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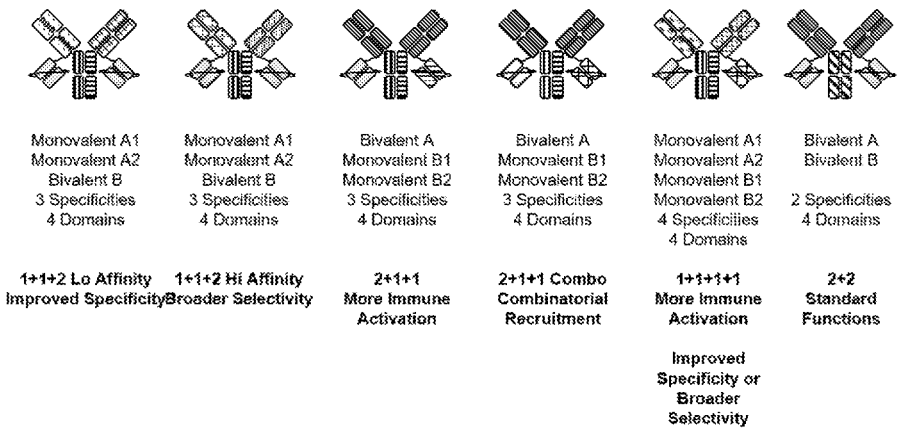
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Figure 1a



(57) Abstract: The present disclosure relates generally to immunoglobulin-related compositions (*e.g.*, heterodimeric trivalent/tetravalent multispecific antibodies) that specifically bind to three or four distinct target antigens. The immunoglobulin-related compositions described herein are useful in methods for detecting and treating cancer in a subject in need thereof.

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HETERODIMERIC TETRAVALENCY AND SPECIFICITY ANTIBODY COMPOSITIONS AND USES THEREOF

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the benefit of and priority to US Provisional Appl. Nos. 62/774,111, filed November 30, 2018, and 62/794,523, filed January 18, 2019, the disclosure of both of which are incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present technology relates generally to the preparation of heterodimeric trivalent/tetravalent multispecific antibodies that specifically bind three or four distinct target antigens, and their uses. The heterodimeric trivalent/tetravalent multispecific antibodies described herein are useful in methods for detecting and treating cancer in a subject in need thereof.

BACKGROUND

[0003] The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

[0004] Many antibody platforms exist, including heterodimeric IgG and BiTE. See Spiess *et al.*, *Mol Immunol* 67:95-106 (2015); Shima *et al.*, *N Engl J Med* 374:2044-2053 (2016); Topp *et al.*, *Lancet Oncol* 16:57-66 (2015). However, no single antibody platform to date has shown a clear and significant functional advantage over others within the clinic.

[0005] In the case of multispecific antibodies that engage immune cells, such as BiTEs, the ideal structure that maximizes anti-tumor activity has not been defined, and likely varies based on the target antigens or the parental antibodies (Wu & Cheung, *Pharmacology & Therapeutics* 182:161-175 (2018). Important properties may include antigen size and proximity to the cell membrane as well as serum half-life. See Bluemel *et al.*, *Cancer Immunol Immunother* 59:1197-1209 (2010); Suzuki *et al.*, *J Immunol* 184:1968-1976 (2010); Yang *et al.*, *Cancer Res* 64:6673-6678 (2004). Even less is understood about the spatial orientation imparted by the antibody on the cell-to-cell interface, the strength of each individual specificity interaction, or the number of interactions. Moreover, the size of the

antibody format, the flexibility of each binding domain, and their relative orientations to one another may influence the capacity to properly or effectively engage multiple antigens at once. Given these different complexities, it is of paramount importance to understand if a given platform design is properly optimized for therapeutic function.

SUMMARY OF THE PRESENT TECHNOLOGY

[0006] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of

forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment, and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149,

157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349.

[0007] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein the VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin

(CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein the VL-4 and VH-4 are capable of specifically binding to a third epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment, and wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589,

597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0008] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a

heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii)a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the fourth epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493,

501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0009] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently

bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b)the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769,

785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349. In some embodiments, both VH-1 and VH-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or both VL-1 and VL-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825,

833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[0010] In yet another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises

in the N-terminal to C-terminal direction: (i)a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293,

301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0011] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-1 or VH-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to

a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or the VL-1 or VL-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153,

2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[0012] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-2 or VH-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349; and/or VL-2 or VL-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345.

[0013] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205

respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965

respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573

respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629 respectively; SEQ ID NOs: 1633 and 1637 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173

respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0014] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421

respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173

respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629 respectively; SEQ ID NOs: 1633 and 1637 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765

respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0015] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301

respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0016] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively;

SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501

respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0017] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-2 and VH-2 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245

respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645

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[0018] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-4 and VH-4 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693

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[0019] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin or the third immunoglobulin binds to a cell surface antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7 +aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30

(TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NT5E), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR- HER3, EGFRvIII, EphA3, ERGT(GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin 5AC, NaPi2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC[MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC[MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B. The first immunoglobulin and the third immunoglobulin may bind to the same epitope on a target cell or two different epitopes on a target cell. In some embodiments, the target cell is a cancer cell.

[0020] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an epitope on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

[0021] In any of the above embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7 +aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP

(MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2. The second immunoglobulin and the fourth immunoglobulin may bind to the same epitope or different epitopes on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil. In some embodiments, the second immunoglobulin binds CD3 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD4, CD8, CD25, CD28, CTLA4, OX40, ICOS, PD-1, PD-L1, 41BB, CD2, CD69, and CD45. In other embodiments, the second immunoglobulin binds CD16 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD56, NKG2D, and KIRDL1/2/3. In certain embodiments, the fourth immunoglobulin binds to an agent selected from the group consisting of a cytokine, a nucleic acid, a hapten, a small molecule, a radionuclide, an immunotoxin, a vitamin, a peptide, a lipid, a carbohydrate, biotin, digoxin, or any conjugated variants thereof.

[0022] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity between about 100 nM to about 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are between 60 and 120 angstroms apart.

[0023] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity that is less than 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are up to 180 angstroms apart.

[0024] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain and has an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE.

[0025] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin

comprises an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin is a CH2-CH3 domain comprising a K409R mutation and the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain comprising a F405L mutation.

[0026] Also disclosed herein are recombinant nucleic acid sequences encoding any of the antibodies described herein. In another aspect, the present technology provides a host cell or vector expressing any nucleic acid sequence encoding any of the antibodies described herein.

[0027] In any of the above embodiments of the immunoglobulin-related compositions of the present technology, the HDTVS antibody may be optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof.

[0028] In one aspect, the present disclosure provides a method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a heterodimeric multispecific antibody disclosed herein. The cancer may be lung cancer, colorectal cancer, skin cancer, breast cancer, ovarian cancer, leukemia, pancreatic cancer, or gastric cancer. Additionally or alternatively, in some embodiments, the heterodimeric multispecific antibody is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent.

[0029] Also disclosed herein are kits for detection and/or treatment of a disease (e.g., cancers), comprising at least one heterodimeric trivalent/tetravalent multispecific antibody of the present technology and instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] **Figure 1a** shows the basic design strategy of each HeteroDimeric TetraValency and Specificity (HDTVS) variant compared with the parental 2+2 IgG-[L]-scFv. The 5 heterodimeric IgG-L-scFv designs display novel biological activities. Each construct uses heterodimerization to achieve tri- or tetra-specificity.

[0031] **Figure 1b** shows a schematic of the 1+1+2 Low affinity design and how it can be used to distinguish single-antigen positive healthy cells from dual-antigen positive target cells. Single antigen positivity would result in inferior immune cell activation over dual antigen positivity.

[0032] **Figure 1c** shows a schematic of the 1+1+2 High affinity design and how it can be used to target either (or both) of two different cellular antigens.

[0033] **Figure 1d** shows a schematic of the 2+1+1 design and how it can be used to improve immune cell activation. Targeting of two different immune cell receptors can be used to more specifically recruit an immune cell population or provide greater immune cell activation or inhibition through cross linking of multiple receptors.

[0034] **Figure 1e** shows a schematic of the 2+1+1 design and how it can be used to broaden immune cell recruitment or combine payload delivery with immunotherapy. Each HDTVS antibody needs only one immune cell receptor for recruitment and activation. The additional domain can then be used to bind payloads (for diagnostics, therapy, recruitment, *etc.*) or additional effector cells.

[0035] **Figure 1f** shows a schematic of the 1+1+1+1 design and how it can be used to combine the benefits of 1+1+2 with 2+1+1. In this embodiment, tetraspecificity can bring better specificity or a broader range of targets, as well and improved immune cell activation or payload delivery.

[0036] **Figure 2a** shows the superior cytotoxicity, binding and *in vivo* potency of the IgG-[L]-scFv design over the IgG-Het and BiTE formats. A 4hr Cr^{51} release assay was used to evaluate cytotoxicity of activated T-cells against M14 melanoma tumor cells. Flow cytometry was used to evaluate differences in antigen binding of each bispecific antibody to huCD3 or GD2 on activated T cells or M14 melanoma tumor cells, respectively. Affinities were measured using SPR on GD2 coated streptavidin chips. Two mouse models were used for assessing *in vivo* potency, a syngeneic transgenic model which has huCD3 expressing murine T cells, and a humanized xenograft model using activated human T-cells engrafted into immunodeficient IL2-$rg^{-/-}$ $Rag2^{-/-}$ BALB/c mice. Mice were implanted subcutaneously with GD2(+) tumors and treated intravenously with a particular test bispecific antibody.

[0037] **Figure 2b** shows the superior cytotoxicity of the IgG-[L]-scFv design over the IgG-het using two additional anti-GD2 sequences.

[0038] **Figure 3** shows the schematics of 4 IgG-[L]-scFv heterodimeric variants along with the parental format and the IgG-Het format. Designs are ranked by their relative potency.

[0039] **Figure 4** shows the *in vitro* binding activity of the various IgG-[L]-scFv variants. GD2 and CD3 affinities were measured using SPR with GD2 or huCD3de coated chips, respectively. Cell binding was assayed by flow cytometry using activated human T cells or M14 melanoma cells. T-cell: tumor cell conjugate formation was measured by flow cytometry using differentially labeled activated human T cells and M14 melanoma tumor cells.

[0040] **Figure 5** shows the *in vitro* cytotoxicity of each IgG-[L]-scFv variant against two cell lines: M14 melanoma and IMR32 neuroblastoma. Cytotoxicity was measured using a 4hr Cr^{51} release assay and activated human T-cells.

[0041] **Figure 6** shows the *in vitro* immune cell activation of each IgG-[L]-scFv variant. Activation was measured by flow cytometry. Naïve purified T cells and M14 melanoma cells were co-cultured for 24 or 96hrs, harvested and stained for CD69 or CD25, respectively. T cells for the 96hr time points were also labeled with Cell Trace Violet (CTV). Culture supernatant was also collected at the 24hr time point for cytokine measurements.

[0042] **Figure 7** shows the *in vivo* activity of each IgG-[L]-scFv variant. Two mouse models were used for assessing *in vivo* potency, a syngeneic transgenic model which has huCD3 expressing murine T cells, and a humanized xenograft model using activated human T-cells engrafted into immunodeficient IL2-$rg^{-/-}$ $Rag2^{-/-}$ BALB/c mice. Mice were implanted subcutaneously with GD2(+) tumors and treated intravenously with a particular test bispecific antibody.

[0043] **Figure 8** shows various dual bivalent bispecific antibody formats compared to the IgG-[L]-scFv design. Cytotoxicity was evaluated using a 4hr Cr^{51} release assay using activated human T cells and M14 melanoma cells. Conjugation activity was measured using flow cytometry. Cell binding was evaluated by flow cytometry using activated human T cells and M14 melanoma cells.

[0044] **Figure 9** shows IgG-[L]-scFv variants which bind CD33 or HER2. Cell binding activities were measured by flow cytometry using Molm13, SKMEL28, or MCF7 cells. Cytotoxicity was assessed using Molm13 cells and activated human T cells in a 4hr Cr^{51} release assay.

[0045] **Figure 10a** shows two 1+1+2 designs (high and low affinity variants). Cell binding and cytotoxicity assays used the GD2(+)HER2(+) cell line U2OS. Cytotoxicity was measured using 4hr Cr^{51} release, and cell binding was evaluated using flow cytometry.

[0046] **Figure 10b** shows two 1+1+2 designs (high and low affinity variants). Cell binding and cytotoxicity assays used the GD2(+) IMR32 neuroblastoma cells or HER2(+) HCC1954 breast cancer cells. Cytotoxicity was measured using 4hr Cr^{51} release, and cell binding was evaluated using flow cytometry.

[0047] **Figures 11a-11e** show exemplary Fc variants that are capable of heterodimerization.

[0048] **Figure 12a** shows various dual bivalent bispecific antibody formats compared *in vivo* to the IgG-[L]-scFv design. Schematics show all four dual bivalent bispecific antibodies expressed.

[0049] **Figure 12b** shows the mean tumor growth for *in vivo* huDKO arming model. Tumor responses were evaluated using a T-cell arming model, where T-cells were preincubated with each BsAb for 20min at a concentration to achieve equal anti-GD2 binding domains (as verified by flow cytometry). These prelabeled or "armed" T-cells were injected intravenously into tumor bearing DKO mice. Each line represents one BsAb. Solid black triangles represent a dose of BsAb armed human activated T-cells (huATC) and IL-2. The dotted black line represents no measurable tumor and the star represents the tumor implantation. Error bars represent standard deviation.

[0050] **Figure 12c** shows tumor growth from individual mice. Each figure represents one treatment group, with schematics (see above) for reference. Each solid line represents a single mouse, and the dotted lines represents the group average.

[0051] **Figure 13** demonstrates the combined binding effect of L1CAM/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody that can bind ganglioside GD2 and adhesion

protein L1CAM simultaneously. Design of the 1+1+2 Lo format antibody is shown on the left side. Homodimeric formats against GD2 and L1CAM were included for reference. For this binding assay, Neuroblastoma cells (IMR32) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the low affinity 1+1+2 HDTVS antibody was stronger than the anti-L1CAM homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody, thus showing improved targeting specificity for tumors expressing both GD2 and L1CAM.

[0052] **Figure 14** demonstrates the combined binding effect of HER2/EGFR 1+1+2 Hi, a heterodimeric 1+1+2Hi format antibody that can bind both HER2 and EGFR, either simultaneously or separately. Design of the 1+1+2 Hi format antibody is shown on the right side. Homodimeric formats against HER2 and EGFR were included for reference. For this binding assay, Desmoplastic Small Cell Round Tumor cells (JN-DSRCT1) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the high affinity 1+1+2 HDTVS antibody was stronger than that of either anti-HER2 or anti-EGFR homodimeric antibodies, while maintaining specificity for both antigens, demonstrating cooperative binding.

[0053] **Figure 15** demonstrates the combined binding effect of GD2/B7H3 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody that can bind both GD2 and B7H3 simultaneously. Design of the 1+1+2 Lo format antibody is shown on the left hand side. Homodimeric formats against GD2 and B7H3, and monovalent control antibodies against GD2 or B7H3 (GD2 or B7H3 ctrl, respectively) were included for reference. For this binding assay, Osteosarcoma cells (U2OS) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the low affinity 1+1+2 HDTVS antibody was similar to the anti-B7H3 homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody. Importantly, GD2/B7H3 1+1+2 Lo also showed improved binding over monovalent control antibodies, demonstrating cooperative binding.

[0054] **Figure 16** demonstrates the cytotoxic selectivity of HER2/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format that can bind both GD2 and HER2 simultaneously. In this

format, a low affinity HER2 sequence was used. Design of the 1+1+2 Lo format antibody is shown below the line graph. Homodimeric formats against GD2 and HER2, and monovalent control antibodies against GD2 or HER2 (GD2 and HER2 ctrl, respectively) were included for reference. For this cytotoxicity assay, Osteosarcoma cells (U2OS) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the indicated antibody and activated human T-cells for four hours at 37°C. After four hours, supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. In this example, the low affinity 1+1+2 heterodimer antibody killed the target cells as effectively as the anti-GD2 and anti-HER2 homodimeric antibodies yet showing clear superiority over the monovalent control formats. This demonstrates the selectivity possible with the 1+1+2Lo design: target cells expressing each individual antigen will be targeted with 10-100-fold lower cytotoxic potency than targets expressing both antigens simultaneously. Using a homodimeric design for either GD2 or HER2 would lose such selectivity.

[0055] **Figure 17a** demonstrates the cytotoxic dual specificity of HER2/GPA33 1+1+2 Hi, a heterodimeric 1+1+2Hi format that can bind both GPA33 and HER2 simultaneously. Design of the 1+1+2 Hi format antibody is shown below the line graph. Homodimeric formats against GPA33 and HER2, and monovalent control antibodies against GPA33 or HER2 were included for reference. For this cytotoxicity assay, Colon cancer cells (Colo205) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the indicated antibody and activated human T-cells for four hours at 37°C. After four hours, the supernatant was harvested and read on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. In this example, the high affinity 1+1+2 heterodimer antibody killed target cells as effectively as the anti-GPA33 homodimeric antibody, but with greater potency than the anti-HER2 homodimeric antibody and monovalent control antibodies. These data demonstrate functional cooperativity between the HER2 and GPA33 antigen-binding domains and illustrate that the dual specificity of a 1+1+2Hi format does not significantly compromise its cytotoxicity against either antigen individually.

[0056] **Figure 17b** demonstrates the combined binding effect of HER2/GPA33 1+1+2 Hi, a heterodimeric 1+1+2Hi format that can bind both HER2 and GPA33, either simultaneously or separately. Design of the 1+1+2 Hi format antibody is shown on the right

hand side. For this binding assay, Colon cancer cells (Colo205) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the affinity binding of the 1+1+2 heterodimer antibody was stronger than either anti-HER2 or anti-GPA33 homodimeric and monovalent control antibodies, while maintaining specificity for both antigens, demonstrating cooperative binding.

[0057] **Figure 18** demonstrates the utility of CD3/CD28 2+1+1, a heterodimeric 2+1+1 design that can bind both CD3 and CD28 on T-cells. Design of the heterodimeric 1+1+2 format antibody is shown below the line graph. Homodimeric formats against CD3 and CD28 were included for reference. For this cytokine assay, naïve human T-cells and Melanoma tumor cells (M14) were co-cultured along with the indicated BsAb for 20 hours before culture supernatants were harvested and analyzed for secreted cytokine IL-2 by flow cytometry. Data was normalized to T-cell cytokine release after 20 hours without target cells or antibody. The CD3/CD28 2+1+1 design showed clearly more potent cytokine release activity than either CD3 or CD28 engagement alone, illustrating cooperative activity from dual CD3/CD28 engagement.

[0058] **Figure 19** demonstrates the combined binding effect of CD3/CD4 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and CD4 simultaneously. Design of the heterodimeric 2+1+1 format antibody is shown on the right side. For this binding assay, active human T cells were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the 2+1+1 heterodimer shows enhanced binding compared to the bivalent CD4 and monomeric CD3 binder (2+1) demonstrating cooperative binding.

[0059] **Figure 20** demonstrates the combined binding effect of CD3/PD-1 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and PD-1 simultaneously. Design of the heterodimeric 2+1+1 format antibody is shown on the right side. For this binding assay active human T cells were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the 2+1+1 heterodimer was better than either anti-PD-1 homodimeric or anti-CD3 monomeric (2+1) binder, demonstrating cooperative binding.

[0060] **Figures 21a-21c** show the unique characteristics of the IgG-L-scFv design, compared to two other common dual bivalent design strategies: the BiTE-Fc and the IgG-H-scFv. **Figure 21a** demonstrates the potent T-cell functional activity of the IgG-L-scFv design compared to other dual bivalent T-cell bispecific antibody formats. Designs of the IgG-L-scFv, BiTE-Fc and the IgG-H-scFv format antibodies are shown below the line graph. For this cytokine assay, naïve T-cells and melanoma tumor cells (M14) were co-cultured along with each BsAb for 20 hours before culture supernatants were harvested and analyzed for secreted cytokine IL-2 by flow cytometry. Data were normalized to T-cell cytokine release after 20 hours without target cells or antibody. In contrast to the IgG-H-scFv (2+2HC) and the BiTE-Fc (2+2B) designs, the IgG-L-scFv format (2+2) demonstrated significant cytokine IL-2 responses *in vitro*, which correlated with stronger *in vivo* activity (shown in **Figure 21c**). **Figure 21b** illustrates the unusually weak T-cell binding activity of the IgG-L-scFv design compared to other dual bivalent T-cell bispecific antibody formats. For this binding assay, T-cells and melanoma tumor cells (M14) were separately incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. Shown is CD3-specific (**Figure 21b**, upper panel), and GD2-specific binding (**Figure 21b**, middle panel). Designs of the IgG-L-scFv, BiTE-Fc and the IgG-H-scFv format antibodies are shown in **Figure 21b** (lower panel). In contrast to their GD2 binding activity, each BsAb demonstrated quite different T-cell binding activities. These data demonstrated how the IgG-L-scFv design is uniquely different than other dual-bivalent designs, with each scFv showing incomplete bivalent binding. Although the inclusion of two scFv domains in the IgG-L-scFv does show improvement over monovalent designs, it still does not compare to the binding activity of the 2+2HC or 2+2B designs, illustrating the sterically hindered binding of this format. **Figure 21c** illustrates the *in vivo* superiority of the IgG-L-scFv design. In contrast to other dual bivalent designs, the IgG-L-scFv format was the only one capable of controlling tumor growth in mice. Here, immunodeficient mice (Balb/c IL-2Rgc-/-, Rag2-/-) were implanted with neuroblastoma cells (IMR32) subcutaneously, before being treated with intravenous activated T-cells and antibody (2-times per week). Tumors sizes were measured by caliper.

[0061] **Figure 22** demonstrates the *in vitro* properties and design of anti-CD33/CD3 IgG-[L]-scFv panel. The *in vitro* cytotoxicity EC_{50}, fold-difference in EC_{50}, antigen valency, heterodimer design and protein purity by SEC-HPLC for anti-CD33/CD3 IgG-[L]-scFv panel are summarized. Fold change is based on the EC_{50} of 2+2. Purity was calculated as the

fraction of protein at correct elution time out of the total protein by area under the curve of the SEC-HPLC chromatogram. For the cytotoxicity assays, CD33-transfected cells (Nalm6) were first incubated with ^{51}Cr for one hour. Afterwards, ^{51}Cr labeled target cells were mixed with serial titrations of the indicated antibody and activated human T-cells for four hours at 37°C. The supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. These results confirm the relative importance of Cis-oriented binding domains in an additional antigen system (CD33) which is much more membrane distal than GD2 (see **Figure 5**).

[0062] **Figure 23** provides a summary of the various HDTVS antibodies tested in the Examples disclosed herein. The table summarizes all successfully produced HDTVS formatted multi-specific antibodies across a variety of antigen models. All clones were expressed in Expi293 cells and heterodimerized using the controlled Fab Arm Exchange method. HDTVS type displays the category of each clone. Fab 1 and scFv 1 (and corresponding Ag1 and Ag3) are attached in a cis-orientation on one heavy chain (linked by the light chain of Fab) while Fab 2 and scFv 2 (and corresponding Ag2 and Ag4) are on a separate heavy chain molecule in a cis-orientation (linked by the light chain of Fab).

DETAILED DESCRIPTION

[0063] It is to be appreciated that certain aspects, modes, embodiments, variations and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology.

[0064] In practicing the present methods, many conventional techniques in molecular biology, protein biochemistry, cell biology, immunology, microbiology and recombinant DNA are used. *See, e.g.*, Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual*, 3rd edition; the series Ausubel *et al.* eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.* (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.* (1995) *PCR 2: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999)

Nucleic Acid Hybridization; Hames and Higgins eds. (1984) *Transcription and Translation; Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); and Herzenberg *et al.* eds (1996) *Weir's Handbook of Experimental Immunology*. Methods to detect and measure levels of polypeptide gene expression products (*i.e.*, gene translation level) are well-known in the art and include the use of polypeptide detection methods such as antibody detection and quantification techniques. (*See also*, Strachan & Read, *Human Molecular Genetics*, Second Edition. (John Wiley and Sons, Inc., NY, 1999)).

[0065] Advances in protein engineering can enhance the functional output of proteins by linking different peptides in sequences, or by arranging them in complexes that do not exist naturally. Antibodies have served as a platform for such enhancements, where antigen binding can be modulated through antigen affinity maturation (Boder *et al.*, *Proc Natl Acad Sci USA* 97:10701-10705 (2000)) or increases in valency (Cuesta *et al.*, *Trends Biotechnol* 28:355-362 (2010)). Fc receptor binding can be modulated through point mutations (Leabman *et al.*, *MAbs* 5:896-903 (2013)) or changes in glycosylation (Xu *et al.*, *Cancer Immun Res* 4: 631-638 (2016)) whereas pharmacokinetics can be influenced through ablation of FcR(n) binding (Suzuki *et al.*, *J Immunol* 184:1968-1976 (2010)) or removal of entire antibody domains. However, no single antibody platform to date has shown a clear and significant functional advantage over others within the clinic.

[0066] The present disclosure provides an antibody platform in which up to 4 different antigen binding domains can be used to simultaneously engage up to 4 different cellular targets, thereby increasing avidity and modulating specificity of the therapeutic antibodies. This platform is based on the heterodimerization of two IgG half molecules, in which each IgG half molecule comprises a heavy chain and a light chain, wherein a scFv is linked to the C-terminus of at least one light chain (*i.e.*, IgG-[L]-scFv platform). The resulting heterodimers are both trivalent/tetravalent and multispecific and are collectively referred to as HDTVS antibodies.

[0067] The native form of the IgG-[L]-scFv platform has bivalent binding to two different targets (2+2) (each integer represents a different specificity, while its value

represents the valency). The present disclosure provides 5 HDTVS platform variants which vary the 4 functional domains (2 Fabs and 2 scFv) in the IgG(L)-scFv format: (1) the Lo1+1+2 HDTVS variant to achieve improved tumor cell specificity, (2) the Hi1+1+2 HDTVS variant to achieve broader tumor cell selectivity, (3) the 2+1+1 HDTVS variant to achieve improved immune cell activation, (4) the 2+1+1 HDTVS variant which allows recruitment of different cells and/or payloads and (5) the 1+1+1+1 HDTVS variant which combines designs from (1) or (2) with (3) or (4) to achieve more effective immune activation or payload delivery with finer specificity or broader selectivity. (**Figures 1a-1f**). In order to test the functional output of these HDTVS variants, one of the 2 Fab domains can be neutralized by using an irrelevant Fab that has no binding to either tumor cells or effector immune cells (*e.g.*, T cells), creating monovalency for tumor. Alternatively, one of the scFv domains can be removed to create monovalency towards effector immune cells (*e.g.*, T cells).

[0068] As described herein, the biological potency of each design is dependent on the biophysical characteristics of the antigen binding domains of the HDTVS variants. Unexpectedly, the changes in valency did not entirely correlate with changes in functional output. As shown in Examples described herein, the biological activity of the tri- and tetra-specific variants of the HDTVS platform is dependent on the antigen/epitope combinations, as well as the relative binding affinities to each target antigen (up to 4 targets total). The Lo1+1+2 HDTVS variant requires its Fab domains to bind to two distinct tumor antigens that are within a proximity of 60-120 angstroms from each other (thus allowing simultaneous binding), and (b) have monovalent and/or effective binding affinities (K_D) that range from about 100 nM to about 100 pM to reduce bystander reactivity with healthy cells. The Hi1+1+2 HDTVS variant on the other hand exploits the high monovalent and/or effective binding affinity (K_D < 100 pM) of its Fab domains such that monovalency is nearly as effective as bivalency. Moreover, the 2+1+1 HDTVS variant exhibited *in vivo* tumor clearance activity that was comparable to that observed with the 2+2 native form of the IgG-[L]-scFv platform. These results were unexpected given that the binding activities of the 2+1+1 HDTVS variant were about 6-fold lower than the 2+2 native form of the IgG-[L]-scFv platform.

[0069] Accordingly, biophysical properties such as orientation (cis vs trans), valency (mono- vs bi-valent) and target affinity (K_D ~nM or <pM) had an unpredictable impact on the functionality of the HDTVS variants (*e.g.*, log-fold enhancement of therapeutic efficacy).

Moreover, the HDTVS antibodies of the present technology show superior therapeutic potency compared to other conventional antibody platforms, such as BiTE or heterodimeric IgG (IgG-Het). These results also demonstrate that different multispecific antibody platforms yield antibodies that possess substantially different biological properties. Without wishing to be bound by theory, it is believed that spatial distances between the antigen binding domains of multispecific antibodies, as well as the relative flexibility and orientation of the individual antigen binding domains may determine their ability to drive cell-to-cell interactions.

Definitions

[0070] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this technology belongs. As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. For example, reference to "a cell" includes a combination of two or more cells, and the like. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, analytical chemistry and nucleic acid chemistry and hybridization described below are those well-known and commonly employed in the art.

[0071] As used herein, a "2+1+1" design refers to a HDTVS antibody in which the two Fab domains recognize and bind to the same target antigen, and the two scFvs recognize and bind to two distinct target antigens. In some embodiments, the two scFvs of the 2+1+1 HDTVS antibody binds to two distinct target antigens that are up to180 angstroms apart from each other in order to engage two separate molecules on the same cell.

[0072] As used herein, the term "about" in reference to a number is generally taken to include numbers that fall within a range of 1%, 5%, or 10% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[0073] As used herein, the "administration" of an agent or drug to a subject includes any route of introducing or delivering to a subject a compound to perform its intended function. Administration can be carried out by any suitable route, including but not limited to, orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or

subcutaneously), rectally, intrathecally, intratumorally or topically. Administration includes self-administration and the administration by another.

[0074] As used herein, the term "antibody" collectively refers to immunoglobulins or immunoglobulin-like molecules including by way of example and without limitation, IgA, IgD, IgE, IgG and IgM, combinations thereof, and similar molecules produced during an immune response in any vertebrate, for example, in mammals such as humans, goats, rabbits and mice, as well as non-mammalian species, such as shark immunoglobulins. As used herein, "antibodies" (includes intact immunoglobulins) and "antigen binding fragments" specifically bind to a molecule of interest (or a group of highly similar molecules of interest) to the substantial exclusion of binding to other molecules (for example, antibodies and antibody fragments that have a binding constant for the molecule of interest that is at least 10^3 M^{-1} greater, at least 10^4 M^{-1} greater or at least 10^5 M^{-1} greater than a binding constant for other molecules in a biological sample). The term "antibody" also includes genetically engineered forms such as chimeric antibodies (for example, humanized murine antibodies), heteroconjugate antibodies (such as, bispecific antibodies). See also, Pierce Catalog and Handbook, 1994-1995 (Pierce Chemical Co., Rockford, Ill.); Kuby, J., *Immunology*, 3rd Ed., W.H. Freeman & Co., New York, 1997.

[0075] More particularly, antibody refers to a polypeptide ligand comprising at least a light chain immunoglobulin variable region or heavy chain immunoglobulin variable region which specifically recognizes and binds an epitope of an antigen. Antibodies are composed of a heavy and a light chain, each of which has a variable region, termed the variable heavy (V_H) region and the variable light (V_L) region. Together, the V_H region and the V_L region are responsible for binding the antigen recognized by the antibody. Typically, an immunoglobulin has heavy (H) chains and light (L) chains interconnected by disulfide bonds. There are two types of light chain, lambda (λ) and kappa (κ). There are five main heavy chain classes (or isotypes) which determine the functional activity of an antibody molecule: IgM, IgD, IgG, IgA and IgE. Each heavy and light chain contains a constant region and a variable region, (the regions are also known as "domains"). In combination, the heavy and the light chain variable regions specifically bind the antigen. Light and heavy chain variable regions contain a "framework" region interrupted by three hypervariable regions, also called "complementarity-determining regions" or "CDRs". The extent of the framework region and CDRs have been defined (see, Kabat *et al.*, *Sequences of Proteins of Immunological Interest*,

U.S. Department of Health and Human Services, 1991, which is hereby incorporated by reference). The Kabat database is now maintained online. The sequences of the framework regions of different light or heavy chains are relatively conserved within a species. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions.

[0076] The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found. An antibody that binds a target antigen will have a specific V_H region and the V_L region sequence, and thus specific CDR sequences. Antibodies with different specificities (*i.e.* different combining sites for different antigens) have different CDRs. Although it is the CDRs that vary from antibody to antibody, only a limited number of amino acid positions within the CDRs are directly involved in antigen binding. These positions within the CDRs are called specificity determining residues (SDRs). "Immunoglobulin-related compositions" as used herein, refers to antibodies (including monoclonal antibodies, polyclonal antibodies, humanized antibodies, chimeric antibodies, recombinant antibodies, multispecific antibodies, bispecific antibodies, *etc*.,) as well as antibody fragments. An antibody or antigen binding fragment thereof specifically binds to an antigen.

[0077] As used herein, the term "antibody-related polypeptide" means antigen binding antibody fragments, including single-chain antibodies, that can comprise the variable region(s) alone, or in combination, with all or part of the following polypeptide elements: hinge region, CH_1, CH_2, and CH_3 domains of an antibody molecule. Also included in the technology are any combinations of variable region(s) and hinge region, CH_1, CH_2, and CH_3 domains. Antibody-related molecules useful in the present methods, *e.g.*, but are not limited to, Fab, Fab′ and $F(ab')_2$, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. Examples include: (i)

a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH_1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH_1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, *Nature* 341: 544-546, 1989), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR). As such "antibody fragments" or "antigen binding fragments" can comprise a portion of a full-length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments or antigen binding fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0078] "Bispecific antibody" or "BsAb", as used herein, refers to an antibody that can bind simultaneously to two targets that have a distinct structure, *e.g.*, two different target antigens, two different epitopes on the same target antigen, or a hapten and a target antigen or epitope on a target antigen. A variety of different bispecific antibody structures are known in the art. In some embodiments, each antigen binding moiety in a bispecific antibody includes V_H and/or V_L regions; in some such embodiments, the V_H and/or V_L regions are those found in a particular monoclonal antibody. In some embodiments, the bispecific antibody contains two antigen binding moieties, each including V_H and/or V_L regions from different monoclonal antibodies. In some embodiments, the bispecific antibody contains two antigen binding moieties, wherein one of the two antigen binding moieties includes an immunoglobulin molecule having V_H and/or V_L regions that contain CDRs from a first monoclonal antibody, and the other antigen binding moiety includes an antibody fragment (*e.g.*, Fab, F(ab'), $F(ab')_2$, Fd, Fv, dAB, scFv, *etc.*) having V_H and/or V_L regions that contain CDRs from a second monoclonal antibody.

[0079] As used herein, the term "diabodies" refers to small antibody fragments with two antigen binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen binding sites. Diabodies are described more fully in, *e.g.*, EP 404,097; WO 93/11161; and 30 Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 90: 6444-6448 (1993).

[0080] As used herein, the terms "single-chain antibodies" or "single-chain Fv (scFv)" refer to an antibody fusion molecule of the two domains of the Fv fragment, V_L and V_H. Single-chain antibody molecules may comprise a polymer with a number of individual molecules, for example, dimer, trimer or other polymers. Furthermore, although the two domains of the F_v fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single-chain F_v (scF_v)). Bird *et al.* (1988) *Science* 242:423-426 and Huston *et al.* (1988) *Proc. Natl. Acad Sci.* USA 85:5879-5883. Such single-chain antibodies can be prepared by recombinant techniques or enzymatic or chemical cleavage of intact antibodies.

[0081] Any of the above-noted antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for binding specificity and neutralization activity in the same manner as are intact antibodies.

[0082] As used herein, an "antigen" refers to a molecule to which an antibody (or antigen binding fragment thereof) can selectively bind. The target antigen may be a protein, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or synthetic compound. In some embodiments, the target antigen may be a polypeptide. An antigen may also be administered to an animal to generate an immune response in the animal.

[0083] The term "antigen binding fragment" refers to a fragment of the whole immunoglobulin structure which possesses a part of a polypeptide responsible for binding to antigen. Examples of the antigen binding fragment useful in the present technology include scFv, $(scFv)_2$, scFvFc, Fab, Fab′ and $F(ab')_2$, but are not limited thereto.

[0084] By "binding affinity" is meant the strength of the total noncovalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by standard methods known in the art, including those described herein. A low-affinity complex contains an antibody that generally tends to dissociate readily from the antigen, whereas a high-affinity complex contains an antibody that generally tends to remain bound to the antigen for a longer duration.

[0085] As used herein, the term "biological sample" means sample material derived from living cells. Biological samples may include tissues, cells, protein or membrane extracts of

cells, and biological fluids (*e.g.*, ascites fluid or cerebrospinal fluid (CSF)) isolated from a subject, as well as tissues, cells and fluids present within a subject. Biological samples of the present technology include, but are not limited to, samples taken from breast tissue, renal tissue, the uterine cervix, the endometrium, the head or neck, the gallbladder, parotid tissue, the prostate, the brain, the pituitary gland, kidney tissue, muscle, the esophagus, the stomach, the small intestine, the colon, the liver, the spleen, the pancreas, thyroid tissue, heart tissue, lung tissue, the bladder, adipose tissue, lymph node tissue, the uterus, ovarian tissue, adrenal tissue, testis tissue, the tonsils, thymus, blood, hair, buccal, skin, serum, plasma, CSF, semen, prostate fluid, seminal fluid, urine, feces, sweat, saliva, sputum, mucus, bone marrow, lymph, and tears. Biological samples can also be obtained from biopsies of internal organs or from cancers. Biological samples can be obtained from subjects for diagnosis or research or can be obtained from non-diseased individuals, as controls or for basic research. Samples may be obtained by standard methods including, *e.g.*, venous puncture and surgical biopsy. In certain embodiments, the biological sample is a breast, lung, colon, or prostate tissue sample obtained by needle biopsy.

