wherein the hinge CH2-CH3 polypeptide comprises an amino acid substitution selected from the group consisting of:

- (i) N297G or N297A;
- (ii) L234A and L235A; and
- (iii) R292C and V302C;

wherein the amino acid numbering is EU numbering according to Kabat.

62. The antibody construct according to claim 61, wherein the hinge CH2-CH3 polypeptide comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

63. The antibody construct of any one of claims 49-62, wherein the first antigen is human CD40 (SEQ ID NO: 1) and the second antigen is human MSLN (SEQ ID NO: 2); and

the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

SEQ ID NOs: 58, 59, and 60, respectively;
SEQ ID NOs: 64, 65, and 66, respectively;
SEQ ID NOs: 70, 71, and 72, respectively;
SEQ ID NOs: 76, 77, and 78, respectively;
SEQ ID NOs: 82, 83, and 84, respectively;
SEQ ID NOs: 88, 89, and 90, respectively;
SEQ ID NOs: 94, 95, and 96, respectively;
SEQ ID NOs: 100, 101, and 102, respectively;
SEQ ID NOs: 106, 107, and 108, respectively;
SEQ ID NOs: 112, 113, and 114, respectively;
SEQ ID NOs: 118, 119, and 120, respectively;
SEQ ID NOs: 124, 125, and 126, respectively; and
SEQ ID NOs: 130, 131, and 132, respectively;

the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

SEQ ID NOs: 136, 137, and 138, respectively;
SEQ ID NOs: 142, 143, and 144, respectively;
SEQ ID NOs: 148, 149, and 150, respectively;
SEQ ID NOs: 154, 155, and 156, respectively;
SEQ ID NOs: 160, 161, and 162, respectively;
SEQ ID NOs: 166, 167, and 168, respectively;
SEQ ID NOs: 172, 173, and 174, respectively;
SEQ ID NOs: 178, 179, and 180, respectively;
SEQ ID NOs: 184, 185, and 186, respectively;
SEQ ID NOs: 190, 191, and 192, respectively;
SEQ ID NOs: 196, 197, and 198, respectively;
SEQ ID NOs: 202, 203, and 204, respectively; and
SEQ ID NOs: 208, 209, and 210, respectively;

the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

SEQ ID NOs: 230, 231, and 232, respectively;
SEQ ID NOs: 236, 237, and 238, respectively;
SEQ ID NOs: 242, 243, and 244, respectively; and
SEQ ID NOs: 248, 249, and 250, respectively;

and the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

SEQ ID NOs: 254, 255, and 256, respectively;

SEQ ID NOs: 260, 261, and 262, respectively;

SEQ ID NOs: 266, 267, and 268, respectively; and

SEQ ID NOs: 272, 273, and 274, respectively.

64. The antibody construct of claim 63, wherein

1) the VL1 and VH1 are selected from the group consisting of:

a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

e) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

f) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

g) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

h) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

i) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

j) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

k) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

l) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

m) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively;

and

2) the VL2 and VH2 are selected from the group consisting of:

a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

c) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH2 comprising a

CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively.

65. The antibody construct of claim 63, wherein:

the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53;

the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54;

the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;

the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226.

66. The antibody construct of claim 65, wherein:

1) the VL1 and VH1 are selected from the group consisting of:

a) a VL1 comprising SEQ ID NO: 5 and a VH1 comprising SEQ ID NO: 6;

b) a VL1 comprising SEQ ID NO: 9 and a VH1 comprising SEQ ID NO: 10;

c) a VL1 comprising SEQ ID NO: 13 and a VH1 comprising SEQ ID NO: 14;

d) a VL1 comprising SEQ ID NO: 17 and a VH1 comprising SEQ ID NO: 18;

e) a VL1 comprising SEQ ID NO: 21 and a VH1 comprising SEQ ID NO: 22;

f) a VL1 comprising SEQ ID NO: 25 and a VH1 comprising SEQ ID NO: 26;

g) a VL1 comprising SEQ ID NO: 29 and a VH1 comprising SEQ ID NO: 30;

h) a VL1 comprising SEQ ID NO: 33 and a VH1 comprising SEQ ID NO: 34;

i) a VL1 comprising SEQ ID NO: 37 and a VH1 comprising SEQ ID NO: 38;