[0086] As used herein, the term "cancer" refers to a neoplasm or tumor resulting from abnormal uncontrolled growth of cells. In some embodiments, cancer refers to a benign tumor or a malignant tumor. In some embodiments, the cancer is associated with a specific cancer antigen.

[0087] As used herein, the term "CDR-grafted antibody" means an antibody in which at least one CDR of an "acceptor" antibody is replaced by a CDR "graft" from a "donor" antibody possessing a desirable antigen specificity.

[0088] As used herein, the term "chimeric antibody" means an antibody in which the Fc constant region of a monoclonal antibody from one species (*e.g.*, a mouse Fc constant region) is replaced, using recombinant DNA techniques, with an Fc constant region from an antibody of another species (*e.g.*, a human Fc constant region). *See generally*, Robinson *et al.*, PCT/US86/02269; Akira *et al.*, European Patent Application 184,187; Taniguchi, European Patent Application 171,496; Morrison *et al.*, European Patent Application 173,494; Neuberger *et al.*, WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.*, European Patent Application 0125,023; Better *et al.*, *Science* 240: 1041-1043, 1988; Liu *et al.*, *Proc. Natl. Acad. Sci. USA* 84: 3439-3443, 1987; Liu *et al.*, *J. Immunol* 139: 3521-3526, 1987; Sun *et al.*, *Proc. Natl. Acad. Sci. USA* 84: 214-218, 1987; Nishimura *et al.*, *Cancer Res*

47: 999-1005, 1987; Wood *et al.*, Nature 314: 446-449, 1885; and Shaw *et al.*, *J. Natl. Cancer Inst.* 80: 1553-1559, 1988.

[0089] As used herein, the term "consensus FR" means a framework (FR) antibody region in a consensus immunoglobulin sequence. The FR regions of an antibody do not contact the antigen.

[0090] As used herein, a "control" is an alternative sample used in an experiment for comparison purpose. A control can be "positive" or "negative." For example, where the purpose of the experiment is to determine a correlation of the efficacy of a therapeutic agent for the treatment for a particular type of disease, a positive control (a compound or composition known to exhibit the desired therapeutic effect) and a negative control (a subject or a sample that does not receive the therapy or receives a placebo) are typically employed.

[0091] As used herein, the term "effective affinity" refers to the binding constant derived from measuring the overall binding kinetics of a compound with two or more simultaneous binding interactions (*e.g.*, with an IgG, IgM, IgA, IgD, or IgE molecule instead of a Fab domain).

[0092] As used herein, the term "effective amount" refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, *e.g.*, an amount which results in the prevention of, or a decrease in a disease or condition described herein or one or more signs or symptoms associated with a disease or condition described herein. In the context of therapeutic or prophylactic applications, the amount of a composition administered to the subject will vary depending on the composition, the degree, type, and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. The compositions can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic compositions may be administered to a subject having one or more signs or symptoms of a disease or condition described herein. As used herein, a "therapeutically effective amount" of a composition refers to composition levels in which the physiological effects of a disease or condition are ameliorated or eliminated. A therapeutically effective amount can be given in one or more administrations.

[0093] As used herein, the term "effector cell" means an immune cell which is involved in the effector phase of an immune response, as opposed to the cognitive and activation phases of an immune response. Exemplary immune cells include a cell of a myeloid or lymphoid origin, *e.g.*, lymphocytes (*e.g.*, B cells and T cells including cytolytic T cells (CTLs)), killer cells, natural killer cells, macrophages, monocytes, eosinophils, neutrophils, polymorphonuclear cells, granulocytes, mast cells, and basophils. Effector cells express specific Fc receptors and carry out specific immune functions. An effector cell can induce antibody-dependent cell-mediated cytotoxicity (ADCC), *e.g.*, a neutrophil capable of inducing ADCC. For example, monocytes, macrophages, neutrophils, eosinophils, and lymphocytes which express FcαR are involved in specific killing of target cells and presenting antigens to other components of the immune system, or binding to cells that present antigens.

[0094] "Effector function" as used herein refers to a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or an antigen. Effector functions include but are not limited to antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cell mediated phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Effector functions include both those that operate after the binding of an antigen and those that operate independent of antigen binding.

[0095] As used herein, the term "epitope" means an antigenic determinant (site on an antigen) capable of specific binding to an antibody. Epitopes usually comprise chemically active surface groupings of molecules such as amino acids or sugar side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents. Thus, in some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies disclosed herein may bind a non-conformational epitope and/or a conformational epitope. To screen for antibodies which bind to an epitope, a routine cross-blocking assay such as that described in Antibodies, *A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if an antibody binds the same site or epitope as a heterodimeric trivalent/tetravalent multispecific antibody of the present technology. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody sequence can be mutagenized such as

by alanine scanning, to identify contact residues. In a different method, peptides corresponding to different regions of a target protein antigen can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

[0096] As used herein, "expression" includes one or more of the following: transcription of the gene into precursor mRNA; splicing and other processing of the precursor mRNA to produce mature mRNA; mRNA stability; translation of the mature mRNA into protein (including codon usage and tRNA availability); and glycosylation and/or other modifications of the translation product, if required for proper expression and function.

[0097] As used herein, the term "gene" means a segment of DNA that contains all the information for the regulated biosynthesis of an RNA product, including promoters, exons, introns, and other untranslated regions that control expression.

[0098] As used herein, a "heterodimerization domain that is incapable of forming a stable homodimer" refers to a member of a pair of distinct but complementary chemical motifs (*e.g.*, amino acids, nucleotides, sugars, lipids, synthetic chemical structures, or any combination thereof) which either exclusively self-assembles as a heterodimer with the second complementary member of the pair, or shows at least a 10^4 fold preference for assembling into a heterodimer with the second complementary member of the pair, or forms a homodimer with an identical member that is not stable under reducing conditions such as >2mM 2-MEA at room temperature for 90 minutes (see *e.g.*, Labrijn, A. F. *et al.*, *Proc. Natl. Acad. Sci.* 110, 5145–50 (2013). Examples of such heterodimerization domains include, but are not limited to CH2-CH3 that include any of the Fc variants/mutations described herein, WinZip-A1B1, a pair of complementary oligonucleotides, and a CH-1 and CL pair.

[0099] As used herein, "Hi1+1+2" refers to a heterodimeric tetravalent multispecific antibody in which the Fab domains (a) bind to two distinct target epitopes and (b) have monovalent binding affinities or effective affinities (K_D) that are < 100 pM.

[00100] As used herein, the term "humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric antibodies which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman

primate having the desired specificity, affinity, and capacity. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance such as binding affinity. Generally, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains (*e.g.*, Fab, Fab′, $F(ab')_2$, or Fv), in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus FR sequence although the FR regions may include one or more amino acid substitutions that improve binding affinity. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally may also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, *Nature* 321:522-525 (1986); Reichmann *et al.*, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). See *e.g.*, Ahmed & Cheung, *FEBS Letters* 588(2):288-297 (2014).

[00101] As used herein, the term "hypervariable region" refers to the amino acid residues of an antibody which are responsible for antigen binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (*e.g.*, around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L, and around about 31-35B (H1), 50-65 (H2) and 95-102 (H3) in the V_H (Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (*e.g.*, residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L, and 26-32 (H1), 52A-55 (H2) and 96-101 (H3) in the V_H (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)).

[00102] As used herein, the term "intact antibody" or "intact immunoglobulin" means an antibody that has at least two heavy (H) chain polypeptides and two light (L) chain polypeptides interconnected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH_1, CH_2 and CH_3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or V_L)

and a light chain constant region. The light chain constant region is comprised of one domain, C_L. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxyl-terminus in the following order: FR_1, CDR_1, FR_2, CDR_2, FR_3, CDR_3, FR_4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

[00103] As used herein, the terms "individual", "patient", or "subject" can be an individual organism, a vertebrate, a mammal, or a human. In some embodiments, the individual, patient or subject is a human.

[00104] As used herein, "Lo1+1+2" refers to a heterodimeric tetravalent multispecific antibody in which the Fab domains (a) bind to two distinct target epitopes that are within a proximity of 60-120 angstroms from each other (thus allowing simultaneous binding), and (b) have monovalent binding affinities or effective affinities (K_D) that range from about 100 nM to about 100 pM.

[00105] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. For example, a monoclonal antibody can be an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies can be prepared using a wide variety of techniques

known in the art including, *e.g.*, but not limited to, hybridoma, recombinant, and phage display technologies. For example, the monoclonal antibodies to be used in accordance with the present methods may be made by the hybridoma method first described by Kohler *et al., Nature* 256:495 (1975), or may be made by recombinant DNA methods (*See*, *e.g.*, U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al., Nature* 352:624-628 (1991) and Marks *et al., J. Mol. Biol.* 222:581-597 (1991), for example.

[00106] As used herein, the term "pharmaceutically-acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal compounds, isotonic and absorption delaying compounds, and the like, compatible with pharmaceutical administration. Pharmaceutically-acceptable carriers and their formulations are known to one skilled in the art and are described, for example, in Remington's Pharmaceutical Sciences (20th edition, ed. A. Gennaro, 2000, Lippincott, Williams & Wilkins, Philadelphia, Pa.).

[00107] As used herein, the term "polyclonal antibody" means a preparation of antibodies derived from at least two (2) different antibody-producing cell lines. The use of this term includes preparations of at least two (2) antibodies that contain antibodies that specifically bind to different epitopes or regions of an antigen.

[00108] As used herein, the term "polynucleotide" or "nucleic acid" means any RNA or DNA, which may be unmodified or modified RNA or DNA. Polynucleotides include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, RNA that is mixture of single- and double-stranded regions, and hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, polynucleotide refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons.

[00109] As used herein, the terms "polypeptide", "peptide" and "protein" are used interchangeably herein to mean a polymer comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, *i.e.*, peptide isosteres. Polypeptide

refers to both short chains, commonly referred to as peptides, glycopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. Polypeptides include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature.

[00110] As used herein, the term "recombinant" when used with reference, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the material is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[00111] As used herein, the term "separate" therapeutic use refers to an administration of at least two active ingredients at the same time or at substantially the same time by different routes.

[00112] As used herein, the term "sequential" therapeutic use refers to administration of at least two active ingredients at different times, the administration route being identical or different. More particularly, sequential use refers to the whole administration of one of the active ingredients before administration of the other or others commences. It is thus possible to administer one of the active ingredients over several minutes, hours, or days before administering the other active ingredient or ingredients. There is no simultaneous treatment in this case.

[00113] As used herein, "specifically binds" refers to a molecule (*e.g.*, an antibody or antigen binding fragment thereof) which recognizes and binds another molecule (*e.g.*, an antigen), but that does not substantially recognize and bind other molecules. The terms "specific binding," "specifically binds to," or is "specific for" a particular molecule (*e.g.*, a polypeptide, or an epitope on a polypeptide), as used herein, can be exhibited, for example, by a molecule having a K_D for the molecule to which it binds to of about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M. The term "specifically binds"

may also refer to binding where a molecule (*e.g.*, an antibody or antigen binding fragment thereof) binds to a particular polypeptide, or an epitope on a particular polypeptide, without substantially binding to any other polypeptide, or polypeptide epitope.

[00114] As used herein, the term "simultaneous" therapeutic use refers to the administration of at least two active ingredients by the same route and at the same time or at substantially the same time.

[00115] As used herein, the term "therapeutic agent" is intended to mean a compound that, when present in an effective amount, produces a desired therapeutic effect on a subject in need thereof.

[00116] "Treating" or "treatment" as used herein covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, *i.e.*, arresting its development; (ii) relieving a disease or disorder, *i.e.*, causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder. In some embodiments, treatment means that the symptoms associated with the disease are, *e.g.*, alleviated, reduced, cured, or placed in a state of remission.

[00117] It is also to be appreciated that the various modes of treatment of disorders as described herein are intended to mean "substantial," which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved. The treatment may be a continuous prolonged treatment for a chronic disease or a single, or few time administrations for the treatment of an acute condition.

Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[00118] The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology can bind simultaneously to three or four targets that have a distinct structure, *e.g.*, 3-4 different target antigens, 3-4 different epitopes on the same target antigen, or a combination of haptens and target antigens or epitopes on a target antigen. A variety of HDTVS antibodies can be produced using molecular engineering. For example, the HDTVS antibodies disclosed herein utilize combinations of the full immunoglobulin framework (*e.g.*, IgG), and single chain variable fragments (scFvs).

[00119] HDTVS antibodies can be made, for example, by combining and/or engineering heavy chains and/or light chains that recognize different epitopes of the same or different antigen. In some embodiments, the HDTVS protein is trivalent and tri-specific, comprising, for example, an immunoglobulin (*e.g.*, IgG) with a binding site for a first antigen (one V_H/V_L pair) and a binding site for a second antigen (a different V_H/V_L pair) and an scFv for a third antigen. In some embodiments, the HDTVS protein is trivalent and bispecific, comprising, for example, an immunoglobulin (*e.g.*, IgG) with two binding sites (two V_H/V_L pairs) for a first antigen, and a scFv for a second antigen. In some embodiments, the HDTVS protein is tetravalent and tri-specific, comprising, for example, an immunoglobulin (*e.g.*, IgG) with a binding site for a first antigen (one V_H/V_L pair) and a binding site for a second antigen (a different V_H/V_L pair) and two identical scFvs for a third antigen. In some embodiments, the HDTVS protein is tetravalent and tri-specific, comprising, for example, an immunoglobulin (*e.g.*, IgG) with two binding sites (two V_H/V_L pairs) for a first antigen, an scFv for a second antigen and an scFv for a third antigen. In some embodiments, the HDTVS protein is tetravalent and tetra-specific, comprising, for example, an immunoglobulin (*e.g.*, IgG) with a binding site for a first antigen (one V_H/V_L pair) and a binding site for a second antigen (different V_H/V_L pair), an scFv for a third antigen and an scFv for a fourth antigen.

[00120] In some embodiments, at least one scFv of the HDTVS antibodies of the present technology binds to an antigen or epitope of a B-cell, a T-cell, a myeloid cell, a plasma cell, or a mast-cell. Additionally or alternatively, in certain embodiments, at least one scFv of the HDTVS antibodies of the present technology binds to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7 +aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2.

[00121] Additionally or alternatively, in certain embodiments, the HDTVS antibodies disclosed herein are capable of binding to cells (*e.g.*, tumor cells) that express a cell surface

antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7 +aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NT5E), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR- HER3, EGFRvIII, EphA3, ERGT(GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin 5AC, NaPi2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC[MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC[MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B.

[00122] Methods for producing the HDTVS antibodies of the present technology include engineered recombinant monoclonal antibodies which have additional cysteine residues so that they crosslink more strongly than the more common immunoglobulin isotypes. *See, e.g.*, FitzGerald *et al.*, *Protein Eng.* 10(10):1221-1225 (1997). HDTVS recombinant fusion proteins can be engineered by linking two or more different single-chain antibody or antibody fragment segments with the needed dual specificities. See, *e.g.*, Coloma *et al.*, *Nature Biotech.* 15:159-163 (1997).

[00123] Recombinant methods can be used to produce a variety of fusion proteins. In some embodiments, a HDTVS antibody according to the present technology comprises an immunoglobulin, which immunoglobulin comprises two heavy chains and two light chains, and two scFvs, wherein each scFv is linked to the C-terminal end of one of the two light

chains of any immunoglobulin disclosed herein. In various embodiments, scFvs are linked to the light chains *via* a linker sequence. In some embodiments, a linker is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more amino acids in length.

[00124] In some embodiments, a linker is characterized in that it tends not to adopt a rigid three-dimensional structure, but rather provides flexibility to the polypeptide (*e.g.*, first and/or second antigen binding sites). In some embodiments, a linker is employed in a HDTVS antibody described herein based on specific properties imparted to the HDTVS antibody such as, for example, an increase in stability. In some embodiments, a HDTVS antibody of the present technology comprises a G_4S linker. In certain embodiments, a HDTVS antibody of the present technology comprises a $(G_4S)_n$ linker, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1 1, 12, 13, 14, 15 or more.

[00125] Exemplary V_H and V_L amino acid sequences that may be employed in the HDTVS antibodies of the present technology are provided in Table 1.

TABLE 1

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR 2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR 1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
a2b b3 (Glycoprotein IIb/IIIa)	DILMTQSPSSMSVSLGDTVSITCHASQGISSNIGWLQQKPGKSFMGLIYYGTNLVDGVPSRFSGSGSGADYSLTISSLDSEDFADYYCVQYAQLPYTFGGGTKLEIK	1	QGISSN	2	YGT	3	VQYAQLPYT	4	EVQLQQSGAELVKPGASVKLSCTASGFNIKDTYVHWVKQRPEQGLEWIGRIDPANGYTKYDPKFQGKATITADTSSNTAYLQLSSLTSEDTAVYYCVRPLYDYYAMDYWGQGTSVTVSS	5	GFNIKDTY	6	IDPANGYT	7	VRPLYDYYAMDY	8
a2b b3 (Glycoprotein IIb/IIIa)	DIQMTQTPSTLSASVGDRVTISCRASQDINNYLNWYQQKPGKAPKLLIYYTSTLHSGVPSRFSGSGSGTDYTLTISSLQPDDFA	9	QDINNY	10	YTS	11	QQGNTLPWT	12	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTNYLIEWVRQAPGQGLEWIGVIYPGSGGTNYNEKFKGRVTLTVDESTNTAYMELSSLRSEDTAVYF	13	GYAFTNYL	14	IYPGSGGT	15	ARRDGNYGWFAY	16

	TYFCQQGNTLPWTFGQGTKVEVK								CARRDGNYGWFAYWGQGTLVTVSS							
a4	DIQMTQSPSSLSASVGDRVTITCKTSQDINKYMAWYQQTPGKAPRLLIHYTSALQPGIPSRFSGSGSGRDYTFTISSLQPEDIATYYCLQYDNLWTFGQGTKVEIK	17	QDINKY	18	YTS	19	LQYDNLWT	20	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDTYIHWVRQAPGQRLEWMGRIDPANGYTKYDPKFQGRVTITADTSASTAYMELSSLRSEDEAVYYCAREGYYGNYGVYAMDYWGQGTLVTVSS	21	GFNIKDTY	22	IDPANGYT	23	AREGYYGNYGVYAMDY	24
a4b7	DVVMTQSPLSLPVTPGEPASISCRSSQSLAKSYGNTYLSWYLQKPGQSPQLLIYGISNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCLQGTHQPYTFGQGTKVEIK	25	QSLAKSYGNTY	26	GIS	27	LQGTHQPYT	28	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTSYWMHWVRQAPGQRLEWIGEIDPSESNTNYNQKFKGRVTLTVDISASTAYMELSSLRSEDTAVYYCARGGYDGWDYAIDYWGQGTLVTVSS	29	GYTFTSYW	30	IDPSESNT	31	ARGGYDGWDYAIDY	32
a4b7 +aEb7	DIQMTQSPSSLSASVGDRVTITCRASESVDDLLHWYQQKPGKAPKLLIKYASQSISGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGNSLPNTFGQGTKVEIK	33	ESVDDL	34	YASQ	35	QQGNSLPNT	36	EVQLVESGGGLVQPGGSLRLSCAASGFFITNNYWGWVRQAPGKGLEWVGYISYSGSTSYNPSLKSRFTISRDTSKNTFYLQMNSLRAEDTAVYYCARTGSSGYFDFWGQGTLVTVSS	37	GFFITNNY	38	ISYSGST	39	ARTGSSGYFDF	40
a5	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKV	41	QSVSSY	42	DAS	43	QQRSNWPPFT	44	QVQLVESGGGVVQPGRSRRLSCAASGFTFSRYTMHWVRQAPGKGLEWVAVISFDGSNKYYVDSVKGRFTISRDNSENTLYLQVNILRAEDTAVYYCAREARGSYAFDIWGQGTMVTV	45	GFTFSRYT	46	ISFDGSNK	47	AREARGSYAFDI	48

	DIK								SS							
Activin receptor type-2B	QSALTQPASVSGSPGQSITISCTGTSSDVGSYNYVNWYQQHPGKAPKLMIYGVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCGTFAGGSYYGVFGGGTKLTVL	49	SSDVGSYNY	50	GVS	51	GTFAGGSYYGV	52	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSSYINWVRQAPGQGLEWMGTINPVSGSTSYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGGWFDYWGQGTLVTVSS	53	GYTFTSSY	54	INPVSGST	55	ARGGWFDY	56
ALK1	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGTSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPITFGQGTRLEIK	57	QSVSSSY	58	GTS	59	QQYGSSPIT	60	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGEYYWNWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARESVAGFDYWGQGTLVTVSS	61	GGSISSGEYY	62	IYYSGST	63	ARESVAGFDY	64
Alpha-synuclein	DIQMTQSPSSLSASVGDRVTITCKSIQTLLYSSNQKNYLAWFQQKPGKAPKLLIYWASIRKSGVPSRFSGSGSGTDFTLTISSLQPEDLATYYCQQYYSYPLTFGGGTKLEIK	65	QTLLYSSNQKNY	66	WAS	67	QQYYSYPLT	68	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASISSGGGSTYYPDNVKGRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARGGAGIDYWGQGTLVTVSS	69	GFTFSNYG	70	ISSGGGST	71	ARGGAGIDYW	72
amyloid beta	DVVMTQSPLSLPVTPGEPASISCKSSQSLLDSDGKTYLNWLLQKPGQSPQRLIYLVSKLDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRTFGQGTKVEIK	73	QSLLDSDGKTY	74	LVS	75	WQGTHFPRT	76	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASIRSGGGRTYYSDNVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYSGSSDYWGQGTLVTVSS	77	GFTFSNYG	78	IRSGGGRT	79	VRYDHYSGSSDY	80

amyloid beta	DVVMTQSPLSLPVTLGQPASISCRSSQSLIYSDGNAYLHWFLQKPGQSPRLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGTKVEIK	81	qSLIYSDGNAY	82	KVS	83	SQSTHVPWT	84	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYSMSWVRQAPGKGLELVAQINSVGNSTYYPDTVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASGDYWGQGTLVTVSS	85	GFTFSRYS	86	INSVGNST	87	ASGDY	88
amyloid beta	DIVMTQSPLSLPVTPGEPASISCRSSQSLVYSNGDTYLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGTKVEIK	89	QSLVYSNGDTY	90	KVS	91	SQSTHVPWT	92	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLELVASINSNGGSTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCASGDYWGQGTTVTVSS	93	GFTFSSYG	94	INSNGGST	95	ASGDYW	96
amyloid beta	DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSDAKTYLNWFQQRPGQSPRRLIYQISRLDPGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCLQGTHYPVLFGQGTRLEIK	97	QSLLYSDAKTY	98	QIS	99	LQGTHYPVL	100	QVQLVQSGAEVKKPGASVKVSCKASGYYTEAYYIHWVRQAPGQGLEWMGRIDPATGNTKYAPRLQDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCASLYSLPVYWGQGTTVTVSS	101	GYYTEAYY	102	IDPATGNT	103	ASLYSLPVY	104
amyloid beta	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK	105	QSISSY	106	AAS	107	QQSYSTPLT	108	QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVIWFDGTKKYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGARRGPYYMDVWGKGTTVTVSS	109	GFAFSSYG	110	IWFDGTKK	111	ARDRGIGARRGPYYMDV	112
APP	DIVLTQSPATLSLSPGERATLS	113	QSVSSS	114	GAS	115	LQIYNMPI	116	QVELVESGGGLVQPGGSLRLSCAA	117	GFTF	118	INASG	119	ARGKGNTHKP	120

	CRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGVPARFSGSGSGTDFTLTISSLEPEDFATYYCLQIYNMPITFGQGTKVEIK		Y				T		SGFTFSSYAMSWVRQAPGKGLEWVSAINASGTRTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVRYFDVWGQGTLVTVSS		SSYA		TRT		YGYVRYFDV	
AXL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPYTFGQGTKLEIK	121	QSVSSSY	122	GAS	123	QQYGSSPYT	124	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSTTSGSGASTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIWIAFDIWGQGTMVTVSS	125	GFTFSSYA	126	TSGSGAST	127	AKIWIAFDI	128
Blood group A	DIQMTQTTSSLSASLGDRVTISCRASQDINNYLNWYQQKPDGTVKLLIHYTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPWTFGGGTKLEIK	129	QDINNY	130	YTS	131	QQGNTLPWT	132	QVQLQQPGAELVKPGTSVKLSCKASGYNFTSYWINWVKLRPGQGLEWIGDIYPGSGITNYNEKFKSKATLTVDTSSSTAYMQLSSLASEDSALYYCAGQYGNLWFAYWGQGTLVTVSS	133	GYNFTSYW	134	IYPGSGIT	135	AGQYGNLWFAY	136
BnDOTA	QAVVIQESALTTPPGETVTLTCGSSTGAVTASNYANWVQEKPDHCFTGLIGGHNNRPPGVPARFSGSLIGDKAALTIAGTQTEDEAIYFCALWYSDHWVIGGGTRLTVL	137	TGAVTASNY	138	GHN	139	ALWYSDHWVIGGG	140	HVKLQESGPGLVQPSQSLSLTCTVSGFSLTDYGVHWVRQSPGKGLEWLGVIWSGGGTAYNTALISRLNIYRDNSKNQVFLEMNSLQAEDTAMYYCARRGSYPYNYFDAWGCGTTVTVSS	141	GFSLTDYG	142	IWSGGGT	143	ARRGSYPYNYFDA	144
CAIX	DIVMTQSQRFMSTTVGDRVSITCKASQNVVSAVAWYQQK	145	QNVVSA	146	SAS	147	QQYSNYPWT	148	DVKLVESGGGLVKLGGSLKLSCAASGFTFSNYYMSWVRQTPEKRLELV	149	GFTFSNYY	150	INSDGGIT	151	ARHRSGYFSMDY	152

	PGQSPKLLIYS ASNRYTGVPD RFTGSGSGTDF TLTISNMQSED LADFFCQQYS NYPWTFGGGT KLEIK								AAINSDGGITYYL DTVKGRFTISRD NAKNTLYLQMSS LKSEDTALFYCA RHRSGYFSMDY WGQGTSVTVSS							
CCL-2	EIVLTQSPATL SLSPGERATLS CRASQSVSDA YLAWYQQKP GQAPRLLIYD ASSRATGVPA RFSGSGSGTDF TLTISSLEPEDF AVYYCHQYIQ LHSFTFGQGT KVEIK	153	QSVSD AY	154	DAS	155	HQYI QLHS FT	156	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSSYGIS WVRQAPGQGLE WMGGIIPIFGTAN YAQKFQGRVTIT ADESTSTAYMEL SSLRSEDTAVYY CARYDGIYGELD FWGQGTLVTVSS	157	GGTF SSYG	158	IIPIFG TA	159	ARYDG IYGELD F	160
CD105 (endoglin)	QIVLSQSPAILS ASPGEKVTMT CRASSSVSYM HWYQQKPGSS PKPWIYATSN LASGVPVRFS GSGSGTSYSLT ISRVEAEDAAT YYCQQWSSNP LTFGAGTKLE LK	161	SSVSY	162	ATS	163	QQW SSNP LT	164	EVKLEESGGGLV QPGGSMKLSCAA SGFTFSDAWMD WVRQSPEKGLE WVAEIRSKASNH ATYYAESVKGRF TISRDDSKSSVYL QMNSLRAEDTGI YYCTRWRRFFDS WGQGTTLTVSS	165	GFTF SDA W	166	IRSKA SNHA T	167	TRWRR FFDS	168
CD115 (CSF1R)	EIVLTQSPATL SLSPGERATLS CKASQSVDYD GDNYMNWYQ QKPGQAPRLLI YAASNLESGIP ARFSGSGSGT DFTLTISSLEPE DFAVYYCHLS NEDLSTFGGG TKVEIK	169	QSVDY DGDNY	170	AAS	171	HLSN EDLS T	172	QVQLVQSGAEV KKPGSSVKVSCK ASGYTFTDNYMI WVRQAPGQGLE WMGDINPYNGG TTFNQKFKGRVT ITADKSTSTAYM ELSSLRSEDTAV YYCARESPYFSN LYVMDYWGQGT LVTVSS	173	GYTF TDN Y	174	INPYN GGT	175	ARESP YFSNL YVMD YW	176
CD116a (CSF2Ra)	QSVLTQPPSVS GAPGQRVTISC TGSGSNIGAPY DVSWYQQLPG TAPKLLIYHN NKRPSGVPDR	177	GSNIG APYD	178	HNN	179	ATVE AGLS GSV	180	QVQLVQSGAEV KKPGASVKVSCK VSGYTLTELSIH WVRQAPGKGLE WMGGFDPEENEI VYAQRFQGRVT	181	GYT LTEL S	182	FDPEE NEI	183	AIVGSF SPLTLG L	184

	FSGSKSGTSASLAITGLQAEDEADYYCATVEAGLSGSVFGGGTKLTVL								MTEDTSTDTAYMELSSLRSEDTAVYYCAIVGSFSPLTLGLWGQGTMVTVSS							
CD11a (LFA-1)	DIQMTQSPSSLSASVGDRVTITCRASKTISKYLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPLTFGQGTKVEIK	185	KTISKY	186	SGS	187	QQHNEYPLT	188	EVQLVESGGGLVQPGGSLRLSCAASGYSFTGHWMNWVRQAPGKGLEWVGMIHPSDSETRYNQKFKDRFTISVDKSKNTLYLQMNSLRAEDTAVYYCARGIYFYGTTYFDYWGQGTLVTVSS	189	GYSFTGHW	190	IHPSDSET	191	ARGIYFYGTTYFDYW	192
CD123	DFVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYLQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPYTFGGGTKLEIK	193	QSLLNSGNQKNY	194	WAS	195	QNDYSYPYT	196	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYYMKWVKQSHGKSLEWIGDIIPSNGATFYNQKFKGKATLTVDRSSSTAYMHLNSLTSEDSAVYYCTRSHLLRASWFAYWGQGTLVTVSA	197	GYTFTDYY	198	IIPSNGAT	199	TRSHLLRASWFAY	200
CD123	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTVL	201	TGAVTTSNY	202	GTN	203	ALWYSNLWV	204	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS	205	GFTFSTYA	206	IRSKYNNYAT	207	VRHGNFGNSYVSWFAY	208
CD134 (OX40)	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATY	209	QDISNY	210	YTS	211	QQGHTLPPT	212	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAPGQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELSSLRSEDTAVYYC	213	GYTFTDSY	214	MYPDNGDS	215	VLAPRWYFSVW	216

	YCQQGHTLPPTFGQGTKVEIK								VLAPRWYFSVWGQGTLVTVSS							
CD137 (41BB)	SYELTQPPSVSVSPGQTASITCSGDNIGDQYAHWYQQKPGQSPVLVIYQDKNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYTGFGSLAVFGGGTKLTVL	217	NIGDQY	218	QDK	219	ATYTGFGSLAV	220	EVQLVQSGAEVKKPGESLRISCKGSGYSFSTYWISWVRQMPGKGLEWMGKIYPGDSYTNYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGYGIFDYWGQGTLVTVSS	221	GYSFSTYW	222	IYPGDSYT	223	ARGYGIFDY	224
CD137 (41BB)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPALTFCGGTKVEIK	225	QSVSSY	226	DAS	227	QQRSNWPPALT	228	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQSPEKGLEWIGEINHGGYVTYNPSLESRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDYGPGNYDWYFDLWGRGTLVTVSS	229	GGSFSGYY	230	INHGGYV	231	ARDYGPGNYDWYFDL	232
CD152 (CTLA4)	DIQMTQSPSSLSASVGDRVTITCRASQSINSYLDWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSTPFTFGPGTKVEIK	233	QSINSY	234	AAS	235	QQYYSTPFT	236	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPRGATLYYYYYGMDVWGQGTTVTVSS	237	GFTFSSYG	238	IWYDGSNK	239	ARDPRGATLYYYYYGMDV	240
CD152 (CTLA4)	EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTK	241	QSVGSSY	242	GAF	243	QQYGSSPWT	244	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDY	245	GFTFSSYT	246	ISYDGNNK	247	ARTGWLGPFDY	248

	VEIK								YWGQGTLVTVSS							
CD16	DTVLTQSPASLAVSLGQRATISCKASQSVDFDGDSFMNWYQQKPGQPPKLLIYTTSNLESGIPARFSASGSGTDFTLNIHPVEEEDTATYYCQQSNEDPYTFGGGTKLEIK	249	QSVDFDGDSF	250	TTS	251	QQSNEDPYT	252	QVTLKESGPGILQPSQTLSLTCSFSGFSLRTSGMGVGWIRQPSGKGLEWLAHIWWDDDKRYNPALKSRLTISKDTSSNQVFLKIASVDTADTATYYCAQINPAWFAYWGQGTLVTVSA	253	GFSLRTSGMG	254	IWWDDDK	255	AQINPAWFAY	256
CD184 (CXCR4)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFVTYYCQQYNSYPRTFGQGTKVEIK	257	QGISSW	258	AAS	259	QQYNSYPRT	260	EVQLVESGGGLVQPGGSLRLSCAAAGFTFSSYSMNWVRQAPGKGLEWVSYISSRSRTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARDYGGQPPYYYYYGMDVWGQGTTVTVSS	261	GFTFSSYS	262	ISSRSRTI	263	ARDYGGQPPYYYYYGMDV	264
CD19	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIK	265	QDISKY	266	HTS	267	QQGNTLPYT	268	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS	269	GVSLPDYG	270	IWGSETT	271	AKHYYYGGSYAMDY	272
CD19	EIVLTQSPDFQSVTPKEKVTITCRASESVDTFGISFMNWFQQKPDQSPKLLIHEASNQGSGVPSRFSGSGSGTDFTLTINSLEAEDAATYYCQQSKEVPFTFGGGTKVEIK	273	ESVDTFGISF	274	EAS	275	QQSKEVPFT	276	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSWMNWVRQAPGKGLEWVGRIYPGDGDTNYNVKFKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARSGFITTVRDFDYWGQGTLVTVSS	277	GFTFSSSW	278	IYPGDGDT	279	ARSGFITTVRDFDY	280

CD19	DIQMTQSPSSLSASVGDSVTITCQASTDISSHLNWYQQKPGKAPELLIYYGSHLLSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCGQGNRLPYTFGQGTKVEIE	281	TDISSH	282	YGS	283	GQGNRLPYT	284	QVQLQESGPGLVKPSETLSLTCAVSGHSISHDHAWSWVRQPPGEGLEWIGFISYSGITNYNPSLQGRVTISRDNSKNTLYLQMNSLRAEDTAVYYCARSLARTTAMDYWGEGTLVTVSS	285	GHSISHDHA	286	ISYSGIT	287	ARSLARTTAMDY	288
CD19	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDFTLTISSLEPEDVAVYYCFQGSVYPFTFGQGTKLEIK	289	SSVSY	290	DTS	291	FQGSVYPFT	292	QVQLQESGPGLVKPSQTLSLTCTVSGGSISTSGMGVGWIRQHPGKGLEWIGHIWWDDDKRYNPALKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDYWGQGTLVTVSS	293	GGSISTSGMG	294	IWWDDDK	295	ARMELWSYYFDY	296
CD19	DIQLTQSPASLAVSLGQRATISCKASQSVDYDGDSYLNWYQQIPGQPPKLLIYDASNLVSGIPPRFSGSGSGTDFTLNIHPVEKVDAATYHCQQSTEDPWTFGGGTKLEIK	297	QSVDYDGDSY	298	DAS	299	QQSTEDPWT	300	QVQLQQSGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQGLEWIGQIWPGDGDTNYNGKFKGKATLTADESSSTAYMQLSSLASEDSAVYFCARRETTTVGRYYYAMDYWGQGTTVTVSS	301	GYAFSSYW	302	IWPGDGDT	303	ARRETTTVGRYYYAMDY	304
CD19	DIVMTQAAPSIPVTPGESVSISCRSSKSLLNSNGNTYLYWFLQRPGQSPQLLIYRMSNLASGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTFGAGTKLEIK	305	KSLLNSNGNTY	306	RMS	307	MQHLEYPLT	308	QVQLQQSGPELIKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEQIGYINPYNDGTKYNEKFKGKATLTSDKSSTAYMELSSLTSEDSAVYYCARGTYYYGSRVFDYWGQGTTLTVTVSS	309	GYTFTSYV	310	INPYNDGT	311	ARGTYYYGSRVFDY	312
CD19	EIVLTQSPAIMSASPGERVTM	313	SGVNY	314	DTS	315	HQR	316	QVQLVQPGAEVVKPGASVKLSCK	317	GYTFTSN	318	IDPSD	319	ARGSNPYYYA	320

	TCSASSGVNY MHWYQQKPG TSPRRWIYDTS KLASGVPARF SGSGSGTDYS LTISSMEPEDA ATYYCHQRGS YTFGGGTKLEI K						GSYT		TSGYTFTSNWMH WVKQAPGQGLE WIGEIDPSDSYTN YNQNFQGKAKL TVDKSTSTAYME VSSLRSDDTAVY YCARGSNPYYYA MDYWGQGTSVT VSS		W		SYT		MDY	
CD192 (CCR2)	DVVMTQSPLS LPVTLGQPASI SCKSSQSLLDS DGKTFLNWFQ QRPGQSPRRLI YLVSKLDSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCW QGTHFPYTFG QGTRLEIK	321	QSLLD SDGKT F	322	LVS	323	WQG THFP YT	324	EVQLVESGGGLV KPGGSLRLSCAA SGFTFSAYAMN WVRQAPGKGLE WVGRIRTKNNN YATYYADSVKD RFTISRDDSKNTL YLQMNSLKTEDT AVYYCTTFYGNG VWGQGTLVTVSS	325	GFTF SAY A	326	IRTKN NNYA T	327	TTFYG NGVW	328
CD194 (CCR4)	DVLMTQSPLS LPVTPGEPASI SCRSSRNIVHI NGDTYLEWYL QKPGQSPQLLI YKVSNRFSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCFQ GSLLPWTFGQ GTKVEIK	329	RNIVHI NGDTY	330	KVS	331	FQGS LLP WT	332	EVQLVESGGDLV QPGRSLRLSCAA SGFIFSNYGMSW VRQAPGKGLEW VATISSASTYSYY PDSVKGRFTISRD NAKNSLYLQMN SLRVEDTALYYC GRHSDGNFAFGY WGQGTLVTVSS	333	GFIF SNY G	334	ISSAS TYS	335	GRHSD GNFAF GY	336
CD195 (CCR5)	DIVMTQSPLSL PVTPGEPASIS CRSSQRLLSSY GHTYLHWYL QKPGQSPQLLI YEVSNRFSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCSQ STHVPLTFGQ GTKVEIK	337	QRLLSS YGHTY	338	EVS	339	SQST HVPL T	340	EVQLVESGGGLV KPGGSLRLSCAA SGYTFSNYWIGW VRQAPGKGLEWI GDIYPGGNYIRN NEKFKDKTTLSA DTSKNTAYLQM NSLKTEDTAVYY CGSSFGSNYVFA WFTYWGQGTLV TVSS	341	GYTF SNY W	342	IYPGG NYI	343	GSSFGS NYVFA WFTY W	344
CD20	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG	345	QSVSS Y	346	DAS	347	QQRS NWPI T	348	EVQLVESGGGLV QPGRSLRLSCAA SGFTFNDYAMH WVRQAPGKGLE	349	GFTF NDY A	350	ISWNS GSI	351	AKDIQ YGNYY YGMD	352

	QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITFGQGTRLEIK								WVSTISWNSGSIGYADSVKGRFTISRDNAKKSLYLQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTTVTVSS						V	
CD20	QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPKPWIYAPSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQQWSFNPPTFGAGTKLELK	353	SSVSY	354	APS	355	QQWSFNPPT	356	QAYLQQSGAELVRPGASVKMSCKASGYTFTSYNMHWVKQTPRQGLEWIGAIYPGNGDTSYNQKFKGKATLTVDKSSSTAYMQLSSLTSEDSAVYFCARVVYYSNSYWYFDVWGTGTTVTVSGPSVFPLAPSS	357	GYTFTSYN	358	IYPGNGDT	359	ARVVYYSNSYWYFDV	360
CD20	QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPKPWIYATSNLASGVPARFSGSGSGTSYSFTISRVEAEDAATYYCQQWTFNPPTFGGGTRLEIK	361	SSVSY	362	ATS	363	QQWTFNPPT	364	QAYLQQSGAELVRPGASVKMSCKASGYTFTSYNMHWVKQTPRQGLEWIGGIYPGNGDTSYNQKFKGKATLTVGKSSSTAYMQLSSLTSEDSAVYFCARYDYNYAMDYWGQGTSVTVSS	365	GYTFTSYN	366	IYPGNGDT	367	ARYDYNYAMDY	368
CD20	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK	369	SSVSY	370	ATS	371	QQWTSNPPT	372	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSA	373	GYTFTSYN	374	IYPGNGDT	375	ARSTYYGGDWYFNV	376
CD20	DIQLTQSPSSLSASVGDRVTMTCRASSSVSYIHWFQQKPGKAPKPWIYATS	377	SSVSY	378	ATS	379	QQWTSNPPT	380	QVQLQQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVKQAPGQGLEWIGAIYPGNGDT	381	GYTFTSYN	382	IYPGNGDT	383	ARSTYYGGDWYFDV	384

	NLASGVPVRF SGSGSGTDYT FTISSLQPEDIA TYYCQQWTSN PPTFGGGTKLE IK								SYNQKFKGKATL TADESTNTAYME LSSLRSEDTAFYY CARSTYYGGDW YFDVWGQGTTV TVSS							
CD20	DIVMTQTPLSL PVTPGEPASIS CRSSKSLLHSN GITYLYWYLQ KPGQSPQLLIY QMSNLVSGVP DRFSGSGSGT DFTLKISRVEA EDVGVYYCA QNLELPYTFG GGTKVEIK	385	KSLLH SNGITY	386	QMS	387	AQN LELP YT	388	QVQLVQSGAEV KKPGSSVKVSCK ASGYAFSYSWIN WVRQAPGQGLE WMGRIFPGDGDT DYNGKFKGRVTI TADKSTSTAYME LSSLRSEDTAVY YCARNVFDGYW LVYWGQGTLVT VSS	389	GYA FSYS W	390	IFPGD GDT	391	ARNVF DGYWL VY	392
CD200	DIQMTQSPSSL SASIGDRVTIT CKASQDINSY LSWFQQKPGK APKLLIYRAN RLVDGVPSRF SGSGSGTDYT LTISSLQPEDF AVYYCLQYDE FPYTFGGGTK LEIK	393	QDINS Y	394	RAN	395	LQY DEFP YT	396	QVQLQQSGSELK KPGASVKISCKA SGYSFTDYIILWV RQNPGKGLEWIG HIDPYYGSSNYN LKFKGRVTITAD QSTTTAYMELSS LRSEDTAVYYCG RSKRDYFDYWG QGTTLTVSS	397	GYSF TDYI	398	IDPYY GSS	399	GRSKR DYFDY W	400
CD22	DIQLTQSPSSL AVSAGENVTM SCKSSQSVLYS ANHKNYLAW YQQKPGQSPK LLIYWASTRES GVPDRFTGSG SGTDFTLTISR VQVEDLAIYY CHQYLSSWTF GGGTKLEIK	401	QSVLY SANHK NY	402	WAS	403	HQY LSSW T	404	QVQLQESGAELS KPGASVKMSCK ASGYTFTSYWLH WIKQRPGQGLE WIGYINPRNDYT EYNQNFKDKATL TADKSSSTAYMQ LSSLTSEDSAVY YCARRDITTFYW GQGTTLTVSS	405	GYTF TSY W	406	INPRN DYT	407	ARRDIT TFY	408
CD221 (IGF1R)	DIQMTQFPSSL SASVGDRVTIT CRASQGIRND LGWYQQKPG KAPKRLIYAA SRLHRGVPSRF SGSGSGTEFTL	409	QGIRN D	410	AAS	411	LQH NSYP CS	412	EVQLLESGGGLV QPGGSLRLSCTA SGFTFSSYAMNW VRQAPGKGLEW VSAISGSGGTTFY ADSVKGRFTISR DNSRTTLYLQMN	413	GFTF SSYA	414	ISGSG GTT	415	AKDLG WSDSY YYYYG MDV	416

	TISSLQPEDFATYYCLQHNSYPCSFGQGTKLEIK								SLRAEDTAVYYCAKDLGWSDSYYYYYGMDVWGQGTTVTVSS							
CD221 (IGF1R)	DIQMTQSPSSLSASLGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAKSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDSATYYCQQYWTFPLTFGGGTKVEIK	417	QGISSY	418	AKS	419	QQYWTFPLT	420	EVQLLQSGGGLVQPGGSLRLSCAASGFMFSRYPMHWVRQAPGKGLEWVGSISGSGGATPYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDFYQILTGNAFDYWGQGTTVTVSS	421	GFMFSRYP	422	ISGSGGAT	423	AKDFYQILTGNAFDY	424
CD221 (IGF1R)	QIVLTQSPAIMSASPGEKVTITCSASSSVSYIHWFQQKPGTSPKVWIYGTSNLASGVPARFTGSGSGTSYSLTISRMEAEDAATYYCQQRSSYPFTFGSGTKLEIK	425	SSVSY	426	GTS	427	QQRSSYPFT	428	EVQLQQSGPELVKPGSSVKISCKASGYSFTAYYMHWVKQSHGKSLEQISGRINPDNGGNSYNQFKFGKAILTVDKSSNTAYMELRSLTSEDSAVYYCAKSTSYDYDGYWFDVWGAGTTVTVSS	429	GYSFTAYY	430	RINPDNGG	431	CAKSTSYDYDGYWFDV	432
CD221 (IGF1R)	SSELTQDPAVSVALGQTVRITCQGDSLRSYYATWYQQKPGQAPILVIYGENKRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCKSRDGSGQHLVFGGGTKLTVL	433	SLRSYY	434	GEN	435	KSRDGSGQHLV	436	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARAPLRFLEWSTQDHYYYYYMDVWGKGTTVTVSS	437	GGTFSSYA	438	IIPIFGTA	439	ARAPLRFLEWSTQDHYYYYYMDV	440
CD221 (IGF1R)	EIVLTQSPGTLSVSPGERATLSCRASQSIGSSLHWYQQKPGQAPRLLIKYASQSLSGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCHQSSRLP	441	QSIGSS	442	YAS	443	HQSSRLPHT	444	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSFAMHWVRQAPGKGLEWISVIDTRGATYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARLGNFYYGMD	445	GFTFSSFA	446	IDTRGAT	447	ARLGNFYYGMDV	448

	HTFGQGTKVEIK								VWGQGTTVTVSS							
CD221 (IGF1R)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASKRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSKWPPWTFGQGTKVESK	449	QSVSSSY	450	DAS	451	QQRSKWPPWT	452	QVELVESGGGVVQPGRSQRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAIIWFDGSSTYYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARELGRRYFDLWGRGTLVSVSS	453	GFTFSSYG	454	IWFDGSST	455	ARELGRRYFDL	456
CD221 (IGF1R)	DIVMTQSPLSLPVTPGEPASISCRSSQSIVHSNGNTYLQWYLQKPGQSPQLLIYKVSNRLYGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPWTFGQGTKVEIK	457	QSIVHSNGNTY	458	KVS	459	FQGSHVPWT	460	QVQLQESGPGLVKPSETLSLTCTVSGYSITGGYLWNWIRQPPGKGLEWIGYISYDGTNNYKPSLKDRVTISRDTSKNQFSLKLSSVTAADTAVYYCARYGRVFFDYWGQGTLVTVSS	461	GYSITGGYL	462	ISYDGTN	463	ARYGRVFFDY	464
CD221 (IGF1R)	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPLTFGQGTKVEIK	465	QSLLHSNGYNY	466	LGS	467	MQGTHWPLT	468	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARWTGRTDAFDIWGQGTMVTVSS	469	GGSISSSNW	470	IYHSGST	471	ARWTGRTDAFDI	472
CD223 (LAG-3)	EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGQGTNLEIK	473	QSISSY	474	DAS	475	QQRSNWPLT	476	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKGLEWIGEINHRGSTNSNPSLKSRVTLSLDTSKNQFSLKLRSVTAADTAVYYCAFGYSDYEYNWFDPWGQGTLVTVSS	477	GGSFSDYY	478	INHRGST	479	AFGYSDYEYNWFDP	480

CD248	DIQMTQSPSSLSASVGDRVTITCRASQNVGTAVAWLQQTPGKAPKLLIYSASNRYTGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYTNYPMYTFGQGTKVQIK	481	QNVGTA	482	SAS	483	QQYTNYPMYT	484	QVQLQESGPGLVRPSQTLSLTCTASGYTFTDYVIHWVKQPPGRGLEWIGYINPYDDDTTYNQKFKGRVTMLVDTSSNTAYLRLSSVTAEDTAVYYCARRGNSYDGYFDYSMDYWGSGTPVTVSS	485	GYTFTDYV	486	INPYDDDT	487	ARRGNSYDGYFDYSMDY	488
CD25	QIVSTQSPAIMSASPGEKVTMTCSASSSRSYMQWYQQKPGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQRSSYTFGGGTKLEIK	489	SSRSY	490	DTS	491	HQRSSYT	492	QLQQSGTVLARPGASVKMSCKASGYSFTRYWMHWIKQRPGQGLEWIGAIYPGNSDTSYNQKFEGKAKLTAVTSASTAYMELSSLTHEDSAVYYCSRDYGYYFDFWGQGTTLTVSS	493	GYSFTRYW	494	IYPGNSDT	495	SRDYGYYFDF	496
CD25	DIQMTQSPSTLSASVGDRVTITCSASSSISYMHWYQQKPGKAPKLLIYTTSNLASGVPARFSGSGSGTEFTLTISSLQPDDFATYYCHQRSTYPLTFGQGTKVEVK	497	SSISY	498	TTS	499	HQRSTYPLT	500	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYRMHWVRQAPGQGLEWIGYINPSTGYTEYNQKFKDKATITADESTNTAYMELSSLRSEDTAVYYCARGGGVFDYWGQGTLVTVSS	501	GYTFTSYR	502	INPSTGYT	503	ARGGGVFDYW	504
CD252 (OX40L)	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSKLHSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQGSALPWTFGQGTKVEIK	505	QDISNY	506	YTS	507	QQGSALPWT	508	QVQLQESGPGLVKPSQTLSLTCAVYGGSFSSGYWNWIRKHPGKGLEYIGYISYNGITYHNPSLKSRITINRDTSKNQYSLQLNSVTPEDTAVYYCARYKYDYDGGHAMDYWGQGTLVTVSS	509	GGSFSSGY	510	ISYNGIT	511	ARYKYDYDGGHAMDY	512
CD254	EIVLTQSPGTLSLSPGERATLS	513	QSVRG	514	GAS	515	QQYGSSP	516	EVQLLESGGGLVQPGGSLRLSCAA	517	GFTF	518	ITGSG	519	AKDPGTTVIMS	520

(RANKL)	CRASQSVRGRYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVFYCQQYGSSPRTFGQGTKVEIK		RY				RT		SGFTFSSYAMSWVRQAPGKGLEWVSGITGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDPGTTVIMSWFDPWGQGTLVTVSS		SSYA		GST		WFDP	
CD257 (BAFF)	EIVLTQSPATLSLSPGERATLSCRASQSVSRYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDSTLTISSLEPEDFAVYYCQQRSNWPRTFGQGTKVEIK	521	QSVSRY	522	DAS	523	QQRSNWPRT	524	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGYYDILTGYYYYFDYWGQGTLVTVSS	525	GGSFSGYY	526	INHSGST	527	ARGYYDILTGYYYYFDY	528
CD257 (BAFF)	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASQYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTEL	529	SLRSYY	530	GKN	531	SSRDSSGNHWV	532	QVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMGGIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLFPHHALSPWGRGTMVTVSS	533	GGTFNNNA	534	IIPMFGTA	535	ARSRDLLLFPHHALSP	536
CD26	QIVLTQSPAIMSASPGEKVTITCSASSSVSYMNWFQQKPGTSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSYPNTFGGGTKLEIK	537	SSVSY	538	STS	539	QQRSSYPNT	540	QVQLQQSGAELVKPGASVKLSCKASGYTFRSYDINWVRQRPEQGLEWIGWIFPGDGSTKYNEKFKGKATLTTDKSSSTAYMQLSRLTSEDSAVYFCARWTVVGPGYFDVWGAGTTVTVSS	541	GYTFRSYD	542	IFPGDGST	543	ARWTVVGPGYFDV	544
CD262 (DR5)	DIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAWYQQKPG	545	QDVGTA	546	WAS	547	QQYSSYRT	548	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYVMSWVRQAPGKGLEW	549	GFTFSSYV	550	ISSGGSYT	551	ARRGDSMITTDYW	552

	KAPKLLIYWASTRHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSYRTFGQGTKVEIK								VATISSGGSYTYYPDSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARRGDSMITTDYWGQGTLVTVSS							
CD262 (DR5)	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVL	553	SLRSYY	554	GKN	555	NSRDSSGNHVV	556	EVQLVQSGGGVERPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRVTISRDNAKNSLYLQMNSLRAEDTAVYYCAKILGAGRGWYFDLWGKGTTVTVSS	557	GFTFDDYG	558	INWNGGST	559	AKILGAGRGWYFDL	560
CD262 (DR5)	EIVLTQSPGTLSLSPGERATLSCRASQGISRSYLAWYQQKPGQAPSLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQFGSSPWTFGQGTKVEIK	561	QGISRSY	562	GAS	563	QQFGSSPWT	564	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYFWSWIRQLPGKGLEWIGHIHNSGTTYYNPSLKSRVTISVDTSKKQFSLRLSSVTAADTAVYYCARDRGGDYYYGMDVWGQGTTVTVSS	565	GGSISSGDYF	566	IHNSGTT	567	ARDRGGDYYYGMDV	568
CD27	DIQMTQSPSSLSASVGDRVTITCRASQGISRWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNTYPRTFGQGTKVEIK	569	QGISRW	570	AAS	571	QQYNTYPRT	572	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYDMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGSGNWGFFDYWGQGTLVTVSS	573	GFTFSSYD	574	IWYDGSNK	575	ARGSGNWGFFDY	576
CD274 (PD-L1)	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVS	577	SSDVGGYNY	578	DVS	579	SSYTSSSTRV	580	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYADTVKGRFTISR	581	GFTFSSYI	582	IYPSGGIT	583	ARIKLGTVTTVDY	584

	NRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVL								DNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQGTLVTVSS							
CD274 (PD-L1)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIK	585	QDVSTA	586	SAS	587	QQYLYHPAT	588	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS	589	GFTFSDSW	590	ISPYGGST	591	ARRHWPGGFDY	592
CD274 (PD-L1)	EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIK	593	QRVSSSY	594	DAS	595	QQYGSLPWT	596	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSS	597	GFTFSRYW	598	IKQDGSEK	599	AREGGWFGELAFDY	600
CD275 (ICOS-L)	DIQMTQSPSSLSASVGDRVTITCRASQGISNWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYDSYPRTFGQGTKVEIK	601	QGISNW	602	AAS	603	QQYDSYPRT	604	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAYIKQDGNEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGILWFGDLPTFWGQGTLVTVSS	605	GFTFSSYW	606	IKQDGNEK	607	AREGILWFGDLPTF	608
CD276 (B7H3)	DIQLTQSPSFLSASVGDRVTITCKASQNVDTNVAWYQQKPGKAPKALIYSASYRYSGVPSRFSGSGSGTDFTLTISSLQPEDFAT	609	QNVDTN	610	SAS	611	QQYNNYPFT	612	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVAYISSDSSAIYYADTVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYY	613	GFTFSSFG	614	ISSDSSAI	615	GRGRENIYYGSRLDY	616

	YYCQQYNNYPFTFGQGTKLEIK								CGRGRENIYYGSRLDYWGQGTTVTVSS							
CD276 (B7H3)	DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLHWYQQKSHESPRLLIKYASQSISGIPSRFSGSGSGSDFTLSINSVEPEDVGVYYCQNGHSFPLTFGAGTKLELK	617	QSISDY	618	YAS	619	QNGHSFPLT	620	QVQLQQSGAELVKPGASVKLSCKASGYTFTNYDINWVRQRPEQGLEWIGWIFPGDGSTQYNEKFKGKATLTTDTSSSTAYMQLSRLTSEDSAVYFCARQTTATWFAYWGQGTLVTVSA	621	GYTFTNYD	622	IFPGDGST	623	ARQTTATWFAY	624
CD279 (PD-1)	DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGSGSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR	625	LSINTF	626	AAS	627	QQSSNTPFT	628	EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFADSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSS	629	GFTFSNFG	630	ISGGGRDT	631	VKWGNIYFDY	632
CD279 (PD-1)	DIQMTQSPSSLSASVGDRVTITCLASQTIGTWLTWYQQKPGKAPKLLIYTATSLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYSIPWTFGGGTKVEIK	633	QTIGTW	634	TAT	635	QQVYSIPWT	636	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYMMSWVRQAPGKGLEWVATISGGGANTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQLYYFDYWGQGTTVTVSS	637	GFTFSSYM	638	ISGGGANT	639	ARQLYYFDY	640
CD279 (PD-1)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEI	641	QSVSSY	642	DAS	643	QQSSNWPRT	644	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWG	645	GITFSNSG	646	IWYDGSKR	647	ATNDDY	648

	K								QGTLVTVSS							
CD279 (PD-1)	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLISAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANHLPFTFGGGTKVEIK	649	QGISSW	650	AAS	651	QQANHLPFT	652	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGLIIPMFDTAGYAQKFQGRVAITVDESTSTAYMELSSLRSEDTAVYYCARAEHSSTGTFDYWGQGTLVTVSS	653	GGTFSSYA	654	IIPMFDTA	655	ARAEHSSTGTFDY	656
CD279 (PD-1)	QPVLTQPLSVSVALGQTARITCGGNNIGSKNVHWYQQKPGQAPVLVIYRDSNRPSGIPERFSGSNSGNTATLTISRAQAGDEADYYCQVWDSSTAVFGTGTKLTVL	657	NIGSKN	658	RDS	659	QVWDSSTAV	660	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMYWVRQVPGKGLEWVSAIDTGGGRTYYADSVKGRFAISRVNAKNTMYLQMNSLRAEDTAVYYCARDEGGGTGWGVLKDWPYGLDAWGQGTLVTVSS	661	GFTFSSYW	662	IDTGGGRT	663	ARDEGGGTGWGVLKDWPYGLDA	664
CD279 (PD-1)	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK	665	KGVSTSGYSY	666	LAS	667	QHSRDLPLT	668	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSS	669	GYTFTNYY	670	INPSNGGT	671	ARRDYRFDMGFDYW	672
CD279 (PD-1)	EIVLTQSPATLSLSPGERATLSCRASQSVRSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFGQGTKV	673	QSVRSY	674	DAS	675	QQRNYWPLT	676	VQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFDTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARPGLAAAYDTGSLDYWGQGTLV	677	GGTFSSYA	678	IIPIFDTA	679	ARPGLAAAYDTGSLDY	680

	EIK								TVSS							
CD3	DIQLTQSPAIMSASPGEKVTMTCRASSSVSYMNWYQQKSGTSPKRWIYDTSKVASGVPYRFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPLTFGAGTKLELK	681	SSVSY	682	DTS	683	QQWSSNPLT	684	DIKLQQSGAELARPGASVKMSCKTSGYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARYYDDHYCLDYWGQGTTLTVSS	685	GYTFTRYT	686	INPSRGYT	687	ARYYDDHYCLDY	688
CD3	DIQLTQPNSVSTSLGSTVKLSCTLSSGNIENNYVHWYQLYEGRSPTTMIYDDDKRPDGVPDRFSGSIDRSSNSAFLTIHNVAIEDEAIYFCHSYVSSFNVFGGGTKLTVL	689	SGNIENNY	690	DDD	691	HSYVSSFNV	692	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFPMAWVRQAPGKGLEWVSTISTSGGRTYYRDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFRQYSGGFDYWGQGTLVTVSS	693	GFTFSSFP	694	ISTSGGRT	695	AKFRQYSGGFDY	696
CD3	DIQMTQTTSSLSASLGDRVTISCRASQDIRNYLNWYQQKPDGTVKLLIYYTSRLHSGVPSKFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPWTFAGGTKLEIK	697	QDIRNY	698	YTS	699	QQGNTLPWTFAGG	700	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWMGLINPYKGVSTYNQKFKDKATLTVDKSSSTAYMELLSLTSEDSAVYYCARSGYYGDSDWYFDVWGQGTTLTVFS	701	GYSFTGYT	702	INPYKGVS	703	ARSGYYGDSDWYFDV	704
CD3	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL	705	TGAVTSGNY	706	GTK	707	VLWYSNRWV	708	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSS	709	GFTFNKYA	710	IRSKYNNYAT	711	VRHGNFGNSYISYWAY	712

CD3	DFVMTQSPDSLAVSLGERVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYSYPYTFGQGTKLEIK	713	QSLLNSGNQKNY	714	WAS	715	QNDYSYPYT	716	EVQLVQSGAELKKPGASVKVSCKASGYTFTDYYMKWVRQAPGQGLEWIGDIIPSNGATFYNQKFKGRVTITVDKSTSTAYMELSSLRSEDTAVYYCARSHLLRASWFAYWGQGTLVTVSS	717	GYTFTDYY	718	IIPSNGAT	719	ARSHLLRASWFAYW	720
CD3	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEIN	721	SSVSY	722	DTS	723	QQWSSNPFT	724	QVQLQQSGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARYYDDHYCLDYWGQGTTLTVSS	725	GYTFTRYT	726	INPSRGYT	727	ARYYDDHYCLDY	728
CD3	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPLTFGGGTKVEIK	729	QSVSSY	730	DAS	731	QQRSNWPPLT	732	QVQLVESGGGVVQPGRSLRLSCAASGFKFSGYGMHWVRQAPGKGLEWVAVIWYDGSKKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQMGYWHFDLWGRGTLVTVSS	733	GFKFSGYG	734	IWYDGSKK	735	ARQMGYWHFDL	736
CD3	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPTFGQGTKVEIK	737	QSISSY	738	AAS	739	QQSYSTPPT	740	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAKGTTGDWFDYWGQGTLVTVSS	741	GYTFTSYY	742	INPSGGST	743	AKGTTGDWFDY	744
CD30 (TNFRS	DIVLTQSPASLAVSLGQRATIS	745	QSVDF	746	AAS	747	QQSNEDP	748	QIQLQQSGPEVVKPGASVKISCKA	749	GYTFTDY	750	IYPGS	751	ANYGN	752

F8)	CKASQSVDFD GDSYMNWYQ QKPGQPPKVLI YAASNLESGIP ARFSGSGSGT DFTLNIHPVEE EDAATYYCQQ SNEDPWTFGG GTKLEIK		DGDSY				WT		SGYTFTDYYITW VKQKPGQGLEWI GWIYPGSGNTKY NEKFKGKATLTV DTSSSTAFMQLSS LTSEDTAVYFCA NYGNYWFAYWG QGTQVTVSA		Y		GNT		YWFAY	
CD30 (TNFRSF8)	DIQMTQSPTSL SASVGDRVTIT CRASQGISSW LTWYQQKPEK APKSLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQYDSYPI TFGQGTRLEIK	753	QGISSW	754	AAS	755	QQY DSYPIT	756	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSAYYWS WIRQPPGKGLEW IGDINHGGGTNY NPSLKSRVTISVD TSKNQFSLKLNS VTAADTAVYYC ASLTAYWGQGSL VTVSS	757	GGSF SAYY	758	INHG GGT	759	ASLTA Y	760
CD319 (SLAMF7)	DIQMTQSPSSL SASVGDRVTIT CKASQDVGIA VAWYQQKPG KVPKLLIYWA STRHTGVPDR FSGSGSGTDFT LTISSLQPEDV ATYYCQQYSS YPYTFGQGTK VEIK	761	QDVGIA	762	WAS	763	QQY SSYPYT	764	EVQLVESGGGLV QPGGSLRLSCAA SGFDFSRYWMS WVRQAPGKGLE WIGEINPDSSTIN YAPSLKDKFIISR DNAKNSLYLQM NSLRAEDTAVYY CARPDGNYWYF DVWGQGTLVTV SS	765	GFDF SRYW	766	INPDS STI	767	ARPDG NYWYF DV	768
CD33	DIVLTQSPTIM SASPGERVTM TCTASSSVNYI HWYQQKSGD SPLRWIFDTSK VASGVPARFS GSGSGTSYSLT ISTMEAEDAA TYYCQQWRS YPLTFGDGTR LELK	769	SSVNY	770	DTS	771	QQW RSYPLT	772	EVKLQESGPELV KPGASVKMSCK ASGYKFTDYVVH WLKQKPGQGLE WIGYINPYNDGT KYNEKFKGKATL TSDKSSSTAYME VSSLTSEDSAVY YCARDYRYEVY GMDYWGQGTSV TVSS	773	GYK FTDYV	774	INPYN DGT	775	ARDYR YEVYG MDY	776
CD33	DIVMTQSPSSL SASLGGKVTIT CKASQDINKYI AWYQHKPGK GPRLLIHYTST	777	QDINKY	778	YTS	779	LQY DNLLT	780	EVKLQQSGPELV KPGTSVKVSCKA SGYSFTDYNMY WVKQSHGKSLE WIGYIDPYKGGTI	781	GYSF TDYN	782	IDPYK GGT	783	AREMI TAYYF DY	784

	LQPGIPSRFSG SGSGRDYSFSI SNLEPEDIATY YCLQYDNLLT FGAGTKLELK								YNQKFKGKATLT VDKSSSTAFMHL NSLTSEDSAVYY CAREMITAYYFD YWGQGSSVTVSS							
CD33	DIVLTQSPASL AVSLGQRATIS CRASESVDNY GISFMNWFQQ KPGQPPKLLIY AASNQGSGVP ARFSGSGSGT DFSLNIHPMEE DDTAMYFCQ QSKEVPWTFG GGTKLEIK	785	ESVDN YGISF	786	AAS	787	QQS KEVP WT	788	EVQLQQSGPELV KPGASVKISCKA SGYTFTDYNMH WVKQSHGKSLE WIGYIYPYNGGT GYNQKFKSKATL TVDNSSSTAYMD VRSLTSEDSAVY YCARGRPAMDY WGQGTSVTVSS	789	GYTF TDY N	790	IYPYN GGT	791	ARGRP AMDY	792
CD33	DIQLTQSPSTL SASVGDRVTIT CRASESLDNY GIRFLTWFQQ KPGKAPKLLM YAASNQGSGV PSRFSGSGSGT EFTLTISSLQP DDFATYYCQQ TKEVPWSFGQ GTKVEVK	793	ESLDN YGIRF	794	AAS	795	QQT KEVP WS	796	EVQLVQSGAEVK KPGSSVKVSCKA SGYTITDSNIHW VRQAPGQSLEWI GYIYPYNGGTDY NQKFKNRATLTV DNPTNTAYMELS SLRSEDTAFYYC VNGNPWLAYWG QGTLVTVSS	797	GYTI TDSN	798	IYPYN GGT	799	VNGNP WLAY	800
CD33	NIMLTQSPSSL AVSAGEKVTM SCKSSQSVFFS SSQKNYLAWY QQIPGQSPKLL IYWASTRESG VPDRFTGSGS GTDFTLTISSV QSEDLAIYYC HQYLSSRTFG GGTKLEIK	801	QSVFFS SSQKN Y	802	WAS	803	HQY LSSR T	804	QVQLQQPGAEV VKPGASVKMSC KASGYTFTSYYI HWIKQTPGQGLE WVGVIYPGNDDI SYNQKFKGKATL TADKSSTTAYMQ LSSLTSEDSAVY YCAREVRLRYFD VWGAGTTVTVSS	805	GYTF TSYY	806	IYPGN DDI	807	AREVR LRYFD V	808
CD33	DIKMTQSPSS MYASLGERVII NCKASQDINS YLSWFQQKPG KSPKTLIYRAN RLVDGVPSRF SGSGSGQDYS LTISSLEYEDM	809	QDINS Y	810	RAN	811	LQY DEFP LT	812	QVQLQQSGPELV RPGTFVKISCKAS GYTFTNYDINWV NQRPGQGLEWIG WIYPGDGSTKYN EKFKAKATLTAD KSSSTAYLQLNN LTSENSAVYFCA	813	GYTF TNY D	814	IYPGD GST	815	ASGYE DAMD Y	816

	GIYYCLQYDE FPLTFGAGTKL ELK								SGYEDAMDYWG QGTSVTVSS							
CD33	DIQMTQSPSSL SASVGDRVTIT CRASESVDNY GISFMNWFQQ KPGKAPKLLL YAASNQGSGV PSRFSGSGSGT DFTLTISSLQP DDFATYYCQQ SKEVPWTFGQ GTKVELK	817	ESVDN YGISF	818	AAS	819	QQS KEVP WT	820	QVQLVQSGAEV KKPGSSVKVSCK ASGYTFTDYNM HWVRQAPGQGL EWLGYIYPYNGG TGYNQKFKSKAT ITADESTNTAYM ELSSLRSEDTAV YYCARGRPAMD YWGQGTLVTVSS	821	GYTF TDY N	822	IYPYN GGT	823	ARGRP AMDY W	824
CD332 (FGFR2)	QSVLTQPPSAS GTPGQRVTISC SGSSSNIGNNY VSWYQQLPGT APKLLIYENY NRPAGVPDRF SGSKSGTSASL AISGLRSEDEA DYYCSSWDDS LNYWVFGGG TKLTVL	825	SSNIGN NY	826	ENY N	827	SSW DDSL NYW V	828	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYAMSW VRQAPGKGLEW VSAISGSGTSTYY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CARVRYNWNHG DWFDPWGQGTL VTVSS	829	GFTF SSYA	830	ISGSG TST	831	ARVRY NWNH GDWFD P	832
CD350 (FZD10)	DIQMTQSPASL SVSVGETVTIT CRASENIYSNL AWYQQKQGK SPQLLVYVAT NLADGVPSRF SGSGSGTQYS LKINSLQSEDF GSYYCQHFW GTPYTFGGGT KLEIK	833	ENIYSN	834	VAT	835	QHF WGT PYT	836	EVQLQQSGAELV KPGASVKLSCTA SGFNINDTYMHW VKQRPEQGLEWI GRIDPANGNTKY DPKFQGKATITA DTSSNTAYLQLS SLTSEDTAVYYC ARGARGSRFAY WGQGTLVTVSA	837	GFNI NDT Y	838	IDPAN GNT	839	ARGAR GSRFA Y	840
CD37	DIQMTQSPSSL SVSVGERVTIT CRASENIRSNL AWYQQKPGK SPKLLVNVAT NLADGVPSRF SGSGSGTDYS LKINSLQPEDF GTYYCQHYW GTTWTFGQGT	841	ENIRSN	842	VAT	843	QHY WGT TWT	844	QVQVQESGPGLV APSQTLSITCTVS GFSLTTSGVSWV RQPPGKGLEWLG VIWGDGSTNYHP SLKSRLSIKKDHS KSQVFLKLNSLT AADTATYYCAK GGYSLAHWGQG	845	GFSL TTSG	846	IWGD GST	847	AKGGY SLAH	848

	KLEIK								TLVTVSS							
CD371 (CLEC12A)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPTFGQGTKVEIK	849	QSISSY	850	AAS	851	QQSYSTPPT	852	QVQLVQSGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAAIWYNARKQDYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRGTGYNWFDPWGQGTLVTVSS	853	GFTFSSYG	854	IWYNARKQ	855	TRGTGYNWFDP	856
CD38	DIVMAQSHKFMSTSVGDRVSITCKASQDVSTVVAWYQQKPGQSPKRLITSASYRYIGVPDRFTGSGSGTDFTFTISSVQAEDLAVTTCQQHYSPYTFGGGTKLEIK	857	ASQDVS	858	ITSA	859	TCQQHYSPYT	860	QVKLVESGGGLVKPGGSLKLSCEASGFTFSSYTLSWVRQTPETRLEWVATISIGGRYTTTPDSVEGRFTISRDNAKNTLYLQMNSLKSEDTAMYYCTRDFNGTSDFWGQGTTLTVSS	861	GFTFSSYT	862	ISIGGRYT	863	TRDFNGTSDF	864
CD38	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPTFGQGTKVEIK	865	QSVSSY	866	DAS	867	QQRSNWPPT	868	EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCAKDKILWFGEPVFDYWGQGTLVTVSS	869	GFTFNSFA	870	ISGSGGGT	871	AKDKILWFGEPVFDY	872
CD38	DIVMTQSHLSMSTSLGDPVSITCKASQDVSTVVAWYQQKPGQSPRRLIYSASYRYIGVPDRFTGSGAGTDFTFTISSVQAEDLAVYYCQQHYSPPYTFGGGTKLEIK	873	QDVSTV	874	SAS	875	QQHYSPPYT	876	QVQLVQSGAEVAKPGTSVKLSCKASGYTFTDYWMQWVKQRPGQGLEWIGTIYPGDGDTGYAQKFQGKATLTADKSSKTVYMHLSSLASEDSAVYYCARGDYYGSNSLDYWGQGTSVTVSS	877	GYTFTDYW	878	IYPGDGDT	879	ARGDYYGSNSLDY	880

CD4	DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSYIYWYQQKPGQPPKLLIYLASILESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQHSRELPWTFGQGTKVEIK	881	KSVSTSGYSY	882	LAS	883	QHSRELPWT	884	EEQLVESGGGLVKPGGSLRLSCAASGFSFSDCRMYWLRQAPGKGLEWIGVISVKSENYGANYAESVRGRFTISRDDSKNTVYLQMNSLKTEDTAVYYCSASYYRYDVGAWFAYWGQGTLVTVSS	885	GFSFSDCR	886	ISVKSENYGA	887	SASYYRYDVGAWFAYW	888
CD4	DIVMTQSPDSLAVSLGERVTMNCKSSQSLLYSTNQKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYSYRTFGGGTKLEIK	889	QSLLYSTNQKNY	890	WAS	891	QQYYSYRT	892	QVQLQQSGPEVVKPGASVKMSCKASGYTFTSYVIHWVRQKPGQGLDWIGYINPYNDGTDYDEKFKGKATLTSDTSTSTAYMELSSLRSEDTAVYYCAREKDNYATGAWFAYWGQGTLVTVSS	893	GYTFTSYV	894	INPYNDGT	895	AREKDNYATGAWFAY	896
CD40	DIQMTQSPSSLSASVGDRVTITCRSSQSLVHSNGNTFLHWYQQKPGKAPKLLIYTVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCSQTTHVPWTFGQGTKVEIK	897	QSLVHSNGNTF	898	TVS	899	SQTTHVPWT	900	EVQLVESGGGLVQPGGSLRLSCAASGYSFTGYYIHWVRQAPGKGLEWVARVIPNAGGTSYNQKFKGRFTLSVDNSKNTAYLQMNSLRAEDTAVYYCAREGIYWWGQGTLVTVSS	901	GYSFTGYY	902	VIPNAGGT	903	AREGIYW	904
CD40	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASNLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPTFGQGTKVEIK	905	QGISSA	906	DAS	907	QQFNSYPT	908	QLQLQESGPGLLKPSETLSLTCTVSGGSISSPGYYGGWIRQPPGKGLEWIGSIYKSGSTYHNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCTRPVVRYFGWFDPWGQGTLVTVSS	909	GGSISSPGYY	910	IYKSGST	911	TRPVVRYFGWFDP	912
CD40	DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSN	913	QSLLYSNGYN	914	LGS	915	MQARQTP	916	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMH	917	GFTFSSYG	918	ISYEESNR	919	ARDGGIAAPGP	920