j) a VL1 comprising SEQ ID NO: 41 and a VH1 comprising SEQ ID NO: 42;

k) a VL1 comprising SEQ ID NO: 45 and a VH1 comprising SEQ ID NO: 46;

l) a VL1 comprising SEQ ID NO: 49 and a VH1 comprising SEQ ID NO: 50; and

m) a VL1 comprising SEQ ID NO: 53 and a VH1 comprising SEQ ID NO: 54;

and

2) the VL2 and VH2 are selected from the group consisting of:

a) a VL2 comprising SEQ ID NO: 213 and a VH2 comprising SEQ ID NO: 214;

b) a VL2 comprising SEQ ID NO: 217 and a VH2 comprising SEQ ID NO: 218;

c) a VL2 comprising SEQ ID NO: 221 and a VH2 comprising SEQ ID NO: 222; and

d) a VL2 comprising SEQ ID NO: 225 and a VH2 comprising SEQ ID NO: 226.

67. A polynucleotide encoding the first light chain of the antibody construct according to any one of claims 49-66 and 76-80.

68. A polynucleotide encoding the second light chain of the antibody construct according to any one of claims 49-66 and 76-80.

69. A polynucleotide encoding the heavy chain fusion protein of the antibody construct according to any one of claims 49-66 and 76-80.

70. A vector comprising:

- a) the polynucleotide according to claim 67,
- b) the polynucleotide according to claim 68,
- c) the polynucleotide according to claim 69, or
- d) any combination of a), b), and c).

71. A host cell transformed or transfected with the polynucleotide according to claim 67, the polynucleotide according to claim 68 and the polynucleotide according to claim 69.

72. A process for producing the antibody construct according to any one of claims 49-66 and 76-80, said process comprising culturing a host cell comprising a polynucleotide encoding the first light chain, a polynucleotide encoding the second light chain and a polynucleotide encoding the heavy chain fusion protein under conditions allowing the expression of the antibody construct, and recovering the produced antibody construct from the culture.

73. A pharmaceutical composition comprising the antibody construct according to any one of claims 49-66 and 76-80 and a carrier, stabilizer, excipient, diluent, solubilizer, surfactant, emulsifier, preservative or adjuvant.

74. A method for treating or ameliorating a solid tumor disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof an effective amount of the antibody construct according to any one of claims 49-66 and 76-80.

75. The method according to claim 74, wherein the solid tumor disease is selected from the group consisting of: ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer disease or a metastatic cancer disease derived from any of the foregoing.

~~76. A kit comprising the antibody construct according to any one of claims 49-66 and 76-80 and, optionally, directions for use.~~

~~77. The antibody construct of any one of claims 49-62, wherein the first antigen is human MSLN (SEQ ID NO: 2) and the second antigen is human CD40 (SEQ ID NO: 1); wherein:~~