	GYNYLDWYLQKPGQSPQVLISLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIR		Y				FT		WVRQAPGKGLEWVAVISYEESNRYHADSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDYWGQGTLVTVSS						DY	
CD40	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKVEIK	921	QGIYSW	922	TAS	923	QQANIFPLT	924	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSS	925	GYTFTGYY	926	INPDSGGT	927	ARDQPLGYCTNGVCSYFDY	928
CD40L	DIQMTQSPSSLSASVGDRVTITCRASEDLYYNLAWYQRKPGKAPKLLIYDTYRLADGVPSRFSGSGSGTDYTLTISSLQPEDFASYYCQQYYKFPFTFGQGTKVEIK	929	EDLYYN	930	DTY	931	QQYYKFPFT	932	EVQLVESGGGLVQPGGSLRLSCAVSGFSSTNYHVHWVRQAPGKGLEWMGVIWGDGDTSYNSVLKSRFTISRDTSKNTVYLQMNSLRAEDTAVYYCARQLTHYYVLAAWGQGTLVTVSS	933	GFSSTNYH	934	IWGDGDT	935	ARQLTHYYVLAA	936
CD40L	DIVLTQSPATLSVSPGERATISCRASQRVSSSTYSYMHWYQQKPGQPPKLLIKYASNLESGVPARFSGSGSGTDFTLTISSVEPEDFATYYCQHSWEIPPTFGGGTKLEIK	937	QRVSSSTYSY	938	YAS	939	QHSWEIPPT	940	QVQLVQSGAEVVKPGASVKLSCKASGYIFTSYYMYWVKQAPGQGLEWIGEINPSNGDTNFNEKFKSKATLTVDKSASTAYMELSSLRSEDTAVYYCTRSDGRNDMDSWGQGTLVTVSS	941	GYIFTSYY	942	INPSNGDT	943	TRSDGRNDMDS	944
CD49b (a2)	DFVMTQSPAFLSVTPGEKVTITCSAQSSVNYIHWYQQKPDQAPKKLIYDTSK	945	SSVNY	946	DTS	947	QQWTTNPLT	948	QVQLQESGPGLVKPSETLSLTCTVSGFSLTNYGIHWIRQPPGKGLEWLGVIWARGFTNYNSA	949	GFSLTNYG	950	IWARGFT	951	ARANDGVYYAMDY	952

	LASGVPSRFSGSGSGTDYTFTISSLEAEDAATYYCQQWTTNPLTFGQGTKVEIK								LMSRLTISKDNSKNQVSLKLSSVTAADTAVYYCARANDGVYYAMDYWGQGTLVTVSS							
CD51 (a5)	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKAPKLLIYYTSKIHSGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQGNTFPYTFGQGTKVEIK	953	QDISNY	954	YTS	955	QQGNTFPYT	956	QVQLQQSGGELAKPGASVKVSCKASGYTFSSFWMHWVRQAPGQGLEWIGYINPRSGYTEYNEIFRDKATMTTDTSTSTAYMELSSLRSEDTAVYYCASFLGRGAMDYWGQGTTVTVSS	957	GYTFSSFW	958	INPRSGYT	959	ASFLGRGAMDY	960
CD52	DIQMTQSPSSLSASVGDRVTITCKASQNIDKYLNWYQQKPGKAPKLLIYNTNNLQTGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCLQHISRPRTFGQGTKVEIK	961	QNIDKY	962	NTN	963	LQHISRPRT	964	QVQLQESGPGLVRPSQTLSLTCTVSGFTFTDFYMNWVRQPPGRGLEWIGFIRDKAKGYTTEYNPSVKGRVTMLVDTSKNQFSLRLSSVTAADTAVYYCAREGHTAAPFDYWGQGSLVTVSS	965	GFTFTDFY	966	IRDKAKGYTT	967	AREGHTAAPFDY	968
CD54(ICAM-1)	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSLSAWLFGGGTKLTVL	969	SSNIGAGYD	970	DNN	971	QSYDSSLSAWL	972	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVAFIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYSGWYFDYWGQGTLVTVSS	973	GFTFSNAW	974	IWYDGSNK	975	ARYSGWYFDY	976
CD56	DVVMTQSPLSLPVTLGQPASISCRSSQIIIHSDGNTYLEWFQQRPGQSPRRLIYKVSNRFSGVPDRFSGSGSGT	977	QIIIHSDGNTY	978	KVS	979	FQGSHVPHT	980	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVAYISSGSFTIYYADSVKGRFTISRDNSKNTLYLQ	981	GFTFSSFG	982	ISSGSFTI	983	ARMRKGYAMDY	984

	DFTLKISRVEAEDVGVYYCFQGSHVPHTFGQGTKVEIK								MNSLRAEDTAVYYCARMRKGYAMDYWGQGTLVTVSS							
CD61 (a4b3)	EIVLTQSPATLSLSPGERATLSCQASQSISNFLHWYQQRPGQAPRLLIRYRSQSISGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSGSWPLTFGGGTKVEIK	985	QSISNF	986	YRS	987	QQSGSWPLT	988	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVAKVSSGGGSTYYLDTVQGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHLHGSFASWGQGTTVTVSS	989	GFTFSSYD	990	VSSGGGST	991	ARHLHGSFAS	992
CD70	QAVVTQEPSLTVSPGGTVTLTCGLKSGSVTSDNFPTWYQQTPGQAPRLLIYNTNTRHSGVPDRFSGSILGNKAALTITGAQADDEAEYFCALFISNPSVEFGGGTQLTVL	993	SGSVTSDNF	994	NTN	995	ALFISNPSVEFGG	996	EVQLVESGGGLVQPGGSLRLSCAASGFTFSVYYMNWVRQAPGKGLEWVSDINNEGGTTYYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCARDAGYSNHVPIFDSWGQGTLVTVSS	997	GFTFSVYY	998	INNEGGTT	999	ARDAGYSNHVPIFDS	1000
CD73 (NT5E)	QSVLTQPPSASGTPGQRVTISCSGSLSNIGRNPVNWYQQLPGTAPKLLIYLDNLRLSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDDSHPGWTFGGGTKLTVL	1001	LSNIGRNP	1002	LDN	1003	ATWDDSHPGWT	1004	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAYSWVRQAPGKGLEWVSAISGSGGRTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLGYGRVDEWGRGTLVTVSS	1005	GFTFSSYA	1006	ISGSGGRT	1007	ARLGYGRVDE	1008
CD74	DIQLTQSPLSLPVTLGQPASISCRSSQSLVHRNGNTYLHWFQQRPGQSPRLLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFC	1009	QSLVHRNGNTY	1010	TVS	1011	SQSSHVPPT	1012	QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGVNWIKQAPGQGLQWMGWINPNTGEPTFDDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCSRSRGKNEA	1013	GYTFTNYG	1014	INPNTGEP	1015	SRSRGKNEAWFAY	1016

	SQSSHVPPTFGAGTRLEIK								WFAYWGQGTLVTVSS							
CEA	QTVLSQSPAILSASPGEKVTMTCRASSSVTYIHWYQQKPGSSPKSWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQHWSSKPPTFGGGTKLEIK	1017	SSVTY	1018	ATS	1019	QHWSSKPPT	1020	EVKLVESGGGLVQPGGSLRLSCATSGFTFTDYYMNWVRQPPGKALEWLGFIGNKANGYTTEYSASVKGRFTISRDKSQSILYLQMNTLRAEDSATYYCTRDRGLRFYFFDYWGQGTTLTVSS	1021	GFTFTDYY	1022	IGNKANGYTT	1023	TRDRGLRFYFDY	1024
CEA	DIQLTQSPSSLSASVGDRVTITCKASQDVGTSVAWYQQKPGKAPKLLIYWTSTRHTGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQYSLYRSFGQGTKVEIK	1025	QDVGTS	1026	WTS	1027	QQYSLYRS	1028	EVQLVESGGGVVQPGRSLRLSCASGFDFTTYWMSWVRQAPGKGLEWIGEIHPDSSTINYAPSLKDRFTISRDNAKNTLFLQMDSLRPEDTGVYFCASLYFGFPWFAYWGQGTPVTVSS	1029	GFDFTTYW	1030	IHPDSSTI	1031	ASLYFGFPWFAY	1032
Claudin-18.2	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPFTFGSGTKLEIK	1033	QSLLNSGNQKNY	1034	WAS	1035	QNDYSYPFT	1036	QVQLQQPGAELVRPGASVKLSCKASGYTFTSYWINWVKQRPGQGLEWIGNIYPSDSYTNYNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCTRSWRGNSFDYWGQGTTLTVSS	1037	GYTFTSYW	1038	IYPSDSYT	1039	TRSWRGNSFDY	1040
cMET	DIQMTQSPSSLSASVGDRVTITCKSSQSLLYTSSQKNYLAWYQQKPGKAPKLLIYWASTRESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYAYPWTFGQGTKVEIK	1041	QSLLYTSSQKNY	1042	WAS	1043	QQYYAYPWT	1044	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWLHWVRQAPGKGLEWVGMIDPSNSDTRFNPNFKDRFTISADTSKNTAYLQMNSLRAEDTAVYYCATYRSYVTPLDYWGQGTLVTVSS	1045	GYTFTSYW	1046	IDPSNSDT	1047	ATYRSYVTPLDY	1048

CRLR	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSTTLGITGLQTGDEADYYCGTWDSRLSAVVFGGGTKLTVL	1049	SSNIGNNY	1050	DNN	1051	GTWDSRLSAVV	1052	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVAVISFDGSIKYSVDSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDRLNYYDSSGYYHYKYYGMAVWGQGTTVTVSS	1053	GFTFSSFG	1054	ISFDGSIK	1055	ARDRLNYYDSSGYYHYKYYGMAV	1056
Dabigatran	DVVMTQSPLSLPVTLGQPASISCKSSQSLLYTDGKTYLYWFLQRPGQSPRRLIYLVSKLDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCLQSTHFPHTFGGGTKVEIK	1057	QSLLYTDGKTY	1058	LVS	1059	LQSTHFPHT	1060	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYIVDWIRQPPGKGLEWIGVIWAGGSTGYNSALRSRVSITKDTSKNQFSLKLSSVTAADTAVYYCASAAYYSYYNYDGFAYWGQGTLVTVSS	1061	GFSLTSYI	1062	IWAGGST	1063	ASAAYYSYYNYDGFAY	1064
DLL3	EIVMTQSPATLSVSPGERATLSCKASQSVSNDVVWYQQKPGQAPRLLIYYASNRYTGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQDYTSPWTFGQGTKLEIK	1065	QSVSND	1066	YAS	1067	QQDYTSPWT	1068	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYADDFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARIGDSSPSDYWGQGTLVTVSS	1069	GYTFTNYG	1070	INTYTGEP	1071	ARIGDSSPSDY	1072
DLL4	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRSNWPPTFGGGTKVEIK	1073	QSVSSY	1074	DAS	1075	QHRSNWPPT	1076	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVSFLWYDGTNKNYVESVKGRFTISRDNSKNMLYLEMNSLRAEDTAVYYCARDHDFRSGYEGWFDPWGQGTLVTVSS	1077	GFTFSSYG	1078	LWYDGTNK	1079	ARDHDFRSGYEGWFDP	1080
DLL4	DIVMTQSPDSLAVSLGERATIS	1081	ESVDN	1082	AAS	1083	QQSKEVP	1084	QVQLVQSGAEVKKPGASVKISCK	1085	GYSFTAY	1086	ISSYN	1087	ARDYDYDVG	1088

	CRASESVDNYGISFMKWFQQKPGQPPKLLIYAASNQGSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSKEVPWTFGGGTKVEIK		YGISF				WT		ASGYSFTAYYIHWVKQAPGQGLEWIGYISSYNGATNYNQKFKGRVTFTTDTSTSTAYMELRSLRSDDTAVYYCARDYDYDVGMDYWGQGTLVTVSS		Y		GAT		MDY	
DNA/histone (H1) complex	ENVLTQSPAIMSASPGEKVTMTCRASSSVSSSYLHWYQQKSGASPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISSVEAEDAATYYCQQYSGYPLTFGGGTKLEIK	1089	SSVSSSY	1090	STS	1091	QQYSGYPLT	1092	QVQLKESGPGLVAPSQSLSITCTVSGFSLTDYGVRWIRQPPGKGLEWLGVIWGGGSTYYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTAMYYCAKEKRRGYYYAMDYWGQGTSVTVSS	1093	GFSLTDYG	1094	IWGGGST	1095	AKEKRRGYYYAMDY	1096
EGFR	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELK	1097	QSIGTN	1098	YAS	1099	QQNNNWPTT	1100	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSA	1101	GFSLTNYG	1102	IWSGGNT	1103	ARALTYYDYEFAY	1104
EGFR	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGGGTKVEIK	1105	QDISNY	1106	DAS	1107	QHFDHLPLA	1108	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMVTVSS	1109	GGSVSSGDYY	1110	IYYSGNT	1111	VRDRVTGAFDI	1112
EGFR	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDAS	1113	QSVSSY	1114	DAS	1115	HQYGSTPLT	1116	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKGLEWIGYIYYSGSTDYN	1117	GGSISSGDYY	1118	IYYSGST	1119	ARVSIFGVGTFDY	1120

	NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGGGTKAEIKR								PSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVTVSS							
EGFR	DIQMTQSPSSLSASVGDRVTITCRSSQNIVHSNGNTYLDWYQQTPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCFQYSHVPWTFGQGTKLQIT	1121	QNIVHSNGNTY	1122	KVS	1123	FQYSHVPWT	1124	QVQLQQSGAEVKKPGSSVKVSCKASGYTFTNYYIYWVRQAPGQGLEWIGGINPTSGGSNFNEKFKTRVTITVDESTNTAYMELSSLRSEDTAFYFCARQGLWFDSDGRGFDFWGQGSTVTVSS	1125	GYTFTNYY	1126	INPTSGGS	1127	ARQGLWFDSDGRGFDFW	1128
EGFR	IQLTQSPSSLSASVGDRVTITCRASQDISSALVWYQQKPGKAPKLLIYDASSLESGVPSARFSGSESGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIK	1129	QDISSA	1130	DAS	1131	QQFNSYPLT	1132	QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVIWDDGSYKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMKDYFDYWGQGTLVTVSS	1133	GFTFSTYG	1134	IWDDGSYK	1135	ARDGITMVRGVMKDYFDY	1136
EGFR	DIQMTQSPSSLSASVGDRVTITCRASQDINNYLAWYQHKPGKGPKLLIHYTSTLHPGIPSRFSGSGSGRDYSFSISSLEPEDIATYYCLQYDNLLYTFGQGTKLEIK	1137	QDINNY	1138	YTS	1139	LQYDNLLYT	1140	QVQLVQSGAEVAKPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLECIGTIYPGDGDTTYTQKFQGKATLTADKSSSTAYMQLSSLRSEDSAVYYCARYDAPGYAMDYWGQGTLVTVSS	1141	GYTFTSYW	1142	IYPGDGDT	1143	ARYDAPGYAMDY	1144
EGFR	DIQMTQSPSSLSASVGDRVTITCSASSSVTYMYWYQQKPGKAPKLLIYDTSNLASGVPSRFSGSGSGTDYTFTI	1145	SSVTY	1146	DTS	1147	QQWSSHIFT	1148	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHWMHWVRQAPGQGLEWIGEFNPSNGRTNYNEKFKSKATMTVDTSTNTAY	1149	GYTFTSHW	1150	FNPSNGRT	1151	ASRDYDYDGRYFDY	1152

	SSLQPEDIATYYCQQWSSHIFTFGQGTKVEIK								MELSSLRSEDTAVYYCASRDYDYDGRYFDYWGQGTLVTVSS							
EGFR	DIQMTQSPSSLSASVGDRVTITCRASQGINNYLNWYQQKPGKAPKRLIYNTNNLQTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSFPTFGQGTKLEIK	1153	QGINNY	1154	NTN	1155	LQHNSFPT	1156	QVQLVQSGAEVKKPGSSVKVSCKASGFTFTDYKIHWVRQAPGQGLEWMGYFNPNSGYSTYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSPGGYYVMDAWGQGTTVTVSS	1157	GFTFTDYK	1158	FNPNSGYS	1159	ARLSPGGYYVMDAW	1160
EGFR HER3	DIQMTQSPSSLSASVGDRVTITCRASQNIATDVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSEPEPYTFGQGTKVEIK	1161	QNIATD	1162	SAS	1163	QQSEPEPYT	1164	EVQLVESGGGLVQPGGSLRLSCAASGFTLSGDWIHWVRQAPGKGLEWVGEISAAGGYTDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARESRVSFEAAMDYWGQGTLVTVSS	1165	GFTLSGDW	1166	ISAAGGYT	1167	ARESRVSFEAAMDY	1168
EGFRvIII	DILMTQSPSSMSVSLGDTVSITCHSSQDINSNIGWLQQRPGKSFKGLIYHGTNLDDEVPSRFSGSGSGADYSLTISSLESEDFADYYCVQYAQFPWTFGGGTKLEIKA	1169	QDINSN	1170	HGT	1171	VQYAQFPWT	1172	DVQLQESGPSLVKPSQSLSLTCTVTGYSITSDFAWNWIRQFPGNKLEWMGYISYSGNTRYNPSLKSRISITRDTSKNQFFLQLNSVTIEDTATYYCVTAGRGFPYWGQGTLVTVSS	1173	GYSITSDFA	1174	ISYSGNT	1175	VTAGRGFPY	1176
EGFRvIII	DIQMTQSPSSMSVSVGDRVTITCHSSQDINSNIGWLQQKPGKSFKGLIYHGTNLDDGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCVQYA	1177	QDINSN	1178	HGT	1179	VQYAQFPWT	1180	QVQLQESGPGLVKPSQTLSLTCTVSGYSISSDFAWNWIRQPPGKGLEWMGYISYSGNTRYQPSLKSRITISRDTSKNQFFLKLNSVTAADTATYYCVTAGRGFPYWGQG	1181	GYSISSDFA	1182	ISYSGNT	1183	VTAGRGFPY	1184

	QFPWTFGGGTKLEIK								TLVTVSS							
EpCAM	ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFGAGTKLEIK	1185	QSLLNSGNQKNY	1186	WAS	1187	QNDYSYPLT	1188	EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGHGLEWIGDIHFPGSGNIHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQGTTVTVSS	1189	ASGYAFTN	1190	GDIHFPGSG	1191	FCARLRNWDEPMDY	1192
EpCAM	ELQMTQSPSSLSASVGDRVTITCRTSQSISSYLNWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQPEDSATYYCQQSYDIPYTFGQGTKLEIK	1193	QSISSY	1194	WAS	1195	QQSYDIPYT	1196	EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDMGWGSGWRPYYYYGMDVWGQGTTVTVSS	1197	GFTFSSYG	1198	ISYDGSNK	1199	AKDMGWGSGWRPYYYYGMDV	1200
EpCAM	DIVLTQSPFSNPVTLGTSASISCRSTKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDRFSSSGSGTDFTLRISRVEAEDVGVYYCAQNLEIPRTFGGGTKLEIK	1201	KSLLHSNGITY	1202	QMS	1203	AQNLEIPRT	1204	QVKLQQSGPELKKPGETVKISCKASGYTFTNYGMNWVKQAPGKGLKWMGWINTYTGESTYADDFKGRFAFSLETSASAAYLQINNLKNEDTATYFCARFAIKGDYWGQGTTVTVSS	1205	GYTFTNYG	1206	INTYTGES	1207	ARFAIKGDY	1208
EpCAM	NIVMTQSPKSMSMSVGERVTLTCKASENVVTYVSWYQQKPEQSPKLLIYGASNRYTGVPDRFTGSGSATDFTLTISSVQAEDLADYHCGQGYSYPYTFGGGTK	1209	ENVVTY	1210	GAS	1211	GQGYSYPYT	1212	QVQLQQSGAELVRPGTSVKVSCKASGYAFTNYLIEWVKQRPGQGLEWIGVINPGSGGTNYNEKFKGKATLTADKSSSTAYMQLSSLTSDDSAVYFCARDGPWFAYWGQGTLVTVSA	1213	GYAFTNYL	1214	INPGSGGT	1215	ARDGPWFAY	1216

	LEIK															
EpCAM	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLITYGASTTASGIPARFSASGSGTDFTLTISSLQSEDFAVYYCQQYNNWPPAYTFGQGTKLEIK	1217	QSVSSN	1218	GAS	1219	QQYNNWPPAYT	1220	QVQLVQSGAEVKKPGSSVKVSCICASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGLLWNYWGQGTLVTVSS	1221	SGGTFSSY	1222	GIIPIFGT	1223	CARGLLWNY	1224
EphA3	DIQMTQSPSFLSASVGDRVTITCRASQGIISYLAWYQQKPEKAPKRLIYAASSLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCGQYANYPYTFGQGTKLEIK	1225	QGIISY	1226	AAS	1227	GQYANYPYT	1228	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYWMNWVRQAPGQGLEWMGDIYPGSGNTNYDEKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGGYYEDFDSWGQGTTVTVSS	1229	GYTFTGYW	1230	IYPGSGNT	1231	ARGGYYEDFDS	1232
ERGT(GalNAc) Tn Antigen	DIQLTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISSVEAEDLGVYFCSQSTHVPTFGGGTKLEIK	1233	QSLVHSNGNTY	1234	KVS	1235	SQSTHVPT	1236	QVQLQQSGGGLVQPGGSMKIFCAASGFTFSDAWMDWVRQSPEKGLEWVAEIRNKANNHETYYAESVKGRFTITRDDSKSRMSLQMNSLRAEDTGIYYCSGGKVRNAYWGQGTTVTVSS	1237	GFTFSDAW	1238	IRNKANNHET	1239	SGGKVRNAY	1240
FLT1	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIK	1241	QSVSSSY	1242	GAS	1243	QQYGSSPLT	1244	QAQVVESGGGVVQSGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVRGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDHYGSGVHHYFYYGLDVWGQGTTVTVSS	1245	GFAFSSYG	1246	IWYDGSNK	1247	ARDHYGSGVHHYFYYGLDV	1248

FOLR1	DIQLTQSPSSLSASVGDRVTITCSVSSSISSNNLHWYQQKPGKAPKPWIYGTSNLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSYPYMYTFGQGTKVEIK	1249	SSISSNN	1250	GTS	1251	QQWSSYPYMYT	1252	EVQLVESGGGVVQPGRSLRLSCSASGFTFSGYGLSWVRQAPGKGLEWVAMISSGGSYTYYADSVKGRFAISRDNAKNTLFLQMDSLRPEDTGVYFCARHGDDPAWFAYWGQGTPVTVSS	1253	GFTFSGYG	1254	ISSGGSYT	1255	ARHGDDPAWFAYW	1256
FOLR1	DIVLTQSPLSLAVSLGQPAIISCKASQSVSFAGTSLMHWYHQKPGQQPRLLIYRASNLEAGVPDRFSGSGSKTDFTLTISPVEAEDAATYYCQQSREYPYTFGGGTKLEIK	1257	QSVSFAGTSL	1258	RAS	1259	QQSREYPYT	1260	QVQLVQSGAEVVKPGASVKISCKASGYTFTGYFMNWVKQSPGQSLEWIGRIHPYDGDTFYNQKFQGKATLTVDKSSNTAHMELLSLTSEDFAVYYCTRYDGSRAMDYWGQGTTVTVSS	1261	GYTFTGYF	1262	IHPYDGDT	1263	TRYDGSRAMDY	1264
frizzled family receptor (FZD)	DIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLG	1265	NIGSFY	1266	DKS	1267	QSYANTLSLV	1268	EVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGKGLEWVSVISGDGSYTYYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLVTVSS	1269	GFTFSHYT	1270	ISGDGSYT	1271	ARNFIKYVFAN	1272
Lewis Y	DVLMTQIPVSLPVSLGDQASISCRSSQIIVHNNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPFTFGSGTKLEIK	1273	QIIVHNNGNTY	1274	KVS	1275	FQGSHVPFT	1276	EVNLVESGGGLVQPGGSLKVSCVTSGFTFSDYYMYWVRQTPEKRLEWVAYISQGGDITDYPDTVKGRFTISRDNAKNSLYLQMSRLKSEDTAMYYCARGLDDGAWFAYWGQGTLVTVSV	1277	GFTFSDYY	1278	ISQGGDIT	1279	ARGLDDGAWFAY	1280
Lewis Y	DIQMTQSPSSLSASVGDRVTIT	1281	QRIVHS	1282	KVS	1283	FQGSHVPF	1284	EVQLVESGGGVVQPGRSLRLSCSTS	1285	GFTFSDY	1286	MSNV	1287	ARGTRDGSWF	1288

	CRSSQRIVHSNGNTYLEWYQQTPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCFQGSHVPFTFGQGTKLQIT		NGNTY				T		GFTFSDYYMYWVRQAPGKGLEWVAYMSNVGAITDYPDTVKGRFTISRDNSKNTLFLQMDSLRPEDTGVYFCARGTRDGSWFAYWGQGTPVTVSS		Y		GAIT		AY	
Lewis X	DIVMTQAAFSNPVTLGTSASISCRSSKSLLYSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDRFSSSGSGTDFTLRISRVEAEDVGVYYCAQNLEVPWTFGGGTKLEIK	1289	KSLLYSNGITY	1290	QMS	1291	AQNLEVPWT	1292	EVKLLESGGGLVQPGGSQKLSCAASGFDFSGYWMSWVRQAPGKGLEWIGEINPDSSTINYTPSLKDKFIISRDNAKNTLYLQMSKVRSEDTALYYCARETGTRFDYWGQGTTLTVSS	1293	SGFDFSGY	1294	EINPDSST	1295	CARETGTRFDY	1296
GCGR	DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQSGVPSRFSGSGSGTEFILTVSSLQPEDFATYYCLQYNSNPFTFGPGTKVDIK	1297	QGIRND	1298	AAS	1299	LQYNSNPFT	1300	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYLMNWVRQAPGKGLEWLANIQEDGIEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREPSHYDILTGYDYYYGMDVWGQGTTVTVSS	1301	GFTFSNYL	1302	IQEDGIEK	1303	AREPSHYDILTGYDYYYGMDV	1304
GD2	EIVMTQSPATLSVSPGERATLSCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIHKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPPLTFGAGTKLELK	1305	QSLVHRNGNTY	1306	KVS	1307	SQSTHVPPLT	1308	EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGAIDPYYGGTSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGMEYWGQGTSVTVSS	1309	GSSFTGYN	1310	IDPYYGGT	1311	VSGMEY	1312
GD2	SIVMTQTPKFLLVSAGDRVTITCKASQSVSNDVTWYQQKAG	1313	QSVSND	1314	SAS	1315	QQDYSS	1316	QVQLKESGPGLVAPSQSLSITCTVSGFSVTNYGVHWVRQPPGKGLEWL	1317	GFSVTNYG	1318	IWAGGIT	1319	ASRGGHYGYALDY	1320

	QSPKLLIYSAS NRYSGVPDRF TGSGYGTAFT FTISTVQAEDL AVYFCQQDYS SFGGGTKLEIK								GVIWAGGITNYN SAFMSRLSISKDN SKSQVFLKMNSL QIDDTAMYYCAS RGGHYGYALDY WGQGTSVTVSS							
GD2	EIVMTQTPATL SVSAGERVTIT CKASQSVSND VTWYQQKPG QAPRLLIYSAS NRYSGVPARF SGSGYGTEFTF TISSVQSEDFA VYFCQQDYSS FGQGTKLEIK	1321	QSVSN D	1322	SAS	1323	QQD YSS	1324	QVQLVESGPGVV QPGRSLRISCAVS GFSVTNYGVHW VRQPPGKGLEWL GVIWAGGITNYN SAFMSRLTISKDN SKNTVYLQMNSL RAEDTAMYYCA SRGGHYGYALD YWGQGTLVTVSS	1325	GFSV TNY G	1326	IWAG GIT	1327	ASRGG HYGYA LDY	1328
GD2 o-acetyl	DVVMTQTPLS LPVSLGDQASI SCRSSQSLLKN NGNTFLHWYL QKSGQSPKLLI YKVSNRLSGV PDRFSGSGSGT YFTLKISRVEA EDLGVYFCSQ STHIPYTFGGG TKLELK	1329	QSLLK NNGNT F	1330	KVS	1331	SQST HIPY T	1332	EVKLVESGGGLV LPGDSLRLSCATS KFTFTDYYMTW VRQPPRKALEQL GFIRNRANGYTT EYNPSVKGRFTIS RDNSQSILYLQM NTLRTEDSATYY CARVSNWAFDY WGQGTTLTVSS	1333	KFTF TDY Y	1334	IRNRA NGYT T	1335	ARVSN WAFDY	1336
GD3	DIQMTQITSSL SVSLGDRVIIS CRASQDIGNFL NWYQQKPDG SLKLLIYYTSR LQSGVPSRFSG WGSGTDYSLT ISNLEEEDIATF FCQQGKTLPY TFGGGTKLEIK	1337	GFTFSN FG	1338	ISSG GSSI	1339	TRG GTGT RSLY YFD Y	1340	DVQLVESGGGLV QPGGSRKLSCAA SGFTFSNFGMHW VRQAPEKGLEW VAYISSGGSSINY ADTVKGRFTISR DNPKNTLFLQMT SLRSEDTAIYYCT RGGTGTRSLYYF DYWGQGATLIVS S	1341	QDIG NF	1342	YTS	1343	QQGKT LP	1344
GD3	DIQMTQTASS LPASLGDRVTI SCSASQDISNY LNWYQQKPD GTVKLLIFYSS NLHSGVPSRFS GGGSGTDYSL TISNLEPEDIAT	1345	QDISN Y	1346	YSS	1347	HQY SKLP WT	1348	EVTLVESGGDFV KPGGSLKVSCAA SGFAFSHYAMSW VRQTPAKRLEW VAYISSGGSGTY YSDSVKGRFTISR DNAKNTLYLQM RSLRSEDSAMYF	1349	GFAF SHY A	1350	ISSGG SGT	1351	TRVKL GTYYF DS	1352

	YFCHQYSKLPWTFGGGTKLEIK								CTRVKLGTYYFDSWGQGTTLTVSS							
GM1	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPPTFGGGTKVEIK	1353	QGISSW	1354	AAS	1355	QQYNSYPPT	1356	EVQLVESGGGLVQPGESLRLSCVASGFTFSRYKMNWVRQAPGKGLEWVSYISRSGRDIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAGTVTTYYYYFGMDVWGHGTTVTVSS	1357	GFTFSRYK	1358	ISRSGRDI	1359	AGTVTTYYYYFGMDV	1360
GM1 fucosyl	DIQMTQSPSSLSASVGDRVTITCRASQGISWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPPTFGGGTKVEIK	1361	QGISW	1362	AAS	1363	QQYNSYPPT	1364	EVQLVESGGGLVQPGESLRLSCVASGFTFSRYKMNWVRQAPGKGLLEWVSYISRSGRDIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAGTVTTYYYYFGMDVWGHGTTVTVSS	1365	GFTFSRYK	1366	YISRSGRD	1367	CAGTVTTYYYYFGMDV	1368
GM1 fucosyl	DIQMTQSPSSLASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISCLQPEDFATYYCQQYNSYPPTFGGGTKVEIK	1369	QGISSW	1370	AAS	1371	QQYNSYPPT	1372	EVQLVESGGGLVQPGESLRLSCVVSGFTFSRYKMNWVRQAPGKGLEWISYISRSGRDIYYADSVKGRFTISRDNAKNSLYLQMSSLRDEDTAVYYCAGTVTTYYYYFGMDVWGLGITVTVSS	1373	GFTFSRYK	1374	ISRSGRDI	1375	AGTVTTYYYYFGMDVWG	1376
GM1 fucosyl	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPPTFGGGTKVEI	1377	QGISSW	1378	AA	1379	QQYNSYPPT	1380	EVQLVESGGGSVQPGESLRLSCVASGFTFSRYKMNWVRQAPGKGLEWVSYISRSGRDIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAGTVTTYYYDFGMDVWGQGTTV	1381	GFTFSRYK	1382	ISRSGRDI	1383	AGTVTTYYYDFGMDV	1384

	K								TVSS							
GM2	QIVLTQSPAIMSASPGEKVTITCSASSSVSYMHWFQQKPGTSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSYPYTFGGGTKLEIK	1385	SSVSY	1386	STS	1387	QQRSSYPYT	1388	EVQLQQSGPELVKPGASVKISCKASGYTFTDYNMDWVKQSHGKSLEWIGYIYPNNGGTGYNQKFKSKATLTVDKSSSTAYMELHSLTSEDSAVYYCATYGHYYGYMFAYWGQGTLVTVSA	1389	GYTFTDYN	1390	IYPNNGGT	1391	ATYGHYYGYMFAY	1392
GPA33	DIVMTQSQKFMSTSVGDRVSITCKASQNVRTVVAWYQQKPGQSPKTLIYLASNRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWSYPLTFGSGTKLEVK	1393	QNVRTV	1394	LAS	1395	LQHWSYPLT	1396	EVKLVESGGGLVKPGGSLKLSCAASGFAFSTYDMSWVRQTPEKRLEWVATISSGGSYTYYLDSVKGRFTISRDSARNTLYLQMSSLRSEDTALYYCAPTTVVPFAYWGQGTLVTVSA	1397	GFAFSTYD	1398	ISSGGSYT	1399	APTTVVPFAY	1400
GPNMB	EIVMTQSPATLSVSPGERATLSCRASQSVDNNLVWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPPWTFGQGTKVEIK	1401	QSVDNN	1402	GAS	1403	QQYNNWPPWT	1404	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSFNYYWSWIRHHPGKGLEWIGYIYYSGSTYSNPSLKSRVTISVDTSKNQFSLTLSSVTAADTAVYYCARGYNWNYFDYWGQGTLVTVSS	1405	GGSISSFNYY	1406	IYYSGST	1407	ARGYNWNYFDY	1408
GUCY2C	EIVMTQSPATLSVSPGERATLSCRASQSVSRNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTIGSLQSEDFAVYYCQQYKTWPRTFGQGTNVEIK	1409	QSVSRN	1410	GAS	1411	QQYKTWPRT	1412	QVQLQQWGAGLLKPSETLSLTCAVFGGSFSGYYWSWIRQPPGKGLEWIGEINHRGNTNDNPSLKSRVTISVDTSKNQFALKLSSVTAADTAVYYCARERGYTYGNFDHWGQGTLVTVSS	1413	GGSFSGYY	1414	INHRGNT	1415	ARERGYTYGNFDH	1416

HER2	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQAYTTPPTFGQGTKVEIK	1417	QDVNTA	1418	SAS	1419	QQAYTTPPT	1420	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS	1421	GFNIKDTY	1422	IYPTNGYT	1423	SRWGGDGFYAMDY	1424
HER2	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK	1425	QDVNTA	1426	SAS	1427	QQHYTTPPT	1428	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS	1429	GFNIKDTY	1430	IYPTNGYT	1431	SRWGGDGFYAMDY	1432
HER2	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIK	1433	QDVSIG	1434	SAS	1435	QQYYIYPYT	1436	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGGSIYNQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSS	1437	GFTFTDYT	1438	VNPNSGGS	1439	ARNLGPSFYFDYW	1440
HER2	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYGVHWYQQLPGTAPKLLIYGNTNRPSGVPDRFSGFKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTKLTVL	1441	SSNIGAGYG	1442	GNT	1443	QSYDSSLSGWV	1444	QVQLVESGGGLVQPGGSLRLSCAASGFTFRSYAMSWVRQAPGKGLEWVSAISGRGDNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKMTSNAFAFDYWGQGTLVTVSS	1445	GFTFRSYA	1446	ISGRGDNT	1447	AKMTSNAFAFDY	1448
HER3	QSALTQPASVSGSPGQSITISC	1449	SSDVG	1450	EVS	1451	CSYAGSSI	1452	EVQLLESGGGLVQPGGSLRLSCAA	1453	GFTFSHY	1454	ISSSG	1455	TRGLKMATIF	1456

	TGTSSDVGSYNVVSWYQQHPGKAPKLIIYEVSQRPSGVSNRFSGSKSGNTASLTISGLQTEDEADYYCCSYAGSSIFVIFGGGTKVTVL		SYNV				FVI		SGFTFSHYVMAWVRQAPGKGLEWVSSISSSGGWTLYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRGLKMATIFDYWGQGTLVTVSS		V		GWT		DY	
HER3	DIQMTQSPSSLSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSFPTTFGQGTKVEIK	1457	QGISNW	1458	GAS	1459	QQYSSFPTT	1460	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINSQGKSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWGDEGFDIWGQGTLVTVSS	1461	GFTFSSYA	1462	INSQGKST	1463	ARWGDEGFDI	1464
HER3	DIEMTQSPDSLAVSLGERATINCRSSQSVLYSSSNRNYLAWYQQNPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPRTFGQGTKVEIK	1465	QSVLYSSSNRNY	1466	WAS	1467	QQYYSTPRT	1468	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVETSKNQFSLKLSSVTAADTAVYYCARDKWTWYFDLWGRGTLVTVSS	1469	GGSFSGYY	1470	INHSGST	1471	ARDKWTWYFDL	1472
HER3	DIVMTQSPDSLAVSLGERATINCKSSQSVLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQSDYSYPYTFGQGTKLEIK	1473	QSVLNSGNQKNY	1474	WAS	1475	QSDYSYPYT	1476	QVQLVQSGAEVKKPGASVKVSCKASGYTFRSSYISWVRQAPGQGLEWMGWIYAGTGSPSYNQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARHRDYYSNSLTYWGQGTLVTVSS	1477	GYTFRSSY	1478	IYAGTGSP	1479	ARHRDYYSNSLTY	1480
HER3	YELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPG	1481	SLRSYY	1482	GKN	1483	NSRDSPGNQWV	1484	QVQLVQSGGGLVQPGGSLRLSCAASGFTFDDYAMHWVRQAPGKGLE	1485	GFTFDDYA	1486	ISWDSGST	1487	ARDLGAYQWVEGFD	1488

	QAPVLVIYGK NNRPSGIPDRF SGSTSGNSASL TITGAQAEDE ADYYCNSRDS PGNQWVFGG GTKVTVL								WVAGISWDSGST GYADSVKGRFTI SRDNAKNSLYLQ MNSLRAEDTALY YCARDLGAYQW VEGFDYWGQGT LVTVSS						Y	
HGFR (cMET)	DIVMTQSPDSL AVSLGERATIN CKSSESVDSY ANSFLHWYQQ KPGQPPKLLIY RASTRESGVP DRFSGSGSGT DFTLTISSLQA EDVAVYYCQ QSKEDPLTFG GGTKVEIK	1489	ESVDS YANSF	1490	RAS	1491	QQS KEDP LT	1492	QVQLVQSGAEV KKPGASVKVSCK ASGYIFTAYTMH WVRQAPGQGLE WMGWIKPNNGL ANYAQKFQGRV TMTRDTSISTAY MELSRLRSDDTA VYYCARSEITTEF DYWGQGTLVTV SS	1493	GYIF TAY T	1494	IKPNN GLA	1495	ARSEIT TEFDY	1496
HGFR (cMET)	DIQMTQSPSSL SASVGDRVTIT CSVSSSVSSIY LHWYQQKPG KAPKLLIYSTS NLASGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQVYSGYP LTFGGGTKVEI K	1497	SSVSSI Y	1498	STS	1499	QVY SGYP LT	1500	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTDYYM HWVRQAPGQGL EWMGRVNPNRR GTTYNQKFEGRV TMTTDTSTSTAY MELRSLRSDDTA VYYCARANWLD YWGQGTTVTVSS	1501	GYTF TDY Y	1502	VNPN RRGT	1503	ARAN WLDY	1504
IgHe	DIQLTQSPSSL SASVGDRVTIT CRASQSVDYD GDSYMNWYQ QKPGKAPKLLI YAASYLESGV PSRFSGSGSGT DFTLTISSLQP EDFATYYCQQ SHEDPYTFGQ GTKVEIK	1505	QSVDY DGDSY	1506	AAS	1507	QQS HEDP YT	1508	EVQLVESGGGLV QPGGSLRLSCAV SGYSITSGYSWN WIRQAPGKGLE WVASITYDGSTN YNPSVKGRITISR DDSKNTFYLQM NSLRAEDTAVYY CARGSHYFGHW HFAVWGQGTLV TVSS	1509	GYSI TSGY S	1510	ITYDG ST	1511	ARGSH YFGHW HFAV	1512
IgHe	EIVMTQSPATL SVSPGERATLS CRASQSIGTNI HWYQQKPGQ APRLLIYYASE SISGIPARFSGS	1513	QSIGTN	1514	YAS	1515	QQS WSW PTT	1516	QVQLVQSGAEV MKPGSSVKVSCK ASGYTFSWYWL EWVRQAPGHGL EWMGEIDPGTFT TNYNEKFKARVT	1517	GYTF SWY W	1518	IDPGT FTT	1519	ARFSH FSGSN YDYFD YW	1520

	GSGTEFTLTIS SLQSEDFAVY YCQQSWSWPT TFGGGTKVEI K								FTADTSTSTAYM ELSSLRSEDTAV YYCARFSHFSGS NYDYFDYWGQG TLVTVSS							
IGLF2	QSVLTQPPSVS AAPGQKVTIS CSGSSSNIENN HVSWYQQLPG TAPKLLIYDN NKRPSGIPDRF SGSKSGTSATL GITGLQTGDE ADYYCETWD TSLSAGRVFG GGTKLTVL	1521	SSNIEN NH	1522	DNN	1523	ETW DTSL SAGR V	1524	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYDIN WVRQATGQGLE WMGWMNPNSG NTGYAQKFQGR VTMTRNTSISTA YMELSSLRSEDT AVYYCARDPYY YYYGMDVWGQ GTTVTVSS	1525	GYTF TSYD	1526	MNPN SGNT	1527	ARDPY YYYYG MDV	1528
Kallikreins	DIQMTQSPSTL SASVGDRVTIT CRASQSISSWL AWYQQKPGK APKLLIYKAST LESGVPSRFSG SGSGTEFTLTI SSLQPDDFAT YYCQQYNTY WTFGQGTKVE IK	1529	QSISSW	1530	KAS	1531	QQY NTY WT	1532	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSHYIMMW VRQAPGKGLEW VSGIYSSGGITVY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CAYRRIGVPRRD EFDIWGQGTMVT VSS	1533	GFTF SHYI	1534	IYSSG GIT	1535	AYRRI GVPRR DEFDI	1536
KIRDL1/2/3	EIVLTQSPVTL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNW MYTFGQGTKL EIK	1537	QSVSS Y	1538	DAS	1539	QQRS NWM YT	1540	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSFYAIS WVRQAPGQGLE WMGGFIPIFGAA NYAQKFQGRVTI TADESTSTAYME LSSLRSDDTAVY YCARIPSGSYYY DYDMDVWGQGT TVTVSS	1541	GGTF SFYA	1542	FIPIFG AA	1543	ARIPSG SYYYD YDMD V	1544
LINGO1	DIQMTQSPAT LSLSPGERATL SCRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV	1545	QSVSS Y	1546	DAS	1547	QQRS NWP MYT	1548	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSAYEMKW VRQAPGKGLEW VSVIGPSGGFTFY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY	1549	GFTF SAYE	1550	IGPSG GFT	1551	ATEGD NDAFD I	1552

	YYCQQRSNWPMYTFGQGTKLEIK								CATEGDNDAFDIWGQGTTVTVSS							
LOXL2	DIVMTQTPLSLSVTPGQPASISCRSSKSLLHSNGNTYLYWFLQKPGQSPQFLIYRMSNLASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQHLEYPYTFGGGTKVEIK	1553	KSLLHSNGNTY	1554	RMS	1555	MQHLEYPYT	1556	QVQLVQSGAEVKKPGASVKVSCKASGYAFTYYLIEWVRQAPGQGLEWIGVINPGSGGTNYNEKFKGRATITADKSTSTAYMELSSLRSEDTAVYFCARNWMNFDYWGQGTTVTVSS	1557	GYAFTYYL	1558	INPGSGGT	1559	ARNWMNFDY	1560
Ly6/PLAUR domain-containing protein 3	ESVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDRLNGPVFGGGTKLTVL	1561	SSNIGAGYV	1562	DNN	1563	AAWDDRLNGPV	1564	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGLWAFDYWGQGTLVTVSS	1565	GFTFSNAW	1566	ISSSGSTI	1567	AREGLWAFDY	1568
MADCAM1	DIVMTQTPLSLSVTPGQPASISCKSSQSLLHTDGTTYLYWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQNIQLPWTFGQGTKVEIK	1569	QSLLHTDGTTY	1570	EVS	1571	MQNIQLPWT	1572	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGINWVRQAPGQGLEWMGWISVYSGNTNYAQKVQGRVTMTADTSTSTAYMDLRSLRSDDTAVYYCAREGSSSSGDYYYGMDVWGQGTTVTVSS	1573	GYTFTSYG	1574	ISVYSGNT	1575	AREGSSSGDYYYGMDV	1576
MAG	DIVMTQSPDSLAVSLGERATINCKSSHSVLYSSNQKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYLSSLTF	1577	HSVLYSSNQKNY	1578	WAS	1579	HQYLSSLT	1580	QVQLVQSGSELKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYADDFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPINYYGINYEGYVMDYW	1581	GYTFTNYG	1582	INTYTGEP	1583	ARNPINYYGINYEGYVMDY	1584

	GQGTKLEIK								GQGTLVTVSS							
Mesothelin	DIALTQPASVSGSPGQSITISCTGTSSDIGGYNSVSWYQQHPGKAPKLMIYGVNNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYDIESATPVFGGGTKLTVL	1585	SSDIGGYNS	1586	GVN	1587	SSYDIESATPV	1588	QVELVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQAPGKGLEWMGIIDPGDSRTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGQLYGGTYMDGWGQGTLVTVSS	1589	GYSFTSYW	1590	IDPGDSRT	1591	ARGQLYGGTYMDG	1592
Mesothelin	DIELTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPGRFSGSGSGNSYSLTISSVEAEDDATYYCQQWSKHPLTFGSGTKVEIK	1593	SSVSY	1594	DTS	1595	QQWSKHPLT	1596	QVQLQQSGPELEKPGASVKISCKASGYSFTGYTMNWVKQSHGKSLEWIGLITPYNGASSYNQKFRGKATLTVDKSSSTAYMDLLSLTSEDSAVYFCARGGYDGRGFDYWGSGTPVTVSS	1597	GYSFTGYT	1598	ITPYNGAS	1599	ARGGYDGRGFDY	1600
MT1-MMP (MMP14)	DIQMTQSPSSLSASVGDRVTITCKASQDVRNTVAWYQQKPGKAPKLLIYSSSYRNTGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHYITPYTFGGGTKVEIK	1601	QDVRNT	1602	SSS	1603	QQHYITPYT	1604	QVQLQESGPGLVKPSETLSLTCTVSGFSLLSYGVHWVRQPPGKGLEWLGVIWTGGTTNYNSALMSRFTISKDDSKNTVYLKMNSLKTEDTAIYYCARYYYGMDYWGQGTLVTVSS	1605	GFSLLSYG	1606	IWTGGTT	1607	ARYYYGMDY	1608
MUC1	DIQLTQSPSSLSASVGDRVTMTCSASSSVSSSYLYWYQQKPGKAPKLWIYSTSNLASGVPARFSGSGSGTDFTLTISSLQPEDSASYFCHQWNRYPYTFGGGTRLEIK	1609	SSVSSSY	1610	STS	1611	HQWNRYPYT	1612	QVQLQQSGAEVKKPGASVKVSCEASGYTFPSYVLHWVKQAPGQGLEWIGYINPYNDGTQYNEKFKGKATLTRDTSINTAYMELSRLRSDDTAVYYCARGFGGSYGFAYWGQGTLVTVSS	1613	GYTFPSYV	1614	INPYNDGT	1615	ARGFGGSYGFAY	1616

Mucin 5AC	QVVLTQSPVI MSASPGEKVT MTCSASSSISY MYWYQQKPG TSPKRWIYDTS KLASGVPARF SGSGSGTSYSL TISNMEAGDA ATYYCHQRDS YPWTFGGGTN LEIK	1617	SSISY	1618	DTS	1619	HQR DSYP WT	1620	QVQLKESGPDLV APSQSLSITCTVS GFSLSKFGVNWV RQPPGKGLEWLG VIWGDGSTSYNS GLISRLSISKENS KSQVFLKLNSLQ ADDTATYYCVKP GGDYWGHGTSV TVSS	1621	GFSL SKFG	1622	IWGD GST	1623	VKPGG DY	1624
NaPi2b	DIQMTQSPSSL SASVGDRVTIT CRSSETLVHSS GNTYLEWYQ QKPGKAPKLLI YRVSNRFSGV PSRFSGSGSGT DFTLTISSLQP EDFATYYCFQ GSFNPLTFGQ GTKVEIK	1625	ETLVH SSGNT Y	1626	RVS	1627	FQGS FNPL T	1628	EVQLVESGGGLV QPGGSLRLSCAA SGFSFSDFAMSW VRQAPGKGLEW VATIGRVAFHTY YPDSMKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCARHRGFDV GHFDFWGQGTL VTVSS	1629	GFSF SDFA	1630	IGRVA FHT	1631	ARHRG FDVGH FDF	1632
NeuGc-GM3	DIVMTQSHKF MSTSVGDRVS ITCKASQDVST AVAWYQQKP GQSPKLLIYSA SYRYTGVPDR FTGSGSGTDFT FTISSVQAEDL AVYYCQQHYS TPWTFGGGTK LELK	1633	QDVST A	1634	SAS	1635	QQH YSTP WT	1636	EVQLKESGPGLV APSQSLSITCTVS GFSLSRYSVHWV RQPPGKGLEWLG MIWGGGSTDYNS ALKSRLSISKDNS KSQVFLKMNSLQ TDDTAMYYCAR SGVREGRAQAW FAYWGQGTLVT VSA	1637	GFSL SRYS	1638	IWGG GST	1639	ARSGV REGRA QAWFA Y	1640
NKG2A	DIQMTQSPSSL SASVGDRVTIT CRASENIYSYL AWYQQKPGK APKLLIYNAK TLAEGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQHHYGTP RTFGGGTKVEI K	1641	ENIYSY	1642	NAK	1643	QHH YGTP RT	1644	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYWM NWVRQAPGQGL EWMGRIDPYDSE THYAQKLQGRV TMTTDTSTSTAY MELRSLRSDDTA VYYCARGGYDF DVGTLYWFFDV WGQGTTVTVSS	1645	GYTF TSY W	1646	IDPYD SET	1647	ARGGY DFDVG TLYWF FDV	1648
notch	QAVVTQEPSL TVSPGGTVTL	1649	TGAVT	1650	GTN	1651	ALW YSN	1652	QVQLVQSGAEV KKPGASVKISCK	1653	GAS VKIS	1654	ILPGT	1655	ARFDG NYGYY	1656

	TCRSSTGAVTTSNYANWFQQKPGQAPRTLIGGTNNRAPGVPARFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNHWVFGGGTKLTV		TSNY				HWV		VSGYTLRGYWIEWVRQAPGKGLEWIGQILPGTGRTNYNEKFKGRVTMTADTSTDTAYMELSSLRSEDTAVYYCARFDGNYGYYAMDYWGQGTTVTVSS		CKVS		GRT		AMDYW	
NOTCH2/NOTCH3 receptors	DIVLTQSPATLSLSPGERATLSCRASQSVRSNYLAWYQQKPGQAPRLLIYGASSRATGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYSNFPITFGQGTKVEIK	1657	QSVRSNY	1658	GAS	1659	QQYSNFPIT	1660	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSGMSWVRQAPGKGLEWVSVIASSGSNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSIFYTTWGQGTLVTVSS	1661	GFTFSSSG	1662	IASSGSNT	1663	ARSIFYTT	1664
NRP1	DIQMTQSPSSLSASVGDRVTITCRASQYFSSYLAWYQQKPGKAPKLLIYGASSRASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLGSPPTFGQGTKVEIK	1665	QYFSSY	1666	GAS	1667	QQYLGSPPT	1668	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYYRMSKVMDVWGQGTLVTVSS	1669	GFTFSSYA	1670	ISPAGGYT	1671	ARGELPYYRMSKVMDV	1672
oxLDL	QSVLTQPPSASGTPGQRVTISCSGSNTNIGKNYVSWYQQLPGTAPKLLIYANSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCASWDASLNGWVFGGGTKLTVL	1673	NTNIGKNY	1674	ANS	1675	ASWDASLNGWV	1676	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSSISVGGHRTYYADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCARIRVGPSGGAFDYWGQGTLVTVSS	1677	GFTFSNAW	1678	ISVGGHRT	1679	ARIRVGPSGGAFDY	1680
P-selectin	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG	1681	QSVSSY	1682	DAS	1683	QQRSNWPLT	1684	EVQLVESGGGLVRPGGSLRLSCAASGFTFSNYDMHWVRQATGKGLE	1685	GFTFSNYD	1686	ITAAGDI	1687	ARGRYSGSGSYYND	1688

	QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK								WVSAITAAGDIYYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARGRYSGSGSYYNDWFDPWGQGTLVTVSS						WFDP	
PCSK9	DIVMTQSPDSLAVSLGERATINCKSSQSVLYRSNNRNFLGWYQQKPGQPPNLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYTTPYTFGQGTKLEIK	1689	QSVLYRSNNRNF	1690	WAS	1691	QQYYTTPYT	1692	EVQLVESGGGLVQPGGSLRLSCAASGFTFNNYAMNWVRQAPGKGLDWVSTISGSGGTTNYADSVKGRFIISRDSSKHTLYLQMNSLRAEDTAVYYCAKDSNWGNFDLWGRGTLVTVSS	1693	GFTFNNYA	1694	ISGSGGTT	1695	AKDSNWGNFDL	1696
PCSK9	ESALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKAPKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCNSYTSTSMVFGGGTKLTVL	1697	SSDVGGYNS	1698	EVS	1699	NSYTSTSMV	1700	EVQLVQSGAEVKKPGASVKVSCKASGYTLTSYGISWVRQAPGQGLEWMGWVSFYNGNTNYAQKLQGRGTMTTDPSTSTAYMELRSLRSDDTAVYYCARGYGMDVWGQGTTVTVSS	1701	GYTLTSYG	1702	VSFYNGNT	1703	ARGYGMDV	1704
PCSK9	DIQMTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQRYSLWRTFGQGTKLEIK	1705	QGISSA	1706	SAS	1707	QQRYSLWRT	1708	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGEISPFGGRTNYNEKFKSRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARERPLYASDLWGQGTTVTVSS	1709	GYTFTSYY	1710	ISPFGGRT	1711	ARERPLYASDL	1712
PDGFRA	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFS	1713	QSVSSY	1714	DAS	1715	QQRSNWPPA	1716	QLQLQESGPGLVKPSETLSLTCTVSGGSINSSSYYWGWLRQSPGKGLEWIGSFFYTGSTYYNPSLRSRLTISV	1717	GGSINSSSYY	1718	FFYTGST	1719	ARQSTYYYGSGNYYGWFDR	1720

	GSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPAFGQGTKVEIK								DTSKNQFSLMLSSVTAADTAVYYCARQSTYYYGSGNYYGWFDRWDQGTLVTVSS							
PDGFRa	DIQMTQSPSSLSASVGDRVSITCRPSQSFSRYINWYQQKPGKAPKLLIHAASSLVGGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYSNPPITFGQGTRLEMK	1721	QSFSRY	1722	AAS	1723	QQTYSNPPIT	1724	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMNWIRQAPGKGLEWVSYISSSGSIIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGRIAARGMDVWGQGTTVTVSS	1725	GFTFSDYY	1726	ISSSGSII	1727	AREGRIAARGMDV	1728
phosphatidylserine	DIQMTQSPSSLSASLGERVSLTCRASQDIGSSLNWLQQGPDGTIKRLIYATSSLDSGVPKRFSGSRSGSDYSLTISSLESEDFVDYYCLQYVSSPPTFGAGTKLELK	1729	QDIGSS	1730	ATS	1731	LQYVSSPPT	1732	EVQLQQSGPELEKPGASVKLSCKASGYSFTGYNMNWVKQSHGKSLEWIGHIDPYYGDTSYNQKFRGKATLTVDKSSSTAYMQLKSLTSEDSAVYYCVKGGYYGHWYFDVWGAGTTVTVSS	1733	GYSFTGYN	1734	IDPYYGDT	1735	VKGGYYGHWYFDV	1736
polysialic acid	DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLYWYLQKPGQSPKPLIYRVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCFQGTHVPYTFGGGTRLEIK	1737	QSLVHSNGNTY	1738	RVS	1739	FQGTHVPYT	1740	QIQLQQSGPELVRPGASVKISCKASGYTFTDYYIHWVKQRPGEGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSSTAYMQLSSLTSEDSAVYFCARGGKFAMDYWGQGTSVTVSS	1741	GYTFTDYY	1742	IYPGSGNT	1743	ARGGKFAMDY	1744
PSMA	DIVMTQSHKFMSTSVGDRVSIICKASQDVGTAVDWYQQKPGQSPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTITNVQSED	1745	QDVGTA	1746	WAS	1747	QQYNSYPLTFGAGTM	1748	EVQLQQSGPELVKPGTSVRISCKTSGYTFTEYTIHWVKQSHGKSLEWIGNINPNNGGTTYNQKFEDKATLTVDKSSSTAYMELRSLTSEDSAVYYCA	1749	GYTFTEYT	1750	INPNNGGT	1751	AAGWNFDY	1752

	LADYFCQQYNSYPLTFGAGTMLDLK								AGWNFDYWGQGTTLTVSS							
PSMA	DIQMTQSPSSLSASVGDRVTITCKASQNVDTNVAWYQQKPGQAPKSLIYSASYRYSDVPSRFSGSASGTDFTLTISSVQSEDFATYYCQQYDSYPYTFGGGTKLEIK	1753	QNVDTN	1754	SAS	1755	QQYDSYPYT	1756	QVQLVESGGGLVKPGESLRLSCAASGFTFSDYYMYWVRQAPGKGLEWVAIISDGGYYTYYSDIIKGRFTISRDNAKNSLYLQMNSLKAEDTAVYYCARGFPLLRHGAMDYWGQGTLVTVSS	1757	GFTFSDYY	1758	ISDGGYYT	1759	ARGFPLLRHGAMDY	1760
PVRL4	DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGGGTKVEIK	1761	QGISGW	1762	AAS	1763	QQANSFPPT	1764	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLSLQMNSLRDEDTAVYYCARAYYYGMDVWGQGTTVTVSS	1765	GFTFSSYN	1766	ISSSSSTI	1767	ARAYYYGMDV	1768
RGMA	QSALTQPRSVSGSPGQSVTISCTGTSSSVGDSIYVSWYQQHPGKAPKLMLYDVTKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCYSYAGTDTLFGGGTKVTVL	1769	SSSVGDSIY	1770	DVT	1771	YSYAGTDTL	1772	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSHGISWVRQAPGQGLDWMGWISPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELSSLRSEDTAVYYCARVGSGPYYYMDVWGQGTLVTVSS	1773	GYTFTSHG	1774	ISPYSGNT	1775	ARVGSGPYYYMDV	1776
CD240D Blood group D antigen	AIRMTQSPSSFSASTGDRVTITCRASQDIRNYVAWYQQKSGKAPKFLIYAASTLQSGVPSRFSGSGSGTDFTLTINSLQSEDFATYYCQQYYNSPPTFGQGTRVEI	1777	QDIRNY	1778	AAS	1779	QQYYNSPPT	1780	QVQLVESGGGVVQPGRSLRLSCTASGFTFKNYAMHWVRQAPAKGLEWVATISYDGRNIQYADSVKGRFTFSRDNSQDTLYLQLNSLRPEDTAVYYCARPVRSRWLQLGLEDAFHIWGQ	1781	GFTFKNYA	1782	ISYDGRNI	1783	ARPVRSRWLQLGLEDAFHI	1784

	T								GTMVTVSS								
root plate-specific spondin 3	DIQMTQSPSSLSASVGDRVTITCKASQSVDYDGDSYMNWYQQKPGKAPKLLIYAASNLESGVPSRFSGSGSGTDFTLTISPVQAEDFATYYCQQSNEDPLTFGAGTKLELK	1785	QSVDYDGDSY	1786	AAS	1787	QQSNEDPLT	1788	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYSIHWVRQAPGQGLEWIGYIYPSNGDSGYNQKFKNRVTMTRDTSTSTAYMELSRLRSEDTAVYYCATYFANNFDYWGQGTTLTVSS	1789	GYTFTDYS	1790	IYPSNGDS	1791	ATYFANNFDYW	1792
serum amyloid P component	DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLIHNAKTLAEGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQHHYGAPLTFGQGTKLEIK	1793	ENIYSY	1794	NAK	1795	QHHYGAPLT	1796	QVQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWMGYIYPGDGNANYNQQFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWGQGTLVTVSS	1797	GFTFATYN	1798	IYPGDGNA	1799	ARGDFDYDGGYYFDS	1800
STEAP-1	DIQMTQSPSSLSASVGDRVTITCKSSQSLLYRSNQKNYLAWYQQKPGKAPKLLIYWASTRESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNYPRTFGQGTKVEIK	1801	QSLLYRSNQKNY	1802	WAS	1803	QQYYNYPRT	1804	EVQLVESGGGLVQPGGSLRLSCAVSGYSITSDYAWNWVRQAPGKGLEWVGYISNSGSTSYNPSLKSRFTISRDTSKNTLYLQMNSLRAEDTAVYYCARERNYDYDDYYYAMDYWGQGTLVTVSS	1805	GYSITSDYA	1806	ISNSGST	1807	ARERNYDYDDYYYAMDY	1808
TACSTD2	DIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQKPGKAPKLLIYSASYRYTGVPDRFSGSGSGTDFTLTISSLQPEDFAVYYCQQHYITPLTFGAGTKVEIK	1809	QDVSIA	1810	SAS	1811	QQHYITPLT	1812	QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCARGGFGSSYWYFDVWGQGSLVTVSS	1813	GYTFTNYG	1814	INTYTGEP	1815	ARGGFGSSYWYFDV	1816

TGFb	ETVLTQSPGTLSLSPGERATLSCRASQSLGSSYLAWYQQKPGQAPRLLIYGASSRAPGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYADSPITFGQGTRLEIK	1817	QSLGSSY	1818	GAS	1819	QQYADSPIT	1820	QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQRFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSS	1821	GYTFSSNV	1822	VIPIVDIA	1823	ASTLGLVLDAMDY	1824
TIGIT	DIVMTQSPDSLAVSLGERATINCKSSQTVLYSSNNKKYLAWYQQKPGQPPNLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPFTFGPGTKVEIK	1825	QTVLYSSNNKKY	1826	WAS	1827	QQYYSTPFT	1828	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGKTYYRFKWYSDYAVSVKGRITINPDTSKNQFSLQLNSVTPEDTAVFYCTRESTTYDLLAGPFDYWGQGTLVTVSS	1829	GDSVSSNSAA	1830	TYYRFKWYS	1831	TRESTTYDLLAGPFDY	1832
TWEAKR	DIQMTQSPSSLSASVGDRVTITCRASQSVSTSSYSYMHWYQQKPGKAPKLLIKYASNLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQHSWEIPYTFGGGTKVEIK	1833	QSVSTSSYSY	1834	YAS	1835	QHSWEIPYT	1836	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVAEIRLKSDNYATHYAESVKGRFTISRDDSKNSLYLQMNSLRAEDTAVYYCTGYYADAMDYWGQGTLVTVSS	1837	GFTFSSYW	1838	IRLKSDNYAT	1839	TGYYADAMDY	1840
TYRP1	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWLMYTFGQGTKLEIK	1841	QSVSSSY	1842	DAS	1843	QQRSNWLMYT	1844	QVQLVQSGSELKKPGASVKISCKASGYTFTSYAMNWVRQAPGQGLESMGWINTNTGNPTYAQGFTGRFVFSMDTSVSTAYLQISSLKAEDTAIYYCAPRYSSSWYLDYWGQGTLVTVSS	1845	GYTFTSYA	1846	INTNTGNP	1847	APRYSSSWYLDY	1848
VEGFR2	DIQMTQSPSSLSASVGDRVTIT	1849	QDIAG	1850	ATS	1851	LQYGSFP	1852	EVQLVESGGGLVQPGGSLRLSCAA	1853	GFTF	1854	ITSGG	1855	VRIGE	1856

	CRASQDIAGSLNWLQQKPGKAIKRLIYATSSLDSGVPKRFSGSRSGSDYTLTISSLQPEDFATYYCLQYGSFPPTFGQGTKVEIK		S				PT		SGFTFSSYGMSWVRQAPGKGLEWVATITSGGSYTYYVDSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRIGEDALDYWGQGTLVTVSS		SSYG		SYT		DALDY	
VEGFR2	DIQMTQSPSSVSASIGDRVTITCRASQGIDNWLGWYQQKPGKAPKLLIYDASNLDTGVPSRFSGSGSGTYFTLTISSLQAEDFAVYFCQQAKAFPPTFGGGTKVDIK	1857	QGIDNW	1858	DAS	1859	QQAKAFPPT	1860	EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARVTDAFDIWGQGTMVTVSS	1861	GFTFSSYS	1862	ISSSSSYI	1863	ARVTDAFDI	1864
VSIR	DIQMTQSPSSLSASVGDRVTITCRASQSIDTRLNWYQQKPGKAPKLLIYSASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSAYNPITFGQGTKVEIK	1865	QSIDTR	1866	SAS	1867	QQSAYNPIT	1868	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSSYGWSYEFDYWGQGTLVTVSS	1869	GGTFSSYA	1870	IIPIFGTA	1871	ARSSYGWSYEFDY	1872
CD171 (L1CAM)	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSSNQKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLALYYCQQYHSYPFTFGSGTKLEIK	1873	QSLLYSSNQKNY	1874	WAS	1875	QQYHSYPFT	1876	QVQLQQPGDELVKPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLEWIGEINPSNGRTNYNEMFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCALYDGYYAMDYWGQGTSVTVSS	1877	GYTFTSYW	1878	INPSNGRT	1879	ALYDGYYAMDY	1880
CD171 (L1CAM)	DIQMTQSSSSFSVSLGDRVTITCKANEDINNRLAWYQQTPG	1881	EDINNR	1882	GAT	1883	QQYWSTPFT	1884	QVQLQQPGAELVKPGASVKLSCKASGYTFTGYWMHWVKQRPGHGLE	1885	GYTFTGYW	1886	INPSNGRT	1887	ARDYYGTSYNFDY	1888

	NSPRLLISGATNLVTGVPSRFSGSGSGKDYTLTITSLQAEDFATYYCQQYWSTPFTFGSGTELEIK								WIGEINPSNGRTNYNERFKSKATLTVDKSSTTAFMQLSGLTSEDSAVYFCARDYYGTSYNFDYWGQGTTLTVSS							
CD19	EIVLTQSPAIMSASPGERVTMTCSASSGVNYMHWYQQKPGTSPRRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEPEDAATYYCHQRGSYTFGGGTKLEIK	1889	SGVNY	1890	DTS	1891	HQRGSYT	1892	QVQLVQPGAEVVKPGASVKLSCKTSGYTFTSNWMHWVKQAPGQGLEWIGEIDPSDSYTNYNQNFQGKAKLTVDKSTSTAYMEVSSLRSDDTAVYYCARGSNPYYYAMDYWGQGTSVTVSS	1893	GYTFTSNW	1894	IDPSDSYT	1895	ARGSNPYYYAMDY	1896
CD28	DIQMTQSPSSLSASVGDRVTITCHASQNIYVWLNWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGQTYPYTFGGGTKVEIK	1897	QNIYVW	1898	KAS	1899	QQGQTYPYT	1900	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYIHWVRQAPGQGLEWIGCIYPGNVNTNYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFCTRSHYGLDWNFDVWGQGTTVTVSS	1901	GYTFTSYY	1902	IYPGNVNT	1903	TRSHYGLDWNFDV	1904
CD4	DIQMTQSPSSLSASLGGKVTIACKASQDINNYIAWYQHKPGKGPRLLIYHTSTLQPGIPSRFSGSGSGRDYSFSISNLEPEDIATYYCIQYNDLFLTTFGGGTKLEIK	1905	QDINNY	1906	HTS	1907	IQYNDLFLTT	1908	EVILVESGGAIVEPGGSLKLSCSASGFTFSNYAMSWVRQTPEKRLEWVAAISDHSTNTYYPDSVKGRFTISRDNAKNTLYLQMNSLRSEDTAIYYCARKYGGDYDPEDYWGQGTTLTVSS	1909	GFTFSNYA	1910	ISDHSTNT	1911	ARKYGGDYDPEDY	1912
CD47	DVLMTQTPLSLPVSLGDQASISCRSSQSIVYSNGNTYLGWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGS	1913	QSIVYSNGNTY	1914	KVS	1915	FQGSHVPYT	1916	QVQLQQPGAELVKPGASVMMSCKASGYTFTNYNMHWVKQTPGQGLEWIGTIYPGNDDTSYNQKFKDKATLTADKSSSAAYM	1917	GYTFTNYN	1918	IYPGNDDT	1919	ARGGYRAMDY	1920

	GTDFTLKISRVEAEDLGVYHCFQGSHVPYTFGGGTKVEIK								QLSSLTSEDSAVYYCARGGYRAMDYWGQGTSVTVSS							
CD8	DVQINQSPSFLAASPGETITNCRTSRSISQYLAWYQEKPGKTNKLLIYSGSTLQSGIPSRFSGSGSGTDFTLTISGLEPEDFAMYYCQQHNENPLTFGAGTKLELK	1921	RSISQY	1922	SGS	1923	QQHNENPLT	1924	QVQLQQSGAELVKPGASVKLSCTASGFNIKDTYIHFVRQRPEQGLEWIGRIDPANDNTLYASKFQGKATITADTSSNTAYMHLCSLTSGDTAVYYCGRGYGYYVFDHWGQGTTLTVSS	1925	GFNIKDTY	1926	IDPANDNT	1927	GRGYGYYVFDH	1928
KIR2DL2	EIVLTQSPVTLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWMYTFGQGTKLEIK	1929	QSVSSY	1930	DAS	1931	QQRSNWMYT	1932	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSFYAISWVRQAPGQGLEWMGGFIPIFGAANYAQKFQGRVTITADESTSTAYMELSSLRSDDTAVYYCARIPSGSYYYDYDMDVWGQGTTVTVSS	1933	GGTFSFYA	1934	FIPIFGAA	1935	ARIPSGSYYYDYDMDV	1936
pMHC[NY-ESO1]	QSELTQPRSVSGSPGQSVTISCTGTSRDVGGYNYVSWYQQHPGKAPKLIIHDVIERSSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCWSFAGSYYVFGTGTDVTVL	1937	SRDVGGYNY	1938	DVI	1939	WSFAGSYYV	1940	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYQMSWVRQAPGKGLEWVSGIVSSGGSTAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGELLPYYGMDVWGQGTTVTVSS	1941	GFTFSTYQ	1942	IVSSGGST	1943	AGELLPYYGMDV	1944
pMHC[MART1]	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYD	1945	SSNIGAGYD	1946	GNS	1947	QSYDNSLSSWV	1948	EVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADKSTSAYMELSSLRSEDTAVYYCARDVGSGSYSLDY	1949	GGTFSSYA	1950	IIPILGIA	1951	ARDVGSGSYSLDY	1952

	NSLSSWVFGG GTKLTVL								WGQGTLVTVSS							
pMHC[MAGEA 1]	SYVLTQPPSVS VAPGQTARIT CGGNNIGSRS VHWYQQKPG QAPVLVVYDD SDRPSGIPERF SGSNSGNMAT LTISRVEAGDE ADYYCQVWD SRTDHWVFGG GTDLTVL	1953	NIGSRS	1954	DDS	1955	QVW DSRT DHW V	1956	EVQLVESGGGLV QPGRSLRLSCAA SGFTFDDYAMH WVRQAPGKGLE WVSGISWNSGSI GYADSVKGRFTI SRDNAKNSLYLQ MNSLRAEDTAV YYCARGRGFHY YYYGMDIWGQG TTVTVSS	1957	GFTF DDY A	1958	ISWNS GSI	1959	ARGRG FHYYY YGMDI	1960
pMHC[T yrosinase]	EVILTQSPLSL PVTPGEPASIS CRSSQSLLHSI GYNYLDWYL QKPGQSPQLLI YLGSNRASGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCM QALQTPLTFG GGTKVEIK	1961	QSLLH SIGYN	1962	LGS	1963	MQA LQTP LT	1964	EVQLVESGGGVV QPGRSLRLSCAA SGFTFRSYGMHW VRQAPGKGLEW VAVISYDGSNKY YTDSVNGRFTISR DNSKNTLYQMN SLRAEDTAVYYC ARGGGYYETSGP DYWGQGTLVTV SS	1965	GFTF RSY G	1966	ISYDG SNK	1967	ARGGG YYETS GPDY	1968
pMHC[T yrosinase]	DVVMTQSPLS PVTPGEPASIS CRSSQSLLHSN GHNYLDWYL QKPGQSQLLIY LGSNRSGVPD RFSGSGSGTDF TLKISRVEAED VGVYYCMQT LQTPLTFGPGT KVDIK	1969	QSLLH SNGHN Y	1970	LGS	1971	MQT LQTP LT	1972	EVQLVETGGGVV QPGRSLRLSCAA SGFTFSSYGMHW VRQAPGKGLEW VAVISYDGSNKY YADSVKGRFTIS DNSKNTLYLQM NSLRAEDTAVYY CAKDRYGWGSS FGHDYWGQGTL TVSS	1973	GFTF SSYG	1974	ISYDG SNK	1975	AKDRY GWGSS FGHDY	1976
pMHC[g p100]	QSVLTQPPSVS AAPGQTVTISC SGSSSNIGRNY VSWFQQVPGR APKLLIYDNN QRPSGIPGRFS ASKSDTSATL DITGLQSGDE AVYYCGTWD STLDLYVFGG	1977	SSNIGR NY	1978	DNN	1979	GTW DSTL DLY V	1980	EVQLVQSGAEVK KPGASVKVSCKA SGYTFTSYYIHW VRQAPGQGLEW MGAINPSGGSTP YAQKFQGRVTM TRDTSTSTVYME LSSLRSEDTAVY YCARDGTYGSGS YPYYYYGMDV	1981	GYTF TSYY	1982	INPSG GST	1983	ARDGT YGSGS YPYYY YGM DV	1984