~~the VL1 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:~~

~~SEQ ID NOs: 230, 231, and 232, respectively;~~

~~SEQ ID NOs: 236, 237, and 238, respectively;~~

~~SEQ ID NOs: 242, 243, and 244, respectively; and~~

~~SEQ ID NOs: 248, 249, and 250, respectively;~~

~~the VH1 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting~~

~~of:~~

~~SEQ ID NOs: 254, 255, and 256, respectively;~~

~~SEQ ID NOs: 260, 261, and 262, respectively;~~

~~SEQ ID NOs: 266, 267, and 268, respectively; and~~

~~SEQ ID NOs: 272, 273, and 274, respectively;~~

~~the VL2 comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:~~

~~SEQ ID NOs: 58, 59, and 60, respectively;~~

~~SEQ ID NOs: 64, 65, and 66, respectively;~~

~~SEQ ID NOs: 70, 71, and 72, respectively;~~

~~SEQ ID NOs: 76, 77, and 78, respectively;~~

~~SEQ ID NOs: 82, 83, and 84, respectively;~~

~~SEQ ID NOs: 88, 89, and 90, respectively;~~

~~SEQ ID NOs: 94, 95, and 96, respectively;~~

~~SEQ ID NOs: 100, 101, and 102, respectively;~~

~~SEQ ID NOs: 106, 107, and 108, respectively;~~

~~SEQ ID NOs: 112, 113, and 114, respectively;~~

~~SEQ ID NOs: 118, 119, and 120, respectively;~~

~~SEQ ID NOs: 124, 125, and 126, respectively; and~~

~~SEQ ID NOs: 130, 131, and 132, respectively;~~

~~and~~

~~the VH2 comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting~~

~~of:~~

~~SEQ ID NOs: 136, 137, and 138, respectively;~~

~~SEQ ID NOs: 142, 143, and 144, respectively;~~

~~SEQ ID NOs: 148, 149, and 150, respectively;~~

SEQ ID NOs: 154, 155, and 156, respectively;
SEQ ID NOs: 160, 161, and 162, respectively;
SEQ ID NOs: 166, 167, and 168, respectively;
SEQ ID NOs: 172, 173, and 174, respectively;
SEQ ID NOs: 178, 179, and 180, respectively;
SEQ ID NOs: 184, 185, and 186, respectively;
SEQ ID NOs: 190, 191, and 192, respectively;
SEQ ID NOs: 196, 197, and 198, respectively;
SEQ ID NOs: 202, 203, and 204, respectively; and
SEQ ID NOs: 208, 209, and 210, respectively.

78. The antibody construct of claim 77, wherein

1) the VL1 and VH1 are selected from the group consisting of:

a) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 230, 231, and 232, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 254, 255, and 256, respectively;

b) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 236, 237, and 238, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 260, 261, and 262, respectively;

c) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 242, 243, and 244, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 266, 267, and 268, respectively; and

d) a VL1 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 248, 249, and 250, respectively; and a VH1 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 272, 273, and 274, respectively;

and

2) the VL2 and VH2 are selected from the group consisting of:

a) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

b) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH2 comprising a CDRH1, a

CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

e) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

d) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

e) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

f) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

g) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

h) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

i) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

j) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

k) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH2 comprising a

CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

l) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

m) a VL2 comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH2 comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.

79. The antibody construct of claim 77, wherein:

the VL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 213, 217, 221, and 225;

the VH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 214, 218, 222, and 226;

the VL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and

the VH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.

80. The antibody construct of claim 79, wherein:

1) the VL1 and VH1 are selected from the group consisting of:

a) a VL1 comprising SEQ ID NO: 213 and a VH1 comprising SEQ ID NO: 214;

b) a VL1 comprising SEQ ID NO: 217 and a VH1 comprising SEQ ID NO: 218;

c) a VL1 comprising SEQ ID NO: 221 and a VH1 comprising SEQ ID NO: 222; and

d) a VL1 comprising SEQ ID NO: 225 and a VH1 comprising SEQ ID NO: 226;

and

2) the VL2 and VH2 are selected from the group consisting of:

a) a VL2 comprising SEQ ID NO: 5 and a VH2 comprising SEQ ID NO: 6;

b) a VL2 comprising SEQ ID NO: 9 and a VH2 comprising SEQ ID NO: 10;

c) a VL2 comprising SEQ ID NO: 13 and a VH2 comprising SEQ ID NO: 14;

d) a VL2 comprising SEQ ID NO: 17 and a VH2 comprising SEQ ID NO: 18;

e) a VL2 comprising SEQ ID NO: 21 and a VH2 comprising SEQ ID NO: 22;

f) a VL2 comprising SEQ ID NO: 25 and a VH2 comprising SEQ ID NO: 26;

g) a VL2 comprising SEQ ID NO: 29 and a VH2 comprising SEQ ID NO: 30;

h) a VL2 comprising SEQ ID NO: 33 and a VH2 comprising SEQ ID NO: 34;

- ~~i) a VL2 comprising SEQ ID NO: 37 and a VH2 comprising SEQ ID NO: 38;~~
- ~~j) a VL2 comprising SEQ ID NO: 41 and a VH2 comprising SEQ ID NO: 42;~~
- ~~k) a VL2 comprising SEQ ID NO: 45 and a VH2 comprising SEQ ID NO: 46;~~
- ~~l) a VL2 comprising SEQ ID NO: 49 and a VH2 comprising SEQ ID NO: 50; and~~
- ~~m) a VL2 comprising SEQ ID NO: 53 and a VH2 comprising SEQ ID NO: 54.~~