	GTHVPVL								WGQGTTVTVSS								
pMHC[MUC1]	ETTLTQSPGTLSLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQQGTKVEIK	1985	ASQSVSS	1986	IYGA	1987	YCQQYGSSPRT	1988	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGPEYCINGVCSLDVWGQGTTVTVSS	1989	GGTFSSYA	1990	IIPIFGTA	1991	ARGPEYCINGVCSLDV	1992
pMHC[MUC1]	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSSPQTFGQGTKVEIK	1993	QSVSSSY	1994	DAS	1995	HQYGSSPQT	1996	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAVHYGDYVFSSMDVWGQGTTVTVSS	1997	GGTFSSYA	1998	IIPIFGTA	1999	AVHYGDYVFSSMDV	2000
pMHC[tax]	EIVLTQSPATLSLSPGERATLSCRASQSVGSYLAWYQQKPGXAPRLLIYDASHRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPMYTFGQGTKLEIK	2001	QSVGSSY	2002	DAS	2003	QQRSNWPPMYT	2004	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYTISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADKSTSTSTAYMELSSLRSEDTAVYYCAGDTDSSGYYGAVDYWGQGTLVTVSS	2005	GGTFSSYT	2006	IIPIFGTA	2007	YCAGDTDSSGYYGAVDY	2008
pMHC[gp100]	NFMLTQPHSVSESPGKTVTISCTGSGGSIDNNYVHWYQQRPGSAPTTVMFEDNQRPSGVPDRFSGSIDSSSNSASLVISGLKTEDEGDYYCQSSDGSKVVFGGGTKLTVL	2009	GGSIDNNY	2010	EDN	2011	QSSDGSKVV	2012	EVQLVQSGGGVVQPGRSLTLSCAASGFTFSSYGMHWVRQAPGKGLEWVSVISYDGSNKYYADSVKGRFTISRDNSKNTLYLMNSLRTEDTAVYYCAKTLSAGEWIGGGAFDIWGHGTMVTVSS	2013	GFTFSSYG	2014	ISYDGSNK	2015	AKTLSAGEWIGGGAFDI	2016

pMHC[NY-ESO1]	DIVMTQSPDSLAVSLGERVTINCKSSQSLLYTSNNRNYLAWYQLKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISGLQAEDVAVYYCQQYYKSPLFGQGTKLEIK	2017	QSLLYTSNNRNY	2018	WAS	2019	QQYYKSPL	2020	QVQLQESGPGLVKPSQTLALTCSVIGGSISSGDYYWSWIRQPPGKGLEWVGYISDSGSTYNEPSLNSRVTISVDTSKNQFSLKLFSMTAADTAVYYCARVRIQGASWGFFDLWGRGTLVSVSS	2021	GGSISSGDYY	2022	ISDSGST	2023	ARVRIQGASWGFFDL	2024
pMHC[NY-ESO1]	EIVMTQSPATLSVSPGERATLSCRASQSFSDDLAWYQQKPGQAPRLLIYAASTRATGIPARFSGRGSGTEFTLTISSLQSEDSAVYYCQQYNNWPQTFGQGTKVEIK	2025	QSFSDD	2026	AAS	2027	QQYNNWPQT	2028	QVQLVQSGVEVKKPGASVKVSCKASGYTFASYGISWVRQAPGQGLEWMGWISVYNGKTNPAERHLGRVTMTTDTSTNTAYMELRNLKSDDTAVYYCAREGGFYGSGSHYRYFAMDVWGQGTTVIVSS	2029	GYTFASYG	2030	ISVYNGKT	2031	AREGGFYGSGSHYRYFAMDV	2032
pMHC[NY-ESO1]	DIVMTQTPLSLPVTLGQPASLSCRSSQSLVFTDGNTYLNWFQQRPGQSPRRLIYKVSSRDPGVPDRFSGTGSGTDFTLEISRVEAEDIGVYYCMQGTHWPPIFGQGTKVEIK	2033	QSLVFTDGNTY	2034	KVS	2035	MQGTHWPPI	2036	QVQLVQSGGGVVRPGGSLRLSCAASGFSFIDYGMSWVRQVPGKGLEWVAGMNWSGDKKGHAESVKGRFIISRDNAKNTLYLEMSSLRVEDTALYFCARGEYSNRFDPRGRGTLVTVSS	2037	GFSFIDYG	2038	MNWSGDKK	2039	ARGEYSNR	2040
pMHC[NY-ESO1]	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLGWYQQKPGQAPRLLIYGASIRATGIPDRFSGSGSGTDFTLTISRLEPDDFAVYYCQHYDNSLITFGHGTRLDIK	2041	QSVSSSY	2042	GAS	2043	QHYDNSLITFGHGTR	2044	EVQLQESGPGLVKPSETLSLTCTVSGGSISSDYWTWIRQPAGKGLEWIGRIYPRGTSNYNPSLKSRVTMSVDTSKNQISLRLSSVTAADTAVYYCAREYYYVTNGYFSPGFDYWGQGTLVTVSS	2045	GGSISSDY	2046	IYPRGTS	2047	AREYYYVTNGYFSPGFDY	2048

pMHC[NY-ESO1]	DIVMTQSPLSLPVTPGEPASISCRSSQSLHSNGYNYLDWYLQKPGQSPQLLIYLVSNRASGVPDRFSGTGSGTDFTLKISRVEAEDVGVYYCMQAVQTPFTFGPGTKVDIK	2049	QSLHSNGYNY	2050	LVS	2051	MQAVQTPFT	2052	EVQLVESGGGVVQPGKSLRLSCAASGFIFSSFAVHWVRQAPGKGLEWVATISSDGSNEDYVDSVKGRFIISRDNSKNTLYLQMNSLRRDDTAVYYCGTGHSTEYYDGLLGVWGHGTTVSVSS	2053	GFIFSSFA	2054	ISSDGSNE	2055	GTGHSTEYYDGLLGV	2056
pMHC[MART1]	QSVVTQPPSVSAAPGRKVTISCSGSSSNIGSNYVSWYQQVPGTAPKLLIYEDDKRPSGIPDRFSGSKGTSATLGITGLQTGDEADYFCATWDRTVNVVRFGGGTRLTV	2057	SSNIGSNY	2058	EDD	2059	ATWDRTVNVVR	2060	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWGSIYYSGTYYNPSLKSRVTISVDTSKNQFSLKLSSTAADTAVYYCARHVGHELDYWGQGTLVTVSS	2061	GGSISSSSYY	2062	IYYSGT	2063	ARHVGHELDY	2064
pMHC[Tyrosinase]	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSIGYNYLHWFLQKGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPPTFGQGTRLEIK	2065	QSLLHSIGYNY	2066	LGS	2067	MQALQTPPT	2068	QLQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISDKSKNQFSLKLSSVTAADTAVYYCVGSPYGDYVLDYWGQGTLVTVSS	2069	GGSISSSNW	2070	IYHSGST	2071	VGSPYGDYVLDY	2072
pMHC[WT-1]	QAVVTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQVPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTKLTVL	2073	SSNIGSNT	2074	SNN	2075	AAWDDSLNGWV	2076	QMQLVQSGAEVKEPGESLRISCKGSGYSFTNFWISWVRQMPGKGLEWMGRVDPGYSYSTYSPSFQGHVTISADKSTSTAYLQWNSLKASDTAMYYCARVQYSGYYDWFDPWGQGTLVTVSS	2077	GYSFTNFW	2078	VDPGYSYS	2079	ARVQYSGYYDWFDP	2080
pMHC[E	DIVMTQSQKFMSTSVGDRVS	2081	QNVHT	2082	LAS	2083	LQHWNN	2084	QVQLKESGPGLVAPSQSLSITCTVS	2085	GFSLTGY	2086	IWGD	2087	ARDPYGYIFD	2088

BNA-1]	ITCKASQNVH TAVAWYQQK AGQSPKALIYL ASNRHTGVPD RFTGSGSGTDF TLTISNVQSED LADYFCLQHW NNPLTFGAGT KLELK		A				PLT		GFSLTGYGVNW VRQPPGKGLEWL GMIWGDGSTDY NSALKSRLSISKD NSKSQVFLKMNS LQTDDTARYYCA RDPYGYIFDYWG QGTTLTVSS		G		GST		Y	
pMHC[LMP2]	DIVMTQSQKF MSTSVGDRVS VTCRASQNVF TNVAWYQQK PGQAPKALIYS TSYRYSGVPD RFTGSGSGTDF TLTISNVQSED LAEYFCQQYIS YPLTFGAGTK LELK	2089	QNVFTN	2090	STS	2091	QQYISYPLT	2092	QVQLKQSGPGLV QPSQSLSITCTVS GFSLTNYGVHW VRQSPGKGLEwl GVIWSGGSTDYN AAFISRLSISKDN SKQVFFKMNSLQ ANDTAIYYCARN WVPYYFDYWGQ GTTLTVSS	2093	GFSLTNYG	2094	IWSGGST	2095	ARNWVPYYFDY	2096
pMHC[gp100]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSN YLAWYQQKP GQAPRLLIYA ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS SRSFGQGTKL EIK	2097	QSVSSNY	2098	AAS	2099	QQYGSSRS	2100	QVQLQESGGGLV KPGGSLRLSCAA SGFTFSSYSMNW VRQAPGKGLEW VSYISSSGSTIYY ADSVRGRFTISRD NAKNTLYLQMN SLRAEDTAVYYC VRGDPYFFYYYG MDIWGQGTTVT VSS	2101	GFTFSSYS	2102	ISSSGSTI	2103	VRGDPYFFYYYGMDI	2104
pMHC[gp100]	DIQLTQSPSSL SASVGDRVIIT CRATQSISTHL NWYQQKPGK APKLLIYSASS LQSGVPSRFSG SGSGSTDFTLT ISSLQPEDFAT YYCQQSYSSP PITFGQGTRLE IK	2105	QSISTH	2106	SAS	2107	QQSYSSPPIT	2108	QVQLQESGPGLV KPSETLSLTCTVS GGSISSNMYYWG WVRQPPGKGLE WIGSIDYSGSTYY NPSLRSRVTMSV DTSKKQFSLKMT SVTAADTAVYYC ARESGSPYYFDY WGQGTLVTVSS	2109	GGSISSNMYY	2110	IDYSGST	2111	ARESGSPYYFDY	2112
pMHC[hTERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG	2113	QSVSSSY	2114	GAS	2115	QQYGTSLTWY	2116	QVQLQESGPGLV KPSETLSLTCTVS GGSISSSSYYWA WIRQPPGKLEWI	2117	GGSISSSSYY	2118	WINHSGST	2119	ARVVAAAGHYYYY	2120

	QAPRLLIYGAS TRATGVPDRF SGSGSGTDFTL ISRLEPEDFAV YYCQQYGTSL TWYFGQGTK VEIK								GEWINHSGSTNY NPSLKSRVTISVD TSKNQFSLNLNS VTAADTAVYYC ARVVAAAGHYY YYYMDVWGKGT TVTVSS						MDV	
pMHC[h TERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSR YLAWYQQKP GQAPRLLIYG ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS SNTFGQGTKL EIK	2121	QSVSS RY	2122	GAS	2123	QQY GSSN T	2124	QVQLQESGPGLV KPSETLSLTCTVS GGSISSSYYWGW IRQPPGKGLEWIG SIYYSGSTYYNPS LKSRVTISVDTSK NQFSLKLSSVTA ADTAVYYCARSR SGSYLNDAFDIW GQGTMVTVSS	2125	GGSI SSSY Y	2126	IYYSG ST	2127	ARSRS GSYLN DAFDI	2128
pMHC[h TERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSS GTFGQGTKVE IK	2129	QSVSSS Y	2130	GAS	2131	QQY GSSS GT	2132	QVQLQQSGAEV KKPGSSVKVSCK ASGGTFSSYAIS WVRQAPGQGLE WMGRIIPILGIAN YAQKFQGRVTIT ADKSTSTAYMEL SSLRSEDTAVYY CARGFRPYYYYG MDVWGQGTTVT VSS	2133	GGTF SSYA	2134	IIPILG IA	2135	ARGFR PYYYY GMDV	2136
pMHC[g p100]	QSVVTQPPSVS GAPGQRVTISC TGSSSNIGAGY DVHWYQQLP GTAPKLLIYG NSNRPSGVPD RFSGSKSGTSA SLAITGLQAED EADYYCQSYD SSLSALFGGGT KLTVL	2137	SSNIGA GYD	2138	GNS	2139	QSY DSSL SAL	2140	QVQLQQSGPGLV KPSETLSLTCTVS GGSIRNYYWSWI RQPPGKGLEWIG YMYYSGGANYN PSLNSRVTISLDT SKNQFSLKLTSV TAADTAVYYCA RIPNYYDRSGYY PGYWYFDLWGR GTLVTVSS	2141	GGSI RNY Y	2142	MYYS GGA	2143	ARIPNY YDRSG YYPGY WYFDL	2144
pMHC[g p100]	DIQLTQSPSSL SASVGDRVTIT CRASQSISTYL NWYQHRPGK APKLLIYSASS LQSGVPSRFSG	2145	QSISTY	2146	SAS	2147	QQS DIIPL T	2148	QVQLQQSGPGLV KPSQTLSLTCAIS GDSISSNSVVWN WIRQSPSRGLEW LGRTYYRSKWY NDYAVSVKSRITI	2149	GDSI SSNS VV	2150	TYYR SKWY N	2151	ARASF GTSGK FDD	2152

	SGSGTDFTLTISSLQPEDFATYYCQQSDIIPLTFGGGTKVEIN								NPDTSKNQFSLQLNSVTPDDTALYYCARASFGTSGKFDDWGQGTLVTVSS							
pMHC[hTERT]	SYVLTQPPSVSEAPGKTARITCEGITIGRKSVHWYQQKPGQAPVLVVYDDTVRPSGVPERFSGSNSGNTATLIISGVEAGDEADYCQVWDSSTDPQVVFGGGTKTVL	2153	TIGRKS	2154	DDT	2155	QVWDSSTDPQVV	2156	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSKNSSWNWIRQSPSRGLEWLGRTYYRSKWYYDYAVSVKGRITFTFPDTSKNQVSLHLNAVTPEDTAMYYCVRGSIFDVWGQGTMVTVSS	2157	GDSVSSKNSS	2158	TYYRSKWYY	2159	CVRGSIFDV	2160
pMHC[hTERT]	NFMLTQPHSVSESPGKTVTISCTGSGGSIATNYVQWYQQRPGSAPATVIYEDDQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNQVFGGGTKLTVL	2161	GGSIATNY	2162	EDD	2163	QSYDSSNQV	2164	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMVRYYYGMDVWGQGTTVTVSS	2165	GGSFSGYY	2166	INHSGST	2167	ARMVRYYYGMDV	2168
pMHC[hTERT]	ETTLTQSPGTLSLSPGERATLSCRASQSVGSNLAWYQQRPGQAPSLLIYGASSRATGVPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGDSPRLYTFGQGTKLEIK	2169	QSVGSN	2170	GAS	2171	QQYGDSPRLYT	2172	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVAYYDSSGYYPYDAFDIWGQGTMVTVSS	2173	GGSFSGYY	2174	INHSGST	2175	ARVAYYDSSGYYPYDAFDI	2176
pMHC[gp100]	DVVMTQSPGTLSVSPGDSATLSCWASQLSDSYVSWYQQKPGQAPRLLIHSASIRAPGIPDRFSGSVSGTEFTLTISGLEPEDFAV	2177	QLSDSY	2178	SAS	2179	HQYGFLPWT	2180	QVQLVQSGAEVKKPGASVKVSCKASGYTFTRYGISWVRQAPGQGLEWMGWISSSNGYTKYAQNLQGRLTLTTDTSTGTAYMELRSLRSEDTAL	2181	GYTFTRYG	2182	ISSSNGYT	2183	ARYDISGLDGFDI	2184

	YSCHQYGFLPWTFGQGTKVEIR								YYCARYDISGLDGFDIWGQGTMVTVSS							
pMHC[gp100]	ETTLTQSPGTLSLSPGERATLSCRASRYINANFLAWYQQKPGQAPRLLIYDASTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPRTFGQGTKVEIK	2185	RYINANF	2186	DAS	2187	QQYGSSPRT	2188	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTATNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDSSGWLYDAFDIWGQGTMVTVSS	2189	GGTFSSYA	2190	IIPIFGTA	2191	CARDSSGWLYDAFDI	2192
pMHC[hTERT]	DIQMTQSPSILSASVGDRVTITCRASQRFGDYLAWYQQKPGQAPKLLIYGASTLQSGVPSRFSGSGSGTEFTLTISGLQPEDFATYYCQQANSFPITFGKGTRLDIR	2193	QRFGDY	2194	GAS	2195	QQANSFPITFGKGTR	2196	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGWINVGNGNAIYSQKFQGRVTITRDTSATTAYMELSSLRSEDTAVYYCARDGERAWDLDYWGQGTLVTVSS	2197	GGTFSSYA	2198	INVGNGNA	2199	ARDGERAWDLDY	2200
pMHC[hTERT]	ETTLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPYTFGQGTKLEIK	2201	QSVSSSY	2202	GAS	2203	QQYGSSPYT	2204	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARELRFLEWSSDAFDIWGQGTMVTVSS	2205	GFTFSSYA	2206	ISYDGSNK	2207	ARELRFLEWSSDAFDI	2208
pMHC[gp100]	ETTLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHDSSPRTFGQGTKVEI	2209	QSVSSSY	2210	GAS	2211	QQHDSSPRT	2212	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFISYDGSDKNFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDSYYDNSAFQADWGQGT	2213	GFTFSSYG	2214	ISYDGSDK	2215	AKDSYYDNSAFQAD	2216

	K								LVTVSS								
pMHC[tax]	EIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK	2217	QSLLHSNGYNY	2218	LGS	2219	MQALQTPRT	2220	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDFDYGDSYYYYGMDVWGQGTTVTVSS	2221	GFTFSSYG	2222	ISYDGSNK	2223	ARDFDYGDSYYYYGMDV	2224
pMHC[gp100]	DVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYKYVNWYLQKPGQSPQLLIYFGSYRASGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQATHWPYTFGQGTRLEIK	2225	QSLLHSNGYKY	2226	FGS	2227	MQATHWPYT	2228	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDYYGDYALLDYWGQGTLVTVSS	2229	GFTFSSYG	2230	ISYDGSNK	2231	ARDYYGDYALLDY	2232
pMHC[gp100]	EIVLTQSPDTLSLSPGEREATLSCRASQSVSHSYLAQYQQKPGQAPRLLIYDTSSRATDIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYVSSPLTFGQGTKLEIK	2233	SQSVSHS	2234	YDT	2235	CQQYVSSPLT	2236	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSTYGLHWVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNGLRAEDTAVYYCAKTVGVTFVSDAFDIWGQGTMVTVSS	2237	GFTFSTYG	2238	ISYDGSNK	2239	AKTVGVTFVSDAFDI	2240
pMHC[NY-ESO1]	QSELTQPRSVSGSPGQSVTISCTGTSRDVGGYNYVSWYQQHPGKAPKLIIHDVIIRPSGVPDRFSGSKSGNTASLTISGLQAEDEAHYYCWSFAGSYYVFGTGTDVTVL	2241	SRDVGGYNY	2242	DVI	2243	WSFAGSYYV	2244	QVQLLESGGGLVQPGGSLRLSCAASGFTFSAYGMGWVRQAPGKGLEWVSSIGSSGGGTAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGELLPYYGMDVWGQGTTVTVSS	2245	GFTFSAYG	2246	IGSSGGGT	2247	AGELLPYYGMDV	2248

GD2	ENVLTQSPAIMSASPGEKVTMTCRASSSVSSSLYHWYQQKSGASPKVWIYSTSNLASGVPGRFSGSGSGTSYSLTISSVEAEDAATYYCQQYSGYPITFGAGTKVEVK	2249	SSVSSSL	2250	STS	2251	QQYSGYPIT	2252	QVQLKESGPVLVAPSQTLSITCTVSGFSLASYNIHWVRQPPGKGLEWLGVIWAGGSTNYNSALMSRLSISKDNSKSQVFLQMNSLQTDDTAMYYCAKRSDDYSWFAYWGCQTLVTVSA	2253	GFSLASYN	2254	IWAGGST	2255	AKRSDDYSWFAY	2256
STEAP_1	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYRSNQKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQYYNYPRTFGGGTKLEIK	2257	QSLLYRSNQKNY	2258	WAS	2259	QQYYNYPRT	2260	DVQVQESGPGLVKPSQSLSLTCTVTGYSITSDYAWNWIRQFPGNKLEWMGYISNSGSTSYNPSLKSRISITRDTSKNQFFLQLISVTTEDTATYYCARERNYDYDDYYYAMDYWGQGTTLTVSA	2261	GYSITSDYA	2262	ISNSGST	2263	ARERNYDYDDYYYAMDY	2264
a4b7	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASNLESGVPSRFSGSGSGTDFTLTISSLQPEDFANYYCQQANSFPWTFGQGTKVEIK	2265	QGISSW	2266	GAS	2267	QQANSFPWT	2268	QVQLVQSGAEVKKPGASVKVSCKVSGYTLSDLSIHWVRQAPGKGLEWMGGFDPQDGETIYAQKFQGRVTMTEDTSTDTAYMELSSLKSEDTAVYYCATGSSSSWFDPWGQGTLVTVSS	2269	GYTLSDLS	2270	FDPQDGET	2271	ATGSSSSWFDP	2272
GPC3	DVVMTQSPLSLPVTPGEPASISCRSSQSLVHSNRNTYLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQNTHVPPTFGQGTKLEIK	2273	QSLVHSNRNTY	2275	KVS	2275	SQNTHVPPT	2276	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEMHWVRQAPGQGLEWMGALDPKTGDTAYSQKFKGRVTLTADKSTSTAYMELSSLTSEDTAVYYCTRFYSYTYWGQGTLVTVSS	2277	GYTFTDYE	2278	LDPKTGDT	2279	TRFYSYTYW	2280
CD262	SELTQDPAVSVALGQTVRIT	2281	SLRSY	2282	GAN	2283	NSADSSG	2284	EVQLVQSGGGVERPGGSLRLSCAA	2285	GFTFDDY	2286	INWQ	2287	AKILGAGRG	2288

(DR5)	CSGDSLRSYYASWYQQKPGQAPVLVIYGANNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSADSSGNHVVFGGGTKLTVL		Y				NHVV		SGFTFDDYAMSWVRQAPGKGLEWVSGINWQGGSTGYADSVKGRVTISRDNAKNSLYLQMNSLRAEDTAVYYCAKILGAGRGWYFDYWGKGTTVTVSS		A		GGST		WYFDY	
CD80	ESALTQPPSVSGAPGQKVTISCTGSTSNIGGYDLHWYQQLPGTAPKLLIYDINKRPSGISDRFSGSKSGTAASLAITGLQTEDEADYYCQSYDSSLNAQVFGGGTRLTVL	2289	TSNIGGYD	2290	DIN	2291	QSYDSSLNAQVFGG	2292	QVQLQESGPGLVKPSETLSLTCAVSGGSISGGYGWGWIRQPPGKGLEWIGSFYSSSGNTYYNPSLKSQVTISTDTSKNQFSLKLNSMTAADTAVYYCVRDRLFSVVGMVYNNWFDVWGPGVLVTVSS	2293	GGSISGGYG	2294	FYSSSGNT	2295	VRDRLFSVVGMVYNNWFDVW	2296
CD22	DVQVTQSPSSLSASVGDRVTITCRSSQSLANSYGNTFLSWYLHKPGKAPQLLIYGISNRFSGVPDRFSGSGSGTDFTLTISSLQPEDFATYYCLQGTHQPYTFGQGTKVEIK	2297	QSLANSYGNTF	2298	GIS	2299	LQGTHQPYT	2300	EVQLVQSGAEVKKPGASVKVSCKASGYRFTNYWIHWVRQAPGQGLEWIGGINPGNNYATYRRKFQGRVTMTADTSTSTVYMELSSLRSEDTAVYYCTREGYGNYGAWFAYWGQGTLVTVSS	2301	GYRFTNYW	2302	INPGNNYA	2304	TREGYGNYGAWFAY	2304
CD23	DIQMTQSPSSLSASVGDRVTITCRASQDIRYYLNWYQQKPGKAPKLLIYVASSLQSGVPSRFSGSGSGTEFTLTVSSLQPEDFATYYCLQVYSTPRTFGQGTKVEIK	2305	QDIRYY	2306	VAS	2307	LQVYSTPRT	2308	EVQLVESGGGLAKPGGSLRLSCAASGFRFTFNNYYMDWVRQAPGQGLEWVSRISSSGDPTWYADSVKGRFTISRENANNTLFLQMNSLRAEDTAVYYCASLTTGSDSWGQGVLVTVSS	2309	GFRFTFNNYY	2310	ISSSGDPT	2311	ASLTTGSDSW	2312
CD20	DIQMTQSPSSLSASVGDRVTITCRASSSVSYMHWYQQKPGK	2313	SSVSY	2314	APS	2315	QQWSFNPPT	2316	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHWVRQAPGKGLE	2317	GYTFTSYN	2318	IYPGNGDT	2319	ARVVYYSNSYWYFDV	2320

	APKPLIYAPSNLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSFNPPTFGQGTKVEIK								WVGAIYPGNGDTSYNQKFKGRFTISVDKSKNTLYLQMNSLRAEDTAVYYCARVVYYSNSYWYFDVWGQGTLVTVSS							
CD37	EIVLTQSPATLSLSPGERATLSCRASENVYSYLAWYQQKPGQAPRLLIYFAKTLAEGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHHSDNPWTFGQGTKVEIK	2321	ENVYSY	2322	FAK	2323	QHHSDNPWT	2324	EVQLVQSGAEVKKPGESLKISCKGSGYSFTGYNMNWVRQMPGKGLEWMGNIDPYYGGTTYNRKFKGQVTISADKSISTAYLQWSSLKASDTAMYYCARSVGPFDSWGQGTLVTVSS	2325	GYSFTGYN	2326	IDPYYGGT	2327	ARSVGPFDS	2328
CD22	DIQMTQSPSSLSASVGDRVTITCRSSQSIVHSVGNTFLEWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCFQGSQFPYTFGQGTKVEIK	2329	QSIVHSVGNTF	2330	KVS	2331	FQGSQFPYT	2332	EVQLVESGGGLVQPGGSLRLSCAASGYEFSRSWMNWVRQAPGKGLEWVGRIYPGDGDTNYSGKFKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARDGSSWDWYFDVWGQGTLVTVSS	2333	GYEFSRSW	2334	IYPGDGDT	2335	ARDGSSWDWYFDV	2336
fibronectin extra domain-B	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYYASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQTGRIPPTFGQGTKVEIK	2337	QSVSSSF	2338	YAS	2339	QQTGRIPPT	2340	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWVRQAPGKGLEWVSSISGSSGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPFPYFDYWGQGTLVTVSS	2341	GFTFSSFS	2342	ISGSSGTT	2343	AKPFPYFDY	2344
CD3	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRLIYDTSKLASGVPSRFSG	2345	SSVSY	2346	DTS	2347	QQWSSNPPT	2348	QVQLVQSGAEVKKPGASVKVSCKASGYTFISYTMHWVRQAPGQGLEWMGYINPRSGYTHYNQKLKDKAT	2349	GYTFISYT	2350	INPRSGYT	2351	ARSAYYDYDGFAY	2352

	SGSGTDFTLTI SSLQPEDFATY YCQQWSSNPP TFGGGTKVEI K								LTADKSASTAYM ELSSLRSEDTAV YYCARSAYYDY DGFAYWGQGTL VTVSS							

*Italics means immune cell target/payload (scFv arm)

[00126] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid

sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment, and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the

CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349.

[00127] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein the VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i)

a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein the VL-4 and VH-4 are capable of specifically binding to a third epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment, and wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs:

21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[00128] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of

forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii)a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the fourth epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149,

157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[00129] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide

chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b)the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337,

393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349. In some embodiments, both VH-1 and VH-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or both VL-1 and VL-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417,

425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[00130] In yet another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first

immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i)a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino

acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[00131] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-1 or VH-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or the VL-1 or VL-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881,

1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[00132] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-2 or VH-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349; and/or VL-2 or VL-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345.

[00133] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161

and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885

respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533

respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629 respectively; SEQ ID NOs: 1633 and 1637 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141

respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[00134] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389

respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141

respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629 respectively; SEQ ID NOs: 1633 and 1637 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733

respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325

respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[00135] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165

respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[00136] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid

sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445

respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[00137] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-2 and VH-2 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193

and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981

respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

[00138] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-4 and VH-4 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645

respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

[00139] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin or the third immunoglobulin binds to a cell surface antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7 +aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin),

CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NT5E), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR- HER3, EGFRvIII, EphA3, ERGT(GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin 5AC, NaPi2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC[MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC[MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B. The first immunoglobulin and the third immunoglobulin may bind to the same epitope on a target cell or two different epitopes on a target cell. In some embodiments, the target cell is a cancer cell.

[00140] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an epitope on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

[00141] In any of the above embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7 +aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195

(CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2. The second immunoglobulin and the fourth immunoglobulin may bind to the same epitope or different epitopes on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil. In some embodiments, the second immunoglobulin binds CD3 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD4, CD8, CD25, CD28, CTLA4, OX40, ICOS, PD-1, PD-L1, 41BB, CD2, CD69, and CD45. In other embodiments, the second immunoglobulin binds CD16 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD56, NKG2D, and KIRDL1/2/3. In certain embodiments, the fourth immunoglobulin binds to an agent selected from the group consisting of a cytokine, a nucleic acid, a hapten, a small molecule, a radionuclide, an immunotoxin, a vitamin, a peptide, a lipid, a carbohydrate, biotin, digoxin, or any conjugated variants thereof.

[00142] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity between about 100 nM to about 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are between 60 and 120 angstroms apart.

[00143] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity that is less than 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are up to 180 angstroms apart.

[00144] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain and has an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE. Non-limiting examples of constant region sequences include:

[00145] Human IgD constant region, Uniprot: P01880 (SEQ ID NO: 2381)

APTKAPDVFPIISGCRHPKDNSPVVLACLITGYHPTSVTVTWYMGTQSQPQRTFPEIQ
RRDSYYMTSSQLSTPLQQWRQGEYKCVVQHTASKSKKEIFRWPESPKAQASSVPTA
QPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEEQEERETKTPECPSHTQPLGVY
LLTPAVQDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNG
SQSQHSRLTLPRSLWNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASS
DPPEAASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWAWSVL
RVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDHGPMK

[00146] Human IgG1 constant region, Uniprot: P01857 (SEQ ID NO: 2382)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00147] Human IgG2 constant region, Uniprot: P01859 (SEQ ID NO: 2383)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVA
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPRE
EQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYT
LPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00148] Human IgG3 constant region, Uniprot: P01860 (SEQ ID NO: 2384)

ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLGDTTHTCPRCP
EPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEM

TKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKS
RWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK

[00149] Human IgM constant region, Uniprot: P01871 (SEQ ID NO: 2385)

GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITLSWKYKNNSDISSTRGFPSV
LRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSV
FVPPRDGFFGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSGVTTDQVQAEAKESG
PTTYKVTSTLTIKESDWLGQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPS
FASIFLTKSTKLTCLVTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEAS
ICEDDWNSGERFTCTVTHTDLPSPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESA
TITCLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEE
WNTGETYTCVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

[00150] Human IgG4 constant region, Uniprot: P01861 (SEQ ID NO: 2386)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE
EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT
LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

[00151] Human IgA1 constant region, Uniprot: P01876 (SEQ ID NO: 2387)

ASPTSPKVFPLSLCSTQPDGNVVIACLVQGFFPQEPLSVTWSESGQGVTARNFPPSQD
ASGDLYTTSSQLTLPATQCLAGKSVTCHVKHYTNPSQDVTVPCPVPSTPPTPSPSTPPT
PSPSCCHPRLSLHRPALEDLLLGSEANLTCTLTGLRDASGVTFTWTPSSGKSAVQGPP
ERDLCGCYSVSSVLPGCAEPWNHGKTFTCTAAYPESKTPLTATLSKSGNTFRPEVHL
LPPPSEELALNELVTLTCLARGFSPKDVLVRWLQGSQELPREKYLTWASRQEPSQGT
TTFAVTSILRVAAEDWKKGDTFSCMVGHEALPLAFTQKTIDRLAGKPTHVNVSVVM
AEVDGTCY

[00152] Human IgA2 constant region, Uniprot: P01877 (SEQ ID NO: 2388)

ASPTSPKVFPLSLDSTPQDGNVVVACLVQGFFPQEPLSVTWSESGQNVTARNFPPSQD
ASGDLYTTSSQLTLPATQCPDGKSVTCHVKHYTNPSQDVTVPCPVPPPPPCCHPRLSL

HRPALEDLLLGSEANLTCTLTGLRDASGATFTWTPSSGKSAVQGPPERDLCGCYSVS
SVLPGCAQPWNHGETFTCTAAHPELKTPLTANITKSGNTFRPEVHLLPPPSEELALNE
LVTLTCLARGFSPKDVLVRWLQGSQELPREKYLTWASRQEPSQGTTTFAVTSILRVA
AEDWKKGDTFSCMVGHEALPLAFTQKTIDRMAGKPTHVNVSVVMAEVDGTCY

[00153] Human Ig kappa constant region, Uniprot: P01834 (SEQ ID NO: 2389)

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[00154] In some embodiments, the immunoglobulin-related compositions of the present technology comprise a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or is 100% identical to SEQ ID NOS: 2381-2388. Additionally or alternatively, in some embodiments, the immunoglobulin-related compositions of the present technology comprise a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or is 100% identical to SEQ ID NO: 2389.

[00155] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin is an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin is a CH2-CH3 domain comprising a K409R mutation and the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain comprising a F405L mutation.

[00156] Also disclosed herein are recombinant nucleic acid sequences encoding any of the antibodies described herein. In another aspect, the present technology provides a host cell or vector expressing any nucleic acid sequence encoding any immunoglobulin-related composition described herein.

[00157] In some embodiments, the immunoglobulin-related compositions of the present technology are chimeric, humanized, or monoclonal. The immunoglobulin-related compositions of the present technology can further be recombinantly fused to a heterologous

polypeptide at the N or C terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, the immunoglobulin-related compositions of the present technology can be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, or toxins. See, *e.g.*, WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 0 396 387.

[00158] In any of the above embodiments of the immunoglobulin-related compositions of the present technology, the HDTVS antibody may be optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof. For a chemical bond or physical bond, a functional group on the immunoglobulin-related composition typically associates with a functional group on the agent. Alternatively, a functional group on the agent associates with a functional group on the immunoglobulin-related composition.

[00159] The functional groups on the agent and immunoglobulin-related composition can associate directly. For example, a functional group (*e.g.*, a sulfhydryl group) on an agent can associate with a functional group (*e.g.*, sulfhydryl group) on an immunoglobulin-related composition to form a disulfide. Alternatively, the functional groups can associate through a cross-linking agent (*i.e.*, linker). Some examples of cross-linking agents are described below. The cross-linker can be attached to either the agent or the immunoglobulin-related composition. The number of agents or immunoglobulin-related compositions in a conjugate is also limited by the number of functional groups present on the other. For example, the maximum number of agents associated with a conjugate depends on the number of functional groups present on the immunoglobulin-related composition. Alternatively, the maximum number of immunoglobulin-related compositions associated with an agent depends on the number of functional groups present on the agent.

[00160] In yet another embodiment, the conjugate comprises one immunoglobulin-related composition associated to one agent. In one embodiment, a conjugate comprises at least one agent chemically bonded (e.g., conjugated) to at least one immunoglobulin-related composition. The agent can be chemically bonded to an immunoglobulin-related composition by any method known to those in the art. For example, a functional group on

the agent may be directly attached to a functional group on the immunoglobulin-related composition. Some examples of suitable functional groups include, for example, amino, carboxyl, sulfhydryl, maleimide, isocyanate, isothiocyanate and hydroxyl.

[00161] The agent may also be chemically bonded to the immunoglobulin-related composition by means of cross-linking agents, such as dialdehydes, carbodiimides, dimaleimides, and the like. Cross-linking agents can, for example, be obtained from Pierce Biotechnology, Inc., Rockford, Ill. The Pierce Biotechnology, Inc. web-site can provide assistance. Additional cross-linking agents include the platinum cross-linking agents described in U.S. Pat. Nos. 5,580,990; 5,985,566; and 6,133,038 of Kreatech Biotechnology, B.V., Amsterdam, The Netherlands.

[00162] Alternatively, the functional group on the agent and immunoglobulin-related composition can be the same. Homobifunctional cross-linkers are typically used to cross-link identical functional groups. Examples of homobifunctional cross-linkers include EGS (i.e., ethylene glycol bis[succinimidylsuccinate]), DSS (i.e., disuccinimidyl suberate), DMA (i.e., dimethyl adipimidate.2HCl), DTSSP (i.e., 3,3'-dithiobis[sulfosuccinimidylpropionate])), DPDPB (i.e., 1,4-di-[3'-(2'-pyridyldithio)-propionamido]butane), and BMH (i.e., bis-maleimidohexane). Such homobifunctional cross-linkers are also available from Pierce Biotechnology, Inc.

[00163] In other instances, it may be beneficial to cleave the agent from the immunoglobulin-related composition. The web-site of Pierce Biotechnology, Inc. described above can also provide assistance to one skilled in the art in choosing suitable cross-linkers which can be cleaved by, for example, enzymes in the cell. Thus the agent can be separated from the immunoglobulin-related composition. Examples of cleavable linkers include SMPT (i.e., 4-succinimidyloxycarbonyl-methyl-a-[2-pyridyldithio]toluene), Sulfo-LC-SPDP (i.e., sulfosuccinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), LC-SPDP (i.e., succinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), Sulfo-LC-SPDP (i.e., sulfosuccinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), SPDP (i.e., N-succinimidyl 3-[2-pyridyldithio]-propionamidohexanoate), and AEDP (i.e., 3-[(2-aminoethyl)dithio]propionic acid HCl).

[00164] In another embodiment, a conjugate comprises at least one agent physically bonded with at least one immunoglobulin-related composition. Any method known to those

in the art can be employed to physically bond the agents with the immunoglobulin-related compositions. For example, the immunoglobulin-related compositions and agents can be mixed together by any method known to those in the art. The order of mixing is not important. For instance, agents can be physically mixed with immunoglobulin-related compositions by any method known to those in the art. For example, the immunoglobulin-related compositions and agents can be placed in a container and agitated, by for example, shaking the container, to mix the immunoglobulin-related compositions and agents.

[00165] The immunoglobulin-related compositions can be modified by any method known to those in the art. For instance, the immunoglobulin-related composition may be modified by means of cross-linking agents or functional groups, as described above.

[00166] *Heterodimerization*. The present technology is dependent on heterodimerization of two IgG-scFv half-molecules through mutations in the heterodimerization domains using techniques known in the art. Any heterodimerization approach where the hinge domain is kept in place may be employed, provided that sufficient antibody stability is achieved.

[00167] *Heterodimerization of CH2-CH3 domains*. Formation of a heterodimeric trivalent/tetravalent multispecific antibody molecule of the present technology requires the interaction of four different polypeptide chains. Such interactions are difficult to achieve with efficiency within a single cell recombinant production system, due to the many variants of potential chain mispairings. One solution to increase the probability of mispairings, is to engineer "knobs-into-holes" type mutations into the desired polypeptide chain pairs. Such mutations favor heterodimerization over homodimerization. For example, with respect to Fc-Fc-interactions, an amino acid substitution (preferably a substitution with an amino acid comprising a bulky side group forming a 'knob', *e.g.*, tryptophan) can be introduced into the CH2 or CH3 domain such that steric interference will prevent interaction with a similarly mutated domain and will obligate the mutated domain to pair with a domain into which a complementary, or accommodating mutation has been engineered, *i.e.*, 'the hole' (*e.g.*, a substitution with glycine). Such sets of mutations can be engineered into a pair of polypeptides that are included within the heterodimeric trivalent/tetravalent molecule (*e.g.*, the second polypeptide chain and the third polypeptide chain), and further, engineered into any portion of the polypeptides chains of said pair. Methods of protein engineering to favor heterodimerization over homodimerization are well known in the art, in particular with respect to the engineering of immunoglobulin-like molecules, and are encompassed herein

(see *e.g.*, Ridgway *et al.*, 1996, *Protein Engr.* 9:617-621, Atwell *et al.*, 1997, *J. Mol. Biol.* 270: 26-35, and Xie *et al.*, 2005, *J. Immunol. Methods* 296:95-101; each of which is hereby incorporated herein by reference in its entirety).

[00168] The design of variant Fc heterodimers from wildtype homodimers is illustrated by the concept of positive and negative design in the context of protein engineering by balancing stability vs. specificity, where mutations are introduced with the goal of driving heterodimer formation over homodimer formation when the polypeptides are expressed in cell culture conditions. Negative design strategies maximize unfavorable interactions for the formation of homodimers, by either introducing bulky sidechains on one chain and small sidechains on the opposite, for example the knobs-into-holes strategy developed by Genentech (Ridgway J B, Presta L G, Carter P. *Protein Eng.* 1996 July; 9(7):617-21; Atwell S, Ridgway J B, Wells J A, Carter P. *J Mol. Biol.* 270(1):26-35 (1997))), or by electrostatic engineering that leads to repulsion of homodimer formation, for example the electrostatic steering strategy developed by Amgen (Gunaskekaran K, *et al. JBC* 285 (25): 19637-19646 (2010)). In these two examples, negative design asymmetric point mutations are introduced into the wild-type CH3 domain to drive heterodimer formation. Other heterodimerization approaches are described in US 20120149876 (*e.g.*, at Tables 1, 6 and 7), and US 20140294836 (*e.g.*, at Figures 15A-B, 16A-B, and 17). Methods for engineering Fc heterodimers using electrostatic steering are described in detail in US 8,592,562.

[00169] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise amino acid modifications selected from the group consisting of: T366Y and Y407T respectively; F405A and T394W respectively; Y349C/T366S/L368A/Y407V and S354C/T366W respectively; K409D/K392D and D399K respectively; T366S/L368A/Y407V and T366W respectively; K409D/K392D and D399K/E356K respectively; L351Y/Y407A and T366A/K409F respectively; L351Y/Y407A and T366V/ K409F respectively; Y407A and T366A/K409F respectively; D399R/S400R/Y407A and T366A/K409F/K392E/T411E respectively; L351Y/F405A/Y407V and T394W respectively; L351Y/F405A/Y407V and T366L respectively; F405A/Y407V and T366I/ K392M/T394W respectively; F405A/Y407V and

T366L/K392M/T394W respectively; F405A/Y407V and T366L/T394W respectively; F405A/Y407V and T366I/T394W respectively; and K409R and F405L respectively.

[00170] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain comprises an amino acid modification at position F405 and amino acid modifications L351Y and Y407V, and the second CH2-CH3 domain comprises amino acid modification T394W. In some embodiments, the amino acid modification at position F405 is F405A, F405I, F405M, F405T, F405S, F405V or F405W.

[00171] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain comprises amino acid modifications at positions L351 and Y407, and the second CH2-CH3 domain comprises an amino acid modification at position T366 and amino acid modification K409F. In some embodiments, the amino acid modification at position L351 is L351Y, L351I, L351D, L351R or L351F. In some embodiments, the amino acid modification at position Y407 is Y407A, Y407V or Y407S. In certain embodiments, the amino acid modification at position T366 is T366A, T366I, T366L, T366M, T366Y, T366S, T366C, T366V or T366W.

[00172] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain or the second CH2-CH3 domain comprises an amino acid modification at positions K392, T411, T366, L368 or S400. The amino acid modification at position K392 may be K392V, K392M, K392R, K392L, K392F or K392E. The amino acid modification at position T411 may be T411N, T411R, T411Q, T411K, T411D, T411E or T411W. The amino acid modification at position S400 may be S400E, S400D, S400R or S400K. The amino acid modification at position T366 may be T366A, T3661, T366L, T366M, T366Y, T366S, T366C, T366V or T366W. The amino acid modification at position L368 may be L368D, L368R, L368T, L368M, L368V, L368F, L368S and L368A.

[00173] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a

second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain comprises amino acid modifications L351Y and Y407A and the second CH2-CH3 domain comprises amino acid modifications T366A and K409F, and optionally wherein the first CH2-CH3 domain or the second CH2-CH3 domain comprises one or more amino acid modifications at position T411, D399, S400, F405, N390, or K392. The amino acid modification at position T411 may be T411N, T411R, T411Q, T411K, T411D, T411E or T411W. The amino acid modification at position D399 may be D399R, D399W, D399Y or D399K. The amino acid modification at position S400 may be S400E, S400D, S400R, or S400K. The amino acid modification at position F405 may be F4051, F405M, F405T, F405S, F405V or F405W. The amino acid modification at position N390 may be N390R, N390K or N390D. The amino acid modification at position K392 may be K392V, K392M, K392R, K392L, K392F or K392E.

[00174] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in **Figure 11a**. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in **Figure 11b**. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in **Figure 11c**. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in **Figure 11d**. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in **Figure 11e**.

[00175] *Other Fc Modifications.* In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology comprise a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region (or the parental Fc region), such that said molecule has an altered affinity for an Fc receptor (*e.g.*, an FcγR), provided that said variant Fc region does not have a substitution at positions that make a direct contact with Fc receptor based on crystallographic and structural analysis of Fc-Fc receptor interactions such as those disclosed by Sondermann *et al.*, *Nature*, 406:267-273 (2000). Examples of positions within the Fc region that make a direct contact with an Fc receptor such as an FcγR, include amino acids 234-239 (hinge region), amino acids 265-269 (B/C loop), amino acids 297-299 (C7E loop), and amino acids 327-332 (F/G) loop.

[00176] In some embodiments, a heterodimeric trivalent/tetravalent multispecific antibody of the present technology has an altered affinity for activating and/or inhibitory receptors, and includes a variant Fc region with one or more amino acid modifications, wherein said one or more amino acid modification is a N297 substitution with alanine, or a K322 substitution with alanine.

[00177] *Glycosylation Modifications.* In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology have an Fc region with variant glycosylation as compared to a parent Fc region. In some embodiments, variant glycosylation includes the absence of fucose; in some embodiments, variant glycosylation results from expression in GnT1 -deficient CHO cells.

[00178] In some embodiments, the antibodies of the present technology, may have a modified glycosylation site relative to an appropriate reference antibody that binds to an antigen of interest, without altering the functionality of the antibody, *e.g.*, binding activity to the antigen. As used herein, "glycosylation sites" include any specific amino acid sequence in an antibody to which an oligosaccharide (*i.e.*, carbohydrates containing two or more simple sugars linked together) will specifically and covalently attach.

[00179] Oligosaccharide side chains are typically linked to the backbone of an antibody *via* either N-or O-linkages. N-linked glycosylation refers to the attachment of an oligosaccharide moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of an oligosaccharide moiety to a hydroxyamino acid, *e.g.*, serine,

threonine. For example, an Fc- glycoform that lacks certain oligosaccharides including fucose and terminal N- acetylglucosamine may be produced in special CHO cells and exhibit enhanced ADCC effector function.

[00180] In some embodiments, the carbohydrate content of an immunoglobulin-related composition disclosed herein is modified by adding or deleting a glycosylation site. Methods for modifying the carbohydrate content of antibodies are well known in the art and are included within the present technology, see, *e.g.*, U.S. Patent No. 6,218,149; EP 0359096B1; U.S. Patent Publication No. US 2002/0028486; International Patent Application Publication WO 03/035835; U.S. Patent Publication No. 2003/0115614; U.S. Patent No. 6,218,149; U.S. Patent No. 6,472,511; all of which are incorporated herein by reference in their entirety. In some embodiments, the carbohydrate content of an antibody (or relevant portion or component thereof) is modified by deleting one or more endogenous carbohydrate moieties of the antibody. In certain embodiments, the present technology includes deleting the glycosylation site of the Fc region of an antibody, by modifying position 297 from asparagine to alanine. Such antibodies lack Fc effector function. In some embodiments, nonspecific FcR-dependent binding in normal tissues is eliminated or reduced (*e.g.*, via N297A mutation in Fc region, which results in aglycosylation).

[00181] Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Engineered glycoforms may be generated by any method known to one skilled in the art, for example by using engineered or variant expression strains, by co-expression with one or more enzymes, for example DI N-acetylglucosaminyltransferase III (GnTIII), by expressing a molecule comprising an Fc region in various organisms or cell lines from various organisms, or by modifying carbohydrate(s) after the molecule comprising Fc region has been expressed. Methods for generating engineered glycoforms are known in the art, and include but are not limited to those described in Umana *et al.*, 1999, *Nat. Biotechnol.* 17: 176-180; Davies *et al.*, 2001, *Biotechnol. Bioeng.* 74:288-294; Shields *et al.*, 2002, *J. Biol. Chem.* 277:26733-26740; Shinkawa *et al.*, 2003, *J. Biol. Chem.* 278:3466-3473; U.S. Patent No. 6,602,684; U.S. Patent Application Serial No. 10/277,370; U.S. Patent Application Serial No. 10/113,929; International Patent Application Publications WO 00/61739A1 ; WO 01/292246A1; WO 02/311140A1; WO 02/30954A1; POTILLEGENT™ technology (Biowa, Inc. Princeton, N.J.); GLYCOMAB™ glycosylation engineering technology (GLYCART biotechnology

AG, Zurich, Switzerland); each of which is incorporated herein by reference in its entirety. See, *e.g.*, International Patent Application Publication WO 00/061739; U.S. Patent Application Publication No. 2003/0115614; Okazaki *et al.*, 2004, *JMB*, 336: 1239-49.

A. Methods of Preparing Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[00182] *General Overview*. The heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure can be produced using a variety of methods well known in the art, including *de novo* protein synthesis and recombinant expression of nucleic acids encoding the binding proteins. Initially, a target antigen is chosen to which an antibody of the present technology can be raised. For example, in some embodiments, an antibody may be raised against a full-length target protein, or to a portion of the target protein. Techniques for generating antibodies directed to such target polypeptides are well known to those skilled in the art. Examples of such techniques include, for example, but are not limited to, those involving display libraries, xeno or human mice, hybridomas, and the like.

[00183] Generally, an antibody is obtained from an originating species. More particularly, the nucleic acid or amino acid sequence of the variable portion of the light chain, heavy chain or both, of an originating species antibody having specificity for a target antigen is obtained. An originating species is any species which was useful to generate the antibody of the present technology or library of antibodies, *e.g.*, rat, mouse, rabbit, chicken, monkey, human, and the like.

[00184] Phage or phagemid display technologies are useful techniques to derive the antibodies of the present technology. Techniques for generating and cloning monoclonal antibodies are well known to those skilled in the art. Expression of sequences encoding antibodies of the present technology, can be carried out in *E. coli*.

[00185] Due to the degeneracy of nucleic acid coding sequences, other sequences which encode substantially the same amino acid sequences as those of the naturally occurring proteins may be used in the practice of the present technology These include, but are not limited to, nucleic acid sequences including all or portions of the nucleic acid sequences encoding the above polypeptides, which are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. It is appreciated that the nucleotide sequence of an immunoglobulin

according to the present technology tolerates sequence homology variations of up to 25% as calculated by standard methods ("Current Methods in Sequence Comparison and Analysis," *Macromolecule Sequencing and Synthesis, Selected Methods and Applications*, pp. 127-149, 1998, Alan R. Liss, Inc.) so long as such a variant yields an operative antibody which recognizes a target of interest. For example, one or more amino acid residues within a polypeptide sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Also included within the scope of the present technology are proteins or fragments or derivatives thereof which are differentially modified during or after translation, *e.g.*, by glycosylation, proteolytic cleavage, linkage to an antibody molecule or other cellular ligands, *etc.* Additionally, an immunoglobulin encoding nucleic acid sequence can be mutated *in vitro* or *in vivo* to create and/or destroy translation, initiation, and/or termination sequences or to create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further *in vitro* modification. Any technique for mutagenesis known in the art can be used, including but not limited to *in vitro* site directed mutagenesis, *J. Biol. Chem.* 253:6551, use of Tab linkers (Pharmacia), and the like.

[00186] *Monoclonal Antibody*. In one embodiment of the present technology, the heterodimeric trivalent/tetravalent multispecific antibody is a monoclonal antibody. For example, in some embodiments, the heterodimeric trivalent/tetravalent multispecific monoclonal antibody may be a human or a mouse heterodimeric trivalent/tetravalent multispecific monoclonal antibody. For preparation of monoclonal antibodies directed towards a target molecule of interest, any technique that provides for the production of antibody molecules by continuous cell line culture can be utilized. Such techniques include, but are not limited to, the hybridoma technique (*See*, *e.g.*, Kohler & Milstein, 1975. *Nature* 256: 495-497); the trioma technique; the human B-cell hybridoma technique (*See*, *e.g.*, Kozbor, *et al.*, 1983. *Immunol. Today* 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (*See*, *e.g.*, Cole, *et al.*, 1985. In: MONOCLONAL

ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies can be utilized in the practice of the present technology and can be produced by using human hybridomas (*See*, *e.g.*, Cote, *et al.*, 1983. *Proc. Natl. Acad. Sci.* USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (*See*, *e.g.*, Cole, *et al.*, 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). For example, a population of nucleic acids that encode regions of antibodies can be isolated. PCR utilizing primers derived from sequences encoding conserved regions of antibodies is used to amplify sequences encoding portions of antibodies from the population and then DNAs encoding polypeptide chains of the heterodimeric trivalent/tetravalent multispecific antibodies or fragments thereof, such as variable domains, are reconstructed from the amplified sequences. Such amplified sequences also can be fused to DNAs encoding other proteins – *e.g.*, a bacteriophage coat, or a bacterial cell surface protein – for expression and display of the fusion polypeptides on phage or bacteria. Amplified sequences can then be expressed and further selected or isolated based, *e.g.*, on the affinity of the expressed antibody or fragment thereof for an antigen or epitope present on the target molecule of interest. Alternatively, hybridomas expressing heterodimeric trivalent/tetravalent multispecific monoclonal antibodies can be prepared by immunizing a subject and then isolating hybridomas from the subject's spleen using routine methods. *See, e.g.*, Milstein *et al.,* (Galfre and Milstein, *Methods Enzymol* (1981) 73: 3-46). Screening the hybridomas using standard methods will produce monoclonal antibodies of varying specificity (*i.e.*, for different epitopes) and affinity. A selected monoclonal antibody with the desired properties, *e.g.*, binding to a target antigen, can be used as expressed by the hybridoma, it can be bound to a molecule such as polyethylene glycol (PEG) to alter its properties, or a cDNA encoding it can be isolated, sequenced and manipulated in various ways. Synthetic dendromeric trees can be added to reactive amino acid side chains, *e.g.*, lysine, to enhance the immunogenic properties of a target protein. Also, CPG-dinucleotide techniques can be used to enhance the immunogenic properties of the target protein. Other manipulations include substituting or deleting particular amino acyl residues that contribute to instability of the antibody during storage or after administration to a subject, and affinity maturation techniques to improve affinity of the antibody towards its target antigen.

[00187] *Hybridoma Technique*. In some embodiments, the antibody of the present technology is a heterodimeric trivalent/tetravalent multispecific monoclonal antibody produced by a hybridoma which includes a B cell obtained from a transgenic non-human

animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell. Hybridoma techniques include those known in the art and taught in Harlow *et al.*, *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 349 (1988); Hammerling *et al.*, *Monoclonal Antibodies And T-Cell Hybridomas,* 563-681 (1981). Other methods for producing hybridomas and monoclonal antibodies are well known to those of skill in the art.

[00188] *Phage Display Technique.* As noted above, the antibodies of the present technology can be produced through the application of recombinant DNA and phage display technology. For example, heterodimeric trivalent/tetravalent multispecific antibodies, can be prepared using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of a phage particle which carries polynucleotide sequences encoding them. Phages with a desired binding property are selected from a repertoire or combinatorial antibody library (*e.g.,* human or murine) by selecting directly with an antigen, typically an antigen bound or captured to a solid surface or bead. Phages used in these methods are typically filamentous phage including fd and M13 with Fab, Fv or disulfide stabilized Fv antibody domains that are recombinantly fused to either the phage gene III or gene VIII protein. In addition, methods can be adapted for the construction of Fab expression libraries (*See*, *e.g.*, Huse, *et al.*,. *Science* 246: 1275-1281, 1989) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for a target antigen, *e.g.*, a target polypeptide or derivatives, fragments, analogs or homologs thereof. Other examples of phage display methods that can be used to make the antibodies of the present technology include those disclosed in Huston *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 85: 5879-5883, 1988; Chaudhary *et al.*, *Proc. Natl. Acad. Sci U.S.A.,* 87: 1066-1070, 1990; Brinkman *et al.*, *J. Immunol. Methods* 182: 41-50, 1995; Ames *et al.*, *J. Immunol. Methods* 184: 177-186, 1995; Kettleborough *et al.*, *Eur. J. Immunol.* 24: 952-958, 1994; Persic *et al.*, *Gene* 187: 9-18, 1997; Burton *et al.*, *Advances in Immunology* 57: 191-280, 1994; PCT/GB91/01134; WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; WO 96/06213; WO 92/01047 (Medical Research Council *et al.*); WO 97/08320 (Morphosys); WO 92/01047 (CAT/MRC); WO 91/17271 (Affymax); and U.S. Pat. Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727 and 5,733,743. Methods useful for displaying polypeptides on the surface of bacteriophage particles by attaching the polypeptides *via* disulfide bonds have been described by Lohning,

U.S. Pat. No. 6,753,136. As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host including mammalian cells, insect cells, plant cells, yeast, and bacteria. For example, techniques to recombinantly produce Fab, Fab′ and $F(ab')_2$ fragments can also be employed using methods known in the art such as those disclosed in WO 92/22324; Mullinax *et al.*, *BioTechniques* 12: 864-869, 1992; and Sawai *et al.*, *AJRI* 34: 26-34, 1995; and Better *et al.*, *Science* 240: 1041-1043, 1988.

[00189] Generally, hybrid antibodies or hybrid antibody fragments that are cloned into a display vector can be selected against the appropriate antigen in order to identify variants that maintain good binding activity, because the antibody or antibody fragment will be present on the surface of the phage or phagemid particle. *See, e.g.,* Barbas III *et al.*, *Phage Display, A Laboratory Manual* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2001). However, other vector formats could be used for this process, such as cloning the antibody fragment library into a lytic phage vector (modified T7 or Lambda Zap systems) for selection and/or screening.

[00190] *Single-Chain Fvs.* The heterodimeric trivalent/tetravalent multispecific antibody of the present technology comprises two single-chain Fvs. According to the present technology, techniques can be adapted for the production of single-chain antibodies specific to a target antigen (*See, e.g.*, U.S. Pat. No. 4,946,778). Examples of techniques which can be used to produce single-chain Fvs and antibodies of the present technology include those described in U.S. Pat. Nos. 4,946,778 and 5,258,498; Huston *et al.*, *Methods in Enzymology*, 203: 46-88, 1991; Shu, L. *et al.*, *Proc. Natl. Acad. Sci. USA,* 90: 7995-7999, 1993; and Skerra *et al.*, *Science* 240: 1038-1040, 1988.

[00191] *Chimeric and Humanized Antibodies.* In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is chimeric. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is humanized. In one embodiment of the present technology, the donor and acceptor antibodies are monoclonal antibodies from different species. For example, the acceptor antibody is a human antibody (to minimize its antigenicity in a human), in which case the resulting CDR-grafted antibody is termed a “humanized” antibody.

[00192] Recombinant heterodimeric trivalent/tetravalent multispecific antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, can be made using standard recombinant DNA techniques, and are within the scope of the present technology. For some uses, including *in vivo* use of the heterodimeric trivalent/tetravalent multispecific antibody of the present technology in humans as well as use of these agents in *in vitro* detection assays, it is possible to use chimeric or humanized heterodimeric trivalent/tetravalent multispecific antibodies. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art. Such useful methods include, *e.g.*, but are not limited to, methods described in International Application No. PCT/US86/02269; U.S. Pat. No. 5,225,539; European Patent No. 184187; European Patent No. 171496; European Patent No. 173494; PCT International Publication No. WO 86/01533; U.S. Pat. Nos. 4,816,567; 5,225,539; European Patent No. 125023; Better, *et al.*, 1988. *Science* 240: 1041-1043; Liu, *et al.*, 1987. *Proc. Natl. Acad. Sci.* USA 84: 3439-3443; Liu, *et al.*, 1987. *J. Immunol.* 139: 3521-3526; Sun, *et al.*, 1987. *Proc. Natl. Acad. Sci.* USA 84: 214-218; Nishimura, *et al.*, 1987. *Cancer Res.* 47: 999-1005; Wood, *et al.*, 1985. *Nature* 314: 446-449; Shaw, *et al.*, 1988. *J. Natl. Cancer Inst.* 80: 1553-1559; Morrison (1985) *Science* 229: 1202-1207; Oi, *et al.* (1986) *BioTechniques* 4: 214; Jones, *et al.*, 1986. *Nature* 321: 552-525; Verhoeyan, *et al.*, 1988. *Science* 239: 1534; Morrison, *Science* 229: 1202, 1985; Oi *et al.*, *BioTechniques* 4: 214, 1986; Gillies *et al.*, *J. Immunol. Methods,* 125: 191-202, 1989; U.S. Pat. No. 5,807,715; and Beidler, *et al.*, 1988. *J. Immunol.* 141: 4053-4060. For example, antibodies can be humanized using a variety of techniques including CDR-grafting (EP 0 239 400; WO 91/09967; U.S. Pat. No. 5,530,101; 5,585,089; 5,859,205; 6,248,516; EP460167), veneering or resurfacing (EP 0 592 106; EP 0 519 596; Padlan E. A., *Molecular Immunology*, 28: 489-498, 1991; Studnicka *et al.*, *Protein Engineering* 7: 805-814, 1994; Roguska *et al.*, *PNAS* 91: 969-973, 1994), and chain shuffling (U.S. Pat. No. 5,565,332). In one embodiment, a cDNA encoding a murine heterodimeric trivalent/tetravalent multispecific monoclonal antibody is digested with a restriction enzyme selected specifically to remove the sequence encoding the Fc constant region, and the equivalent portion of a cDNA encoding a human Fc constant region is substituted (*See* Robinson *et al.*, PCT/US86/02269; Akira *et al.*, European Patent Application 184,187; Taniguchi, European Patent Application 171,496; Morrison *et al.*, European Patent Application 173,494; Neuberger *et al.*, WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.*, European Patent Application 125,023; Better *et al.* (1988) *Science* 240: 1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci.* USA 84: 3439-3443; Liu *et al.*

(1987) *J Immunol* 139: 3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84: 214-218; Nishimura *et al.* (1987) *Cancer Res* 47: 999-1005; Wood *et al.* (1985) *Nature* 314: 446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80: 1553-1559; U.S. Pat. No. 6,180,370; U.S. Pat. Nos. 6,300,064; 6,696,248; 6,706,484; 6,828,422.

[00193] In one embodiment, the present technology provides the construction of humanized heterodimeric trivalent/tetravalent multispecific antibodies that are unlikely to induce a human anti-mouse antibody (hereinafter referred to as "HAMA") response, while still having an effective antibody effector function. As used herein, the terms "human" and "humanized", in relation to antibodies, relate to any antibody which is expected to elicit a therapeutically tolerable weak immunogenic response in a human subject. In one embodiment, the present technology provides for a humanized heterodimeric trivalent/tetravalent multispecific antibody comprising both heavy chain and light chain polypeptides.

[00194] *CDR Antibodies*. In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is a CDR antibody. Generally the donor and acceptor antibodies used to generate the heterodimeric trivalent/tetravalent multispecific CDR antibody are monoclonal antibodies from different species; typically the acceptor antibody is a human antibody (to minimize its antigenicity in a human), in which case the resulting CDR-grafted antibody is termed a "humanized" antibody. The graft may be of a single CDR (or even a portion of a single CDR) within a single V_H or V_L of the acceptor antibody, or can be of multiple CDRs (or portions thereof) within one or both of the V_H and V_L. Frequently, all three CDRs in all variable domains of the acceptor antibody will be replaced with the corresponding donor CDRs, though one need replace only as many as necessary to permit adequate binding of the resulting CDR-grafted antibody to the target antigen. Methods for generating CDR-grafted and humanized antibodies are taught by Queen *et al.* U.S. Pat. No. 5,585,089; U.S. Pat. No. 5,693,761; U.S. Pat. No. 5,693,762; and Winter U.S. 5,225,539; and EP 0682040. Methods useful to prepare V_H and V_L polypeptides are taught by Winter *et al.*, U.S. Pat. Nos. 4,816,397; 6,291,158; 6,291,159; 6,291,161; 6,545,142; EP 0368684; EP0451216; and EP0120694.

[00195] After selecting suitable framework region candidates from the same family and/or the same family member, either or both the heavy and light chain variable regions are produced by grafting the CDRs from the originating species into the hybrid framework

regions. Assembly of hybrid antibodies or hybrid antibody fragments having hybrid variable chain regions with regard to either of the above aspects can be accomplished using conventional methods known to those skilled in the art. For example, DNA sequences encoding the hybrid variable domains described herein (*i.e.*, frameworks based on the target species and CDRs from the originating species) can be produced by oligonucleotide synthesis and/or PCR. The nucleic acid encoding CDR regions can also be isolated from the originating species antibodies using suitable restriction enzymes and ligated into the target species framework by ligating with suitable ligation enzymes. Alternatively, the framework regions of the variable chains of the originating species antibody can be changed by site-directed mutagenesis.

[00196] Since the hybrids are constructed from choices among multiple candidates corresponding to each framework region, there exist many combinations of sequences which are amenable to construction in accordance with the principles described herein. Accordingly, libraries of hybrids can be assembled having members with different combinations of individual framework regions. Such libraries can be electronic database collections of sequences or physical collections of hybrids.

[00197] This process typically does not alter the acceptor antibody's FRs flanking the grafted CDRs. However, one skilled in the art can sometimes improve antigen binding affinity of the resulting heterodimeric trivalent/tetravalent multispecific CDR-grafted antibody by replacing certain residues of a given FR to make the FR more similar to the corresponding FR of the donor antibody. Suitable locations of the substitutions include amino acid residues adjacent to the CDR, or which are capable of interacting with a CDR (*See*, *e.g.*, US 5,585,089, especially columns 12-16). Or one skilled in the art can start with the donor FR and modify it to be more similar to the acceptor FR or a human consensus FR. Techniques for making these modifications are known in the art. Particularly if the resulting FR fits a human consensus FR for that position, or is at least 90% or more identical to such a consensus FR, doing so may not increase the antigenicity of the resulting modified heterodimeric trivalent/tetravalent multispecific CDR-grafted antibody significantly compared to the same antibody with a fully human FR.

[00198] *Expression of Recombinant Heterodimeric Trivalent/Tetravalent Multispecific Antibodies.* The desired nucleic acid sequences can be produced by recombinant methods (*e.g.*, PCR mutagenesis of an earlier prepared variant of the desired polynucleotide) or by

solid-phase DNA synthesis. Because of the degeneracy of the genetic code, a variety of nucleic acid sequences encode each immunoglobulin amino acid sequence, and the present disclosure includes all nucleic acids encoding the binding proteins described herein, which are suitable for use in accordance with the present disclosure.

[00199] Once the nucleotide sequence of the heterodimeric trivalent/tetravalent multispecific antibodies are determined, the nucleotide sequence may be manipulated using methods well known in the art, *e.g.*, recombinant DNA techniques, site directed mutagenesis, PCR, *etc.* (see, for example, the techniques described in Sambrook *et al.*, 2001, *Molecular Cloning, A Laboratory Manual*, 3rd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.; and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate, for example, antibodies having a different amino acid sequence, for example by generating amino acid substitutions, deletions, and/or insertions. In one embodiment, human libraries or any other libraries available in the art, can be screened by standard techniques known in the art, to clone the nucleic acids encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure.

[00200] As noted above, the antibodies of the present technology can be produced through the application of recombinant DNA technology. Recombinant polynucleotide constructs encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology typically include an expression control sequence operably-linked to the coding sequences of heterodimeric trivalent/tetravalent multispecific antibody chains, including naturally-associated or heterologous promoter regions. As such, another aspect of the technology includes vectors containing one or more nucleic acid sequences encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology. Methods which are well known to those skilled in the art can be used to construct expression vectors containing the coding sequences for the molecules of the present disclosure and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. See, for example, the techniques described in Sambrook *et al.*, 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel *et al.* eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY. For recombinant expression of one or more of the polypeptides of the present technology, the

nucleic acid containing all or a portion of the nucleotide sequence encoding the heterodimeric trivalent/tetravalent multispecific antibody is inserted into an appropriate cloning vector, or an expression vector (*i.e.*, a vector that contains the necessary elements for the transcription and translation of the inserted polypeptide coding sequence) by recombinant DNA techniques well known in the art and as detailed below. Methods for producing diverse populations of vectors have been described by Lerner *et al.*, U.S. Pat. Nos. 6,291,160 and 6,680,192.

[00201] In general, expression vectors useful in recombinant DNA techniques are often in the form of plasmids. In the present disclosure, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the present technology is intended to include such other forms of expression vectors that are not technically plasmids, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions. Such viral vectors permit infection of a subject and expression of a construct in that subject. In some embodiments, the expression control sequences are eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences encoding the heterodimeric trivalent/tetravalent multispecific antibody, and the collection and purification of the heterodimeric trivalent/tetravalent multispecific antibody, *e.g.*, cross-reacting heterodimeric trivalent/tetravalent multispecific antibodies. *See generally*, U.S. 2002/0199213. These expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors contain selection markers, *e.g.*, ampicillin-resistance or hygromycin-resistance, to permit detection of those cells transformed with the desired DNA sequences. Vectors can also encode signal peptide, *e.g.*, pectate lyase, useful to direct the secretion of extracellular antibody fragments. *See* U.S. Pat. No. 5,576,195.

[00202] The recombinant expression vectors of the present technology comprise a nucleic acid encoding a protein having binding properties to a molecule of interest and in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression that is operably-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is

intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, *e.g.*, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences) or under certain environmental conditions (*e.g.*, inducible regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of polypeptide desired, *etc.* Typical regulatory sequences useful as promoters of recombinant polypeptide expression (*e.g.*, a heterodimeric trivalent/tetravalent multispecific antibody), include, *e.g.*, but are not limited to, promoters of 3-phosphoglycerate kinase and other glycolytic enzymes. Inducible yeast promoters include, among others, promoters from alcohol dehydrogenase, isocytochrome C, and enzymes responsible for maltose and galactose utilization. In one embodiment, a polynucleotide encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology is operably-linked to an *ara B* promoter and expressible in a host cell. *See* U.S. Pat. 5,028,530. The expression vectors of the present technology can be introduced into host cells to thereby produce polypeptides or peptides, including fusion polypeptides, encoded by nucleic acids as described herein (*e.g.*, heterodimeric trivalent/tetravalent multispecific antibody, *etc.*).

[00203] Another aspect of the present technology pertains to heterodimeric trivalent/tetravalent multispecific antibody-expressing host cells, which contain a nucleic acid encoding one or more heterodimeric trivalent/tetravalent multispecific antibodies. A variety of host-expression vector systems may be utilized to express the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure. Such host-expression systems represent vehicles by which the coding sequences of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express the molecules of the present

disclosure *in situ*. These include, but are not limited to, microorganisms such as bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA, expression vectors containing coding sequences for the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; yeast (*e.g.*, *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing sequences encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing the sequences encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus (CaMV) and tobacco mosaic virus (TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing sequences encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 293T, 3T3 cells, lymphotic cells (see U.S. Pat. No. 5,807,715), Per C.6 cells (human retinal cells developed by Crucell) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[00204] The recombinant expression vectors of the present technology can be designed for expression of a heterodimeric trivalent/tetravalent multispecific antibody in prokaryotic or eukaryotic cells. For example, a heterodimeric trivalent/tetravalent multispecific antibody can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors), fungal cells, *e.g.*, yeast, yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, *e.g.*, using T7 promoter regulatory sequences and T7 polymerase. Methods useful for the preparation and screening of polypeptides having a predetermined property, *e.g.*, heterodimeric trivalent/tetravalent multispecific antibody, *via* expression of stochastically generated polynucleotide sequences have been previously described. *See* U.S. Pat. Nos. 5,763,192; 5,723,323; 5,814,476; 5,817,483; 5,824,514; 5,976,862; 6,492,107; 6,569,641.

[00205] Expression of polypeptides in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion polypeptides. Fusion vectors add a number of amino acids to a polypeptide encoded therein, usually to the amino terminus of the recombinant polypeptide. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant polypeptide; (ii) to increase the solubility of the recombinant polypeptide; and (iii) to aid in the purification of the recombinant polypeptide by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant polypeptide to enable separation of the recombinant polypeptide from the fusion moiety subsequent to purification of the fusion polypeptide. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding polypeptide, or polypeptide A, respectively, to the target recombinant polypeptide.

[00206] Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann *et al.*, (1988) *Gene* 69: 301-315) and pET 11d (Studier *et al.*, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89). Methods for targeted assembly of distinct active peptide or protein domains to yield multifunctional polypeptides *via* polypeptide fusion have been described by Pack *et al.*, U.S. Pat. Nos. 6,294,353; 6,692,935. One strategy to maximize recombinant polypeptide expression, *e.g.*, a heterodimeric trivalent/tetravalent multispecific antibody, in *E. coli* is to express the polypeptide in host bacteria with an impaired capacity to proteolytically cleave the recombinant polypeptide. *See*, *e.g.*, Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in the expression host, *e.g.*, *E. coli* (*See*, *e.g.*, Wada, *et al.*, 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the present technology can be carried out by standard DNA synthesis techniques.