81. An antigen binding protein that specifically binds and agonizes human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

the VL comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

- SEQ ID NOs: 58, 59, and 60, respectively;
- SEQ ID NOs: 64, 65, and 66, respectively;
- SEQ ID NOs: 70, 71, and 72, respectively;
- SEQ ID NOs: 76, 77, and 78, respectively;
- SEQ ID NOs: 82, 83, and 84, respectively;
- SEQ ID NOs: 88, 89, and 90, respectively;
- SEQ ID NOs: 94, 95, and 96, respectively;
- SEQ ID NOs: 100, 101, and 102, respectively;
- SEQ ID NOs: 106, 107, and 108, respectively;
- SEQ ID NOs: 112, 113, and 114, respectively;
- SEQ ID NOs: 118, 119, and 120, respectively;
- SEQ ID NOs: 124, 125, and 126, respectively; and
- SEQ ID NOs: 130, 131, and 132, respectively;

and

the VH comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

- SEQ ID NOs: 136, 137, and 138, respectively;
- SEQ ID NOs: 142, 143, and 144, respectively;
- SEQ ID NOs: 148, 149, and 150, respectively;
- SEQ ID NOs: 154, 155, and 156, respectively;
- SEQ ID NOs: 160, 161, and 162, respectively;
- SEQ ID NOs: 166, 167, and 168, respectively;
- SEQ ID NOs: 172, 173, and 174, respectively;
- SEQ ID NOs: 178, 179, and 180, respectively;
- SEQ ID NOs: 184, 185, and 186, respectively;
- SEQ ID NOs: 190, 191, and 192, respectively;
- SEQ ID NOs: 196, 197, and 198, respectively;

SEQ ID NOs: 202, 203, and 204, respectively; and

SEQ ID NOs: 208, 209, and 210, respectively.

82. The antibody construct of claim 81, wherein

the VL and VH are selected from the group consisting of:

a) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

b) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

c) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

d) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;

e) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;

f) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;

g) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;

h) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;

i) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

j) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

k) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

l) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

m) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.

83. The antibody construct of claim 81, wherein:

the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and

the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.

84. The antibody construct of claim 83, wherein:

the VL2 and VH2 are selected from the group consisting of:

- a) a VL comprising SEQ ID NO: 5 and a VH comprising SEQ ID NO: 6;
- b) a VL comprising SEQ ID NO: 9 and a VH comprising SEQ ID NO: 10;
- c) a VL comprising SEQ ID NO: 13 and a VH comprising SEQ ID NO: 14;
- d) a VL comprising SEQ ID NO: 17 and a VH comprising SEQ ID NO: 18;
- e) a VL comprising SEQ ID NO: 21 and a VH comprising SEQ ID NO: 22;
- f) a VL comprising SEQ ID NO: 25 and a VH comprising SEQ ID NO: 26;
- g) a VL comprising SEQ ID NO: 29 and a VH comprising SEQ ID NO: 30;
- h) a VL comprising SEQ ID NO: 33 and a VH comprising SEQ ID NO: 34;

- i) a VL comprising SEQ ID NO: 37 and a VH comprising SEQ ID NO: 38;
- j) a VL comprising SEQ ID NO: 41 and a VH comprising SEQ ID NO: 42;
- k) a VL comprising SEQ ID NO: 45 and a VH comprising SEQ ID NO: 46;
- l) a VL comprising SEQ ID NO: 49 and a VH comprising SEQ ID NO: 50; and
- m) a VL comprising SEQ ID NO: 53 and a VH comprising SEQ ID NO: 54.

85. The antibody construct according to any one of claims 81-84, wherein the heavy chain comprises an amino acid substitution selected from the group consisting of:

- (i) N297G or N297A;
- (ii) L234A and L235A; and
- (iii) R292C and V302C;

wherein the amino acid numbering is EU numbering according to Kabat.

86. The antibody construct according to claim 85, wherein the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

87. The antibody construct according to any one of claims 81-86, wherein the antigen binding protein further comprises a light chain CL polypeptide linked to the VL, wherein the CL polypeptide is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.

88. The antibody construct according to any one of claims 81-87, wherein the antigen binding protein further comprises a heavy chain CH1-hinge-CH2-CH3 polypeptide wherein the CH1-hinge-CH2-CH3 polypeptide is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.

~~89. The antibody construct according to any one of claims 81-88, wherein the antigen binding protein further comprises a second antigen binding portion that specifically binds a second antigen.~~

~~90. The antibody construct according to claim 89, wherein the second antigen is a tumor associated antigen (TAA).~~