[00207] In another embodiment, the heterodimeric trivalent/tetravalent multispecific antibody expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerevisiae* include pYepSec1 (Baldari, *et al.*, 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, *Cell* 30: 933-943, 1982), pJRY88 (Schultz *et al.*, *Gene* 54: 113-123, 1987), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (Invitrogen Corp, San Diego, Calif.). Alternatively, a heterodimeric trivalent/tetravalent multispecific antibody can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of polypeptides, *e.g.*, heterodimeric trivalent/tetravalent multispecific antibody, in cultured insect cells (*e.g.*, SF9 cells) include the pAc series (Smith, *et al.*, *Mol. Cell. Biol.* 3: 2156-2165, 1983) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

[00208] In yet another embodiment, a nucleic acid encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include, *e.g.*, but are not limited to, pCDM8 (Seed, *Nature* 329: 840, 1987) and pMT2PC (Kaufman, *et al.*, *EMBO J.* 6: 187-195, 1987). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells that are useful for expression of the heterodimeric trivalent/tetravalent multispecific antibody of the present technology, see, *e.g.*, Chapters 16 and 17 of Sambrook, *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

[00209] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid in a particular cell type (*e.g.*, tissue-specific regulatory elements). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, *et al.*, *Genes Dev.* 1: 268-277, 1987), lymphoid-specific promoters (Calame and Eaton, *Adv. Immunol.* 43: 235-275, 1988), promoters of T cell receptors (Winoto and Baltimore, *EMBO J.* 8: 729-733, 1989) and immunoglobulins (Banerji, *et al.*, 1983. *Cell* 33: 729-740; Queen and Baltimore, *Cell* 33: 741-748, 1983.), neuron-specific

promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle, *Proc. Natl. Acad. Sci. USA* 86: 5473-5477, 1989), pancreas-specific promoters (Edlund, *et al.*, 1985. Science 230: 912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, *e.g.*, the murine hox promoters (Kessel and Gruss, *Science* 249: 374-379, 1990) and the α-fetoprotein promoter (Campes and Tilghman, *Genes Dev.* 3: 537-546, 1989).

[00210] Another aspect of the present methods pertains to host cells into which a recombinant expression vector of the present technology has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[00211] A host cell can be any prokaryotic or eukaryotic cell. For example, a heterodimeric trivalent/tetravalent multispecific antibody can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells. Mammalian cells are a suitable host for expressing nucleotide segments encoding immunoglobulins or fragments thereof. *See* Winnacker, *From Genes To Clones*, (VCH Publishers, NY, 1987). A number of suitable host cell lines capable of secreting intact heterologous proteins have been developed in the art, and include Chinese hamster ovary (CHO) cell lines, various COS cell lines, HeLa cells, L cells and myeloma cell lines. In some embodiments, the cells are non-human. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus can be an effective expression system for immunoglobulins (Foecking *et al.*, 1998, *Gene* 45:101; Cockett *et al.*, 1990, *BioTechnology* 8:2).

[00212] Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer, and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Queen *et al.*, *Immunol. Rev.* 89: 49, 1986. Illustrative expression control sequences are promoters derived from endogenous genes,

cytomegalovirus, SV40, adenovirus, bovine papillomavirus, and the like. Co *et al.*, *J Immunol.* 148: 1149, 1992. Other suitable host cells are known to those skilled in the art.

[00213] Vector DNA can be introduced into prokaryotic or eukaryotic cells *via* conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, electroporation, biolistics or viral-based transfection. Other methods used to transform mammalian cells include the use of polybrene, protoplast fusion, liposomes, electroporation, and microinjection (*See generally*, Sambrook *et al.*, *Molecular Cloning*). Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals. The vectors containing the DNA segments of interest can be transferred into the host cell by well-known methods, depending on the type of cellular host.

[00214] For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding the heterodimeric trivalent/tetravalent multispecific antibody or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

[00215] A host cell that includes a heterodimeric trivalent/tetravalent multispecific antibody of the present technology, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a recombinant heterodimeric trivalent/tetravalent multispecific antibody. In one embodiment, the method comprises culturing the host cell (into which a recombinant expression vector encoding the heterodimeric trivalent/tetravalent multispecific antibody has been introduced) in a suitable medium such that the heterodimeric

trivalent/tetravalent multispecific antibody is produced. In another embodiment, the method further comprises the step of isolating the heterodimeric trivalent/tetravalent multispecific antibody from the medium or the host cell. Once expressed, collections of the heterodimeric trivalent/tetravalent multispecific antibody, *e.g.,* the heterodimeric trivalent/tetravalent multispecific antibodies or the heterodimeric trivalent/tetravalent multispecific antibody-related polypeptides are purified from culture media and host cells. The heterodimeric trivalent/tetravalent multispecific antibody can be purified according to standard procedures of the art, including HPLC purification, column chromatography, gel electrophoresis and the like. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody is produced in a host organism by the method of Boss *et al.,* U.S. Pat. No. 4,816,397. Usually, heterodimeric trivalent/tetravalent multispecific antibody chains are expressed with signal sequences and are thus released to the culture media. However, if the heterodimeric trivalent/tetravalent multispecific antibody chains are not naturally secreted by host cells, the heterodimeric trivalent/tetravalent multispecific antibody chains can be released by treatment with mild detergent. Purification of recombinant polypeptides is well known in the art and includes ammonium sulfate precipitation, affinity chromatography purification technique, column chromatography, ion exchange purification technique, gel electrophoresis and the like (*See generally* Scopes, Protein Purification (Springer-Verlag, N.Y., 1982).

[00216] Polynucleotides encoding heterodimeric trivalent/tetravalent multispecific antibodies, *e.g.*, the heterodimeric trivalent/tetravalent multispecific antibody coding sequences, can be incorporated in transgenes for introduction into the genome of a transgenic animal and subsequent expression in the milk of the transgenic animal. *See*, *e.g.*, U.S. Pat. Nos. 5,741,957, 5,304,489, and 5,849,992. Suitable transgenes include coding sequences for light and/or heavy chains in operable linkage with a promoter and enhancer from a mammary gland specific gene, such as casein or β-lactoglobulin. For production of transgenic animals, transgenes can be microinjected into fertilized oocytes, or can be incorporated into the genome of embryonic stem cells, and the nuclei of such cells transferred into enucleated oocytes.

[00217] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody, vectors which direct the expression of high

levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, *EMBO J.* 2:1791), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, *Nucleic Acids Res.* 13:3101-3109; Van Heeke & Schuster, 1989, *J. Biol. Chem.* 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to a matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[00218] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (*e.g.*, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (*e.g.*, the polyhedrin promoter).

[00219] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the immunoglobulin molecule in infected hosts (*e.g.*, see Logan & Shenk, 1984, *Proc. Natl. Acad. Sci. USA* 81:355-359). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, *etc.* (see Bittner *et al.*, 1987, *Methods in Enzymol.* 153:51-544).

[00220] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. For example, in certain embodiments, the polypeptides of a heterodimeric trivalent/tetravalent multispecific antibody of the present disclosure may be expressed as a single gene product (*e.g.*, as a single polypeptide chain, *i.e.*, as a polyprotein precursor), requiring proteolytic cleavage by native or recombinant cellular mechanisms to form the separate polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure. The present disclosure thus encompasses engineering a nucleic acid sequence to encode a polyprotein precursor molecule comprising the polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure, which includes coding sequences capable of directing post translational cleavage of said polyprotein precursor. Post-translational cleavage of the polyprotein precursor results in the polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure.

[00221] The post translational cleavage of the precursor molecule comprising the polypeptides of a heterodimeric trivalent/tetravalent multispecific antibody of the present disclosure may occur *in vivo* (*i.e.*, within the host cell by native or recombinant cell systems/mechanisms, *e.g.* furin cleavage at an appropriate site) or may occur *in vitro* (*e.g.*, incubation of said polypeptide chain in a composition comprising proteases or peptidases of known activity and/or in a composition comprising conditions or reagents known to foster the desired proteolytic action). Purification and modification of recombinant proteins are well known in the art such that the design of the polyprotein precursor could include a number of embodiments readily appreciated by a skilled artisan. Any known proteases or peptidases known in the art can be used for the described modification of the precursor molecule, *e.g.*, thrombin (which recognizes the amino acid sequence LVPR^GS (SEQ ID NO: 2500)), or factor Xa (which recognizes the amino acid sequence I(E/D)GR^ (SEQ ID NO: 2501) (Nagani *et al.*, 1985, *PNAS USA* 82:7252-7255, and reviewed in Jenny *et al.*, 2003, *Protein Expr. Purif.* 31:1-11, each of which is incorporated by reference herein in its entirety)), enterokinase (which recognizes the amino acid sequence DDDDK^ (SEQ ID NO: 2502) (Collins-Racie *et al.*, 1995, *Biotechnol.* 13:982-987 hereby incorporated by reference herein in its entirety)), furin (which recognizes the amino acid sequence RXXR^, with a preference for RX(K/R)R^ (SEQ ID NO: 2503 and SEQ ID NO: 2504, respectively) (additional R at P6

position appears to enhance cleavage)), and AcTEV (which recognizes the amino acid sequence ENLYFQ^G (SEQ ID NO: 2505) (Parks *et al.*, 1994, *Anal. Biochem.* 216:413 hereby incorporated by reference herein in its entirety)) and the Foot and Mouth Disease Virus Protease C3.

[00222] Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 293T, 3T3, WI38, BT483, Hs578T, HTB2, BT20 and T47D, CRL7030 and Hs578Bst.

[00223] For long-term, high-yield production of recombinant proteins, stable expression is desirable. For example, cell lines which stably express an antibody of the present disclosure may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibodies of the present disclosure. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure.

[00224] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler *et al.*, 1977, *Cell* 11: 223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, *Proc. Natl. Acad. Sci. USA* 48: 202), and adenine phosphoribosyltransferase (Lowy *et al.*, 1980, *Cell* 22: 817) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to

methotrexate (Wigler *et al.*, 1980, *Proc. Natl. Acad. Sci. USA* 77:357; O'Hare *et al.*, 1981, *Proc. Natl. Acad. Sci. USA* 78: 1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, *Proc. Natl. Acad. Sci. USA* 78: 2072); neo, which confers resistance to the aminoglycoside G-418 *Clinical Pharmacy* 12: 488-505; Wu and Wu, 1991, 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, 1993, *Science* 260:926-932; and Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; May, 1993, TIB TECH 11(5):155-215). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), 1993, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY; Kriegler, 1990, *Gene Transfer and Expression*, A Laboratory Manual, Stockton Press, NY; and in Chapters 12 and 13, Dracopoli *et al.* (eds), 1994, *Current Protocols in Human Genetics*, John Wiley & Sons, NY.; Colberre-Garapin *et al.*, 1981, *J. Mol. Biol.* 150:1; and hygro, which confers resistance to hygromycin (Santerre *et al.*, 1984, *Gene* 30:147).

[00225] The expression levels of a heterodimeric trivalent/tetravalent multispecific antibody of the present disclosure can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol. 3 (Academic Press, New York, 1987). When a marker in the vector system expressing an antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the selection marker gene. Since the amplified region is associated with the nucleotide sequence of a polypeptide of the heterodimeric trivalent/tetravalent multispecific antibody molecule, production of the polypeptide will also increase (Crouse *et al.*, 1983, *Mol. Cell. Biol.* 3:257).

[00226] The host cell may be co-transfected with a plurality of expression vectors of the present disclosure, wherein each expression vector encodes at least one and no more than three of the first, second, third, or fourth polypeptide chains of the heterodimeric trivalent/tetravalent multispecific antibody. Alternatively, a single vector may be used which encodes the first, second, third, and fourth polypeptide chains of the heterodimeric trivalent/tetravalent multispecific antibody. The coding sequences for the polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure may comprise cDNA or genomic DNA.

[00227] Once a molecule of the present disclosure (*i.e.*, heterodimeric trivalent/tetravalent multispecific antibodies) has been recombinantly expressed, it may be purified by any

method known in the art for purification of polypeptides, polyproteins or heterodimeric trivalent/tetravalent multispecific antibodies (*e.g.*, analogous to antibody purification schemes based on antigen selectivity) for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen (optionally after Protein A selection where the heterodimeric trivalent/tetravalent multispecific antibodies molecule comprises an Fc domain (or portion thereof)), and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of polypeptides, polyproteins or heterodimeric trivalent/tetravalent multispecific antibodies.

[00228] *Labeled Heterodimeric trivalent/tetravalent multispecific antibodies.* In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is coupled with a label moiety, *i.e.*, detectable group. The particular label or detectable group conjugated to the heterodimeric trivalent/tetravalent multispecific antibody is not a critical aspect of the technology, so long as it does not significantly interfere with the specific binding of the heterodimeric trivalent/tetravalent multispecific antibody of the present technology to its target antigens. The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and imaging. In general, almost any label useful in such methods can be applied to the present technology. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Labels useful in the practice of the present technology include magnetic beads (*e.g.,* Dynabeads™), fluorescent dyes (*e.g.*, fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (*e.g.*, ^{3}H, ^{14}C, ^{35}S, ^{125}I, ^{121}I, ^{131}I, ^{112}In, ^{99}mTc), other imaging agents such as microbubbles (for ultrasound imaging), ^{18}F, ^{11}C, ^{15}O, (for Positron emission tomography), ^{99m}TC, ^{111}In (for Single photon emission tomography), enzymes (*e.g.*, horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and calorimetric labels such as colloidal gold or colored glass or plastic (*e.g.,* polystyrene, polypropylene, latex, and the like) beads. Patents that describe the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241, each incorporated herein by reference in their entirety and for all purposes. *See also* Handbook of Fluorescent Probes and Research Chemicals (6^{th} Ed., Molecular Probes, Inc., Eugene OR.).

[00229] The label can be coupled directly or indirectly to the desired component of an assay according to methods well known in the art. As indicated above, a wide variety of

labels can be used, with the choice of label depending on factors such as required sensitivity, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions.

[00230] Non-radioactive labels are often attached by indirect means. Generally, a ligand molecule (*e.g.*, biotin) is covalently bound to the molecule. The ligand then binds to an anti-ligand (*e.g.*, streptavidin) molecule which is either inherently detectable or covalently bound to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound. A number of ligands and anti-ligands can be used. Where a ligand has a natural anti-ligand, *e.g.*, biotin, thyroxine, and cortisol, it can be used in conjunction with the labeled, naturally-occurring anti-ligands. Alternatively, any haptenic or antigenic compound can be used in combination with an antibody, *e.g.,* a heterodimeric trivalent/tetravalent multispecific antibody.

[00231] The molecules can also be conjugated directly to signal generating compounds, *e.g.*, by conjugation with an enzyme or fluorophore. Enzymes of interest as labels will primarily be hydrolases, particularly phosphatases, esterases and glycosidases, or oxidoreductases, particularly peroxidases. Fluorescent compounds useful as labeling moieties, include, but are not limited to, *e.g.*, fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, and the like. Chemiluminescent compounds useful as labeling moieties, include, but are not limited to, *e.g.*, luciferin, and 2,3-dihydrophthalazinediones, *e.g.*, luminol. For a review of various labeling or signal-producing systems which can be used, see U.S. Pat. No. 4,391,904.

[00232] Means of detecting labels are well known to those of skill in the art. Thus, for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it can be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence. The fluorescence can be detected visually, by means of photographic film, by the use of electronic detectors such as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels can be detected by providing the appropriate substrates for the enzyme and detecting the resulting reaction product. Finally simple colorimetric labels can be detected simply by observing the color associated with the label. Thus, in various dipstick assays, conjugated gold often appears pink, while various conjugated beads appear the color of the bead.

[00233] Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies, *e.g.*, the heterodimeric trivalent/tetravalent multispecific antibodies. In this case, antigen-coated particles are agglutinated by samples comprising the target antibodies. In this format, none of the components need be labeled and the presence of the target antibody is detected by simple visual inspection.

[00234] *Fusion Proteins*. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is a fusion protein. In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology, when fused to a second protein, can be used as an antigenic tag. Examples of domains that can be fused to polypeptides include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but can occur through linker sequences. Moreover, fusion proteins of the present technology can also be engineered to improve characteristics of the heterodimeric trivalent/tetravalent multispecific antibodies. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of the heterodimeric trivalent/tetravalent multispecific antibody to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties can be added to a heterodimeric trivalent/tetravalent multispecific antibody to facilitate purification. Such regions can be removed prior to final preparation of the heterodimeric trivalent/tetravalent multispecific antibody. The addition of peptide moieties to facilitate handling of polypeptides may be accomplished using familiar and routine techniques in the art. The heterodimeric trivalent/tetravalent multispecific antibody of the present technology can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In select embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., Chatsworth, Calif), among others, many of which are commercially available. As described in Gentz *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 821-824, 1989, for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. Wilson *et al.*, *Cell* 37: 767, 1984.

[00235] Thus, any of these above fusion proteins can be engineered using the polynucleotides or the polypeptides of the present technology. Also, in some embodiments, the fusion proteins described herein show an increased half-life *in vivo*.

[00236] Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can be more efficient in binding and neutralizing other molecules compared to the monomeric secreted protein or protein fragment alone. Fountoulakis *et al.*, *J. Biochem.* 270: 3958-3964, 1995.

[00237] Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or a fragment thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, *e.g.*, improved pharmacokinetic properties. *See* EP-A 0232 262. Alternatively, deleting or modifying the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion can hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, *e.g.*, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. Bennett *et al.*, *J. Molecular Recognition* 8: 52-58, 1995; Johanson *et al.*, *J. Biol. Chem.*, 270: 9459-9471, 1995.

[00238] In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology may be conjugated to a therapeutic agent or a payload. Examples of a payload include a toxin, a protein such as tumor necrosis factor, interferons including, but not limited to, α-interferon (IFN-α), β-interferon (IFN-β), nerve growth factor (NGF), platelet derived growth factor (PDGF), tissue plasminogen activator (TPA), an apoptotic agent (*e.g.*, TNF-α, TNF-β, AIM I as disclosed in PCT Publication No. WO 97/33899), AIM II (see, PCT Publication No. WO 97/34911), Fas ligand (Takahashi *et al.*, *J. Immunol.*, 6:1567-1574, 1994), and VEGI (PCT Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent (*e.g.*, angiostatin or endostatin), or a biological response modifier such as, for example, a lymphokine (*e.g.*, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF"), macrophage colony stimulating factor, ("M-CSF"), or a growth factor (e.g., growth hormone ("GH"); proteases, or ribonucleases. Examples of therapeutic agents include paclitaxol, cytochalasin

B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Other examples of therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

B. Identifying and Characterizing the Heterodimeric Trivalent/ Tetravalent Multispecific Antibodies of the Present Technology

[00239] *Methods for identifying and/or screening the heterodimeric trivalent/ tetravalent multispecific antibodies of the present technology.* Methods useful to identify and screen antibodies that possess the desired specificity to a target antigen include any immunologically-mediated techniques known within the art. Components of an immune response can be detected *in vitro* by various methods that are well known to those of ordinary skill in the art. For example, (1) cytotoxic T lymphocytes can be incubated with radioactively labeled target cells and the lysis of these target cells detected by the release of radioactivity; (2) helper T lymphocytes can be incubated with antigens and antigen presenting cells and the synthesis and secretion of cytokines measured by standard methods (Windhagen A *et al.*, *Immunity,* 2: 373-80, 1995); (3) antigen presenting cells can be incubated with whole protein antigen and the presentation of that antigen on MHC detected by either T lymphocyte activation assays or biophysical methods (Harding *et al.*, *Proc. Natl. Acad. Sci.*, 86: 4230-4, 1989); (4) mast cells can be incubated with reagents that cross-link their Fc-epsilon receptors and histamine release measured by enzyme immunoassay (Siraganian *et al.*, *TIPS,* 4: 432-437, 1983); and (5) enzyme-linked immunosorbent assay (ELISA).

[00240] Similarly, products of an immune response in either a model organism (*e.g.*, mouse) or a human subject can also be detected by various methods that are well known to those of ordinary skill in the art. For example, (1) the production of antibodies in response to

vaccination can be readily detected by standard methods currently used in clinical laboratories, *e.g.*, an ELISA; (2) the migration of immune cells to sites of inflammation can be detected by scratching the surface of skin and placing a sterile container to capture the migrating cells over scratch site (Peters *et al.*, *Blood,* 72: 1310-5, 1988); (3) the proliferation of peripheral blood mononuclear cells (PBMCs) in response to mitogens or mixed lymphocyte reaction can be measured using ^{3}H-thymidine; (4) the phagocytic capacity of granulocytes, macrophages, and other phagocytes in PBMCs can be measured by placing PBMCs in wells together with labeled particles (Peters *et al.*, *Blood,* 72: 1310-5, 1988); and (5) the differentiation of immune system cells can be measured by labeling PBMCs with antibodies to CD molecules such as CD4 and CD8 and measuring the fraction of the PBMCs expressing these markers.

[00241] In one embodiment, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using display of target antigen peptides on the surface of replicable genetic packages. *See*, *e.g.*, U.S. Pat. Nos. 5,514,548; 5,837,500; 5,871,907; 5,885,793; 5,969,108; 6,225,447; 6,291,650; 6,492,160; EP 585 287; EP 605522; EP 616640; EP 1024191; EP 589 877; EP 774 511; EP 844 306. Methods useful for producing/selecting a filamentous bacteriophage particle containing a phagemid genome encoding for a binding molecule with a desired specificity has been described. *See*, *e.g.*, EP 774 511; US 5871907; US 5969108; US 6225447; US 6291650; US 6492160.

[00242] In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using display of target antigen peptides on the surface of a yeast host cell. Methods useful for the isolation of scFv polypeptides by yeast surface display have been described by Kieke *et al.*, *Protein Eng.* 1997 Nov; 10(11): 1303-10.

[00243] In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using ribosome display. Methods useful for identifying ligands in peptide libraries using ribosome display have been described by Mattheakis *et al.*, *Proc. Natl. Acad. Sci. USA* 91: 9022-26, 1994; and Hanes *et al.*, *Proc. Natl. Acad. Sci. USA* 94: 4937-42, 1997.

[00244] In certain embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using tRNA display of target antigen

peptides. Methods useful for *in vitro* selection of ligands using tRNA display have been described by Merryman *et al.*, *Chem. Biol.*, 9: 741-46, 2002.

[00245] In one embodiment, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using RNA display. Methods useful for selecting peptides and proteins using RNA display libraries have been described by Roberts *et al. Proc. Natl. Acad. Sci. USA*, 94: 12297-302, 1997; and Nemoto *et al.*, *FEBS Lett.*, 414: 405-8, 1997. Methods useful for selecting peptides and proteins using unnatural RNA display libraries have been described by Frankel *et al.*, *Curr. Opin. Struct. Biol.*, 13: 506-12, 2003.

[00246] In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are expressed in the periplasm of gram negative bacteria and mixed with labeled target antigen. *See* WO 02/34886. In clones expressing recombinant polypeptides with affinity for a target antigen, the concentration of the labeled target antigen bound to the heterodimeric trivalent/tetravalent multispecific antibodies is increased and allows the cells to be isolated from the rest of the library as described in Harvey *et al.*, *Proc. Natl. Acad. Sci.* 22: 9193-98 2004 and U.S. Pat. Publication No. 2004/0058403.

[00247] After selection of the desired heterodimeric trivalent/tetravalent multispecific antibodies, it is contemplated that said antibodies can be produced in large volume by any technique known to those skilled in the art, *e.g.*, prokaryotic or eukaryotic cell expression and the like. For example, the heterodimeric trivalent/tetravalent multispecific antibodies can be produced by using conventional techniques to construct an expression vector that encodes an antibody heavy chain and/or light chain in which the CDRs and, if necessary, a minimal portion of the variable region framework, that are required to retain original species antibody binding specificity (as engineered according to the techniques described herein) are derived from the originating species antibody and the remainder of the antibody is derived from a target species immunoglobulin which can be manipulated as described herein, thereby producing a vector for the expression of a hybrid antibody heavy chain.

[00248] *Measurement of Antigen Binding.* In some embodiments, an antigen binding assay refers to an assay format wherein a target antigen and a heterodimeric trivalent/tetravalent multispecific antibody are mixed under conditions suitable for binding between the target antigen and the heterodimeric trivalent/tetravalent multispecific antibody and assessing the amount of binding between the target antigen and the heterodimeric

trivalent/tetravalent multispecific antibody. The amount of binding is compared with a suitable control, which can be the amount of binding in the absence of the target antigen, the amount of the binding in the presence of a non-specific immunoglobulin composition, or both. The amount of binding can be assessed by any suitable method. Binding assay methods include, *e.g.*, ELISA, radioimmunoassays, scintillation proximity assays, fluorescence energy transfer assays, liquid chromatography, membrane filtration assays, and the like. Biophysical assays for the direct measurement of target antigen binding to a heterodimeric trivalent/tetravalent multispecific antibody are, *e.g.*, nuclear magnetic resonance, fluorescence, fluorescence polarization, surface plasmon resonance (BIACORE chips) and the like. Specific binding is determined by standard assays known in the art, *e.g.*, radioligand binding assays, ELISA, FRET, immunoprecipitation, SPR, NMR (2D-NMR), mass spectroscopy and the like. If the specific binding of a candidate heterodimeric trivalent/tetravalent multispecific antibody is at least 1 percent greater than the binding observed in the absence of the candidate heterodimeric trivalent/tetravalent multispecific antibody, the candidate heterodimeric trivalent/tetravalent multispecific antibody is useful as a heterodimeric trivalent/tetravalent multispecific antibody of the present technology.

[00249] *Measurement of Target Antigen Neutralization.* As used here, "target antigen neutralization" refers to reduction of the activity and/or expression of a target antigen through the binding of a heterodimeric trivalent/tetravalent multispecific antibody disclosed herein. The capacity of heterodimeric trivalent/tetravalent multispecific antibodies of the present technology to neutralize activity/expression of a target antigen may be assessed *in vitro* or *in vivo* using methods known in the art.

Uses of the Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[00250] *General.* The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are useful in methods known in the art relating to the localization and/or quantitation of a target antigen (*e.g.*, for use in measuring levels of the target antigen within appropriate physiological samples, for use in diagnostic methods, for use in imaging the target antigen, and the like). Antibodies of the present technology are useful to isolate a target antigen by standard techniques, such as affinity chromatography or immunoprecipitation. A heterodimeric trivalent/tetravalent multispecific antibody of the present technology can facilitate the purification of natural immunoreactive target antigens

from biological samples, *e.g.*, mammalian sera or cells as well as recombinantly-produced immunoreactive target antigens expressed in a host system. Moreover, heterodimeric trivalent/tetravalent multispecific antibodies can be used to detect an immunoreactive target antigen (*e.g.*, in plasma, a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the immunoreactive molecule. The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology can be used diagnostically to monitor immunoreactive target antigen levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen. As noted above, the detection can be facilitated by coupling (*i.e.*, physically linking) the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology to a detectable substance.

[00251] *Detection of target antigen.* An exemplary method for detecting the presence or absence of an immunoreactive target antigen in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a heterodimeric trivalent/tetravalent multispecific antibody of the present technology capable of detecting an immunoreactive target antigen such that the presence of an immunoreactive target antigen is detected in the biological sample. Detection may be accomplished by means of a detectable label attached to the antibody.

[00252] The term "labeled" with regard to the heterodimeric trivalent/tetravalent multispecific antibody is intended to encompass direct labeling of the antibody by coupling (*i.e.*, physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reactivity with another compound that is directly labeled, such as a secondary antibody. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin.

[00253] In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies disclosed herein are conjugated to one or more detectable labels. For such uses, heterodimeric trivalent/tetravalent multispecific antibodies may be detectably labeled by covalent or non-covalent attachment of a chromogenic, enzymatic, radioisotopic, isotopic, fluorescent, toxic, chemiluminescent, nuclear magnetic resonance contrast agent or other label.

[00254] Examples of suitable chromogenic labels include diaminobenzidine and 4-hydroxyazo-benzene-2-carboxylic acid. Examples of suitable enzyme labels include malate dehydrogenase, staphylococcal nuclease, Δ-5-steroid isomerase, yeast-alcohol dehydrogenase, α-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, β-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, and acetylcholine esterase.

[00255] Examples of suitable radioisotopic labels include ^{3}H, ^{111}In, ^{125}I, ^{131}I, ^{32}P, ^{35}S, ^{14}C, ^{51}Cr, ^{57}To, ^{58}Co, ^{59}Fe, ^{75}Se, ^{152}Eu, ^{90}Y, ^{67}Cu, ^{217}Ci, ^{211}At, ^{212}Pb, ^{47}Sc, ^{109}Pd, *etc.* ^{111}In is an exemplary isotope where *in vivo* imaging is used since it avoids the problem of dehalogenation of the ^{125}I or ^{131}I-labeled heterodimeric trivalent/tetravalent multispecific antibodies by the liver. In addition, this isotope has a more favorable gamma emission energy for imaging (Perkins *et al*, *Eur. J. Nucl. Med.* 70:296-301 (1985); Carasquillo *et al.*, *J. Nucl. Med.* 25:281-287 (1987)). For example, ^{111}In coupled to monoclonal antibodies with 1-(P-isothiocyanatobenzyl)-DPTA exhibits little uptake in non-tumorous tissues, particularly the liver, and enhances specificity of tumor localization (Esteban *et al.*, *J. Nucl. Med.* 28:861-870 (1987)). Examples of suitable non-radioactive isotopic labels include ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Tr, and ^{56}Fe.

[00256] Examples of suitable fluorescent labels include an ^{152}Eu label, a fluorescein label, an isothiocyanate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, a Green Fluorescent Protein (GFP) label, an o-phthaldehyde label, and a fluorescamine label. Examples of suitable toxin labels include diphtheria toxin, ricin, and cholera toxin.

[00257] Examples of chemiluminescent labels include a luminol label, an isoluminol label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, and an aequorin label. Examples of nuclear magnetic resonance contrasting agents include heavy metal nuclei such as Gd, Mn, and iron.

[00258] The detection method of the present technology can be used to detect an immunoreactive target antigen in a biological sample *in vitro* as well as *in vivo*. *In vitro* techniques for detection of an immunoreactive target antigen include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, radioimmunoassay, and immunofluorescence. Furthermore, *in vivo* techniques for detection of an

immunoreactive target antigen include introducing into a subject a labeled heterodimeric trivalent/tetravalent multispecific antibody. For example, the heterodimeric trivalent/tetravalent multispecific antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. In one embodiment, the biological sample contains target antigen molecules from the test subject.

[00259] *Immunoassay and Imaging.* A heterodimeric trivalent/tetravalent multispecific antibody of the present technology can be used to assay immunoreactive target antigen levels in a biological sample (*e.g.*, human plasma) using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. Jalkanen, M. *et al.*, *J. Cell. Biol.* 101: 976-985, 1985; Jalkanen, M. *et al.*, *J. Cell. Biol.* 105: 3087-3096, 1987. Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes or other radioactive agent, such as iodine (^{125}I, ^{121}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99}mTc), and fluorescent labels, such as fluorescein, rhodamine, and green fluorescent protein (GFP), as well as biotin.

[00260] In addition to assaying immunoreactive target antigen levels in a biological sample, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology may be used for *in vivo* imaging of the target antigen. Antibodies useful for this method include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which can be incorporated into the heterodimeric trivalent/tetravalent multispecific antibodies by labeling of nutrients for the relevant scFv clone.

[00261] A heterodimeric trivalent/tetravalent multispecific antibody which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (*e.g.*, ^{131}I, ^{112}In, ^{99}mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (*e.g.*, parenterally, subcutaneously, or intraperitoneally) into the subject. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a

radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99}mTc. The labeled heterodimeric trivalent/tetravalent multispecific antibody will then accumulate at the location of cells which contain the specific target antigen. For example, labeled heterodimeric trivalent/tetravalent multispecific antibodies of the present technology will accumulate within the subject in cells and tissues in which the target antigen has localized.

[00262] Thus, the present technology provides a diagnostic method of a medical condition, which involves: (a) assaying the expression of immunoreactive target antigen by measuring binding of a heterodimeric trivalent/tetravalent multispecific antibody of the present technology in cells or body fluid of an individual; (b) comparing the amount of immunoreactive target antigen present in the sample with a standard reference, wherein an increase or decrease in immunoreactive target antigen levels compared to the standard is indicative of a medical condition.

[00263] *Affinity Purification.* The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology may be used to purify immunoreactive target antigen from a sample. In some embodiments, the antibodies are immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir *et al.*, "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10 (1986); Jacoby *et al.*, *Meth. Enzym.* 34 Academic Press, N.Y. (1974)).

[00264] The simplest method to bind the antigen to the antibody-support matrix is to collect the beads in a column and pass the antigen solution down the column. The efficiency of this method depends on the contact time between the immobilized antibody and the antigen, which can be extended by using low flow rates. The immobilized antibody captures the antigen as it flows past. Alternatively, an antigen can be contacted with the antibody-support matrix by mixing the antigen solution with the support (*e.g.*, beads) and rotating or rocking the slurry, allowing maximum contact between the antigen and the immobilized antibody. After the binding reaction has been completed, the slurry is passed into a column for collection of the beads. The beads are washed using a suitable washing buffer and then the pure or substantially pure antigen is eluted.

[00265] An antibody or target antigen of interest can be conjugated to a solid support, such as a bead. In addition, a first solid support such as a bead can also be conjugated, if desired, to a second solid support, which can be a second bead or other support, by any suitable means, including those disclosed herein for conjugation of a molecule to a support. Accordingly, any of the conjugation methods and means disclosed herein with reference to conjugation of a molecule to a solid support can also be applied for conjugation of a first support to a second support, where the first and second solid support can be the same or different.

[00266] Appropriate linkers, which can be cross-linking agents, for use for conjugating a molecule to a solid support include a variety of agents that can react with a functional group present on a surface of the support, or with the molecule, or both. Reagents useful as cross-linking agents include homo-bi-functional and, in particular, hetero-bi-functional reagents. Useful bi-functional cross-linking agents include, but are not limited to, *N*-SIAB, dimaleimide, DTNB, N-SATA, N-SPDP, SMCC and 6-HYNIC. In one exemplary embodiment, a cross-linking agent can be selected to provide a selectively cleavable bond between a target polypeptide and the solid support. For example, a photolabile cross-linker, such as 3-amino-(2-nitrophenyl)propionic acid can be employed as a means for cleaving a target polypeptide from a solid support. (Brown *et al., Mol. Divers*, pp, 4-12 (1995); Rothschild *et al., Nucl. Acids Res.,* 24:351-66 (1996); and US. Pat. No. 5,643,722). Other cross-linking reagents are well-known in the art. (*See*, *e.g.*, Wong (1991), *supra*; and Hermanson (1996), *supra*).

[00267] An antibody or target polypeptide can be immobilized on a solid support, such as a bead, through a covalent amide bond formed between a carboxyl group functionalized bead and the amino terminus of the target polypeptide or, conversely, through a covalent amide bond formed between an amino group functionalized bead and the carboxyl terminus of the target polypeptide. In addition, a bi-functional trityl linker can be attached to the support, *e.g.*, to the 4-nitrophenyl active ester on a resin, such as a Wang resin, through an amino group or a carboxyl group on the resin *via* an amino resin. Using a bi-functional trityl approach, the solid support can require treatment with a volatile acid, such as formic acid or trifluoroacetic acid to ensure that the target polypeptide is cleaved and can be removed. In such a case, the target polypeptide can be deposited as a beadless patch at the bottom of a

well of a solid support or on the flat surface of a solid support. After addition of a matrix solution, the target polypeptide can be desorbed into a MS.

[00268] Hydrophobic trityl linkers can also be exploited as acid-labile linkers by using a volatile acid or an appropriate matrix solution, *e.g.*, a matrix solution containing 3-HPA, to cleave an amino linked trityl group from the target polypeptide. Acid lability can also be changed. For example, trityl, monomethoxytrityl, dimethoxytrityl or trimethoxytrityl can be changed to the appropriate *p*-substituted, or more acid-labile tritylamine derivatives, of the target polypeptide, *i.e.*, trityl ether and tritylamine bonds can be made to the target polypeptide. Accordingly, a target polypeptide can be removed from a hydrophobic linker, *e.g.*, by disrupting the hydrophobic attraction or by cleaving tritylether or tritylamine bonds under acidic conditions, including, if desired, under typical MS conditions, where a matrix, such as 3-HPA acts as an acid.

[00269] Orthogonally cleavable linkers can also be useful for binding a first solid support, *e.g.*, a bead to a second solid support, or for binding a molecule of interest to a solid support. Using such linkers, a first solid support, *e.g.*, a bead, can be selectively cleaved from a second solid support, without cleaving the target antigen from the support; the target antigen then can be cleaved from the bead at a later time. For example, a disulfide linker, which can be cleaved using a reducing agent, such as DTT, can be employed to bind a bead to a second solid support, and an acid cleavable bi-functional trityl group could be used to immobilize a target antigen to the support. As desired, the linkage of the target antigen to the solid support can be cleaved first, *e.g.*, leaving the linkage between the first and second support intact. Trityl linkers can provide a covalent or hydrophobic conjugation and, regardless of the nature of the conjugation, the trityl group is readily cleaved in acidic conditions.

[00270] For example, a bead can be bound to a second support through a linking group which can be selected to have a length and a chemical nature such that high density binding of the beads to the solid support, or high density binding of the target antigens to the beads, is promoted. Such a linking group can have, *e.g.*, "tree-like" structure, thereby providing a multiplicity of functional groups per attachment site on a solid support. Examples of such linking group; include polylysine, polyglutamic acid, penta-erythrole and *tris*-hydroxy-aminomethane.

[00271] *Noncovalent Binding Association.* An antibody or target antigen can be conjugated to a solid support, or a first solid support can also be conjugated to a second solid support, through a noncovalent interaction. For example, a magnetic bead made of a ferromagnetic material, which is capable of being magnetized, can be attracted to a magnetic solid support, and can be released from the support by removal of the magnetic field. Alternatively, the solid support can be provided with an ionic or hydrophobic moiety, which can allow the interaction of an ionic or hydrophobic moiety, respectively, with a target antigen, *e.g.*, a polypeptide containing an attached trityl group or with a second solid support having hydrophobic character.

[00272] A solid support can also be provided with a member of a specific binding pair and, therefore, can be conjugated to a target antigen or a second solid support containing a complementary binding moiety. For example, a bead coated with avidin or with streptavidin can be bound to a target antigen (*e.g.*, a polypeptide) having a biotin moiety incorporated therein, or to a second solid support coated with biotin or derivative of biotin, such as iminobiotin.

[00273] It should be recognized that any of the binding members disclosed herein or otherwise known in the art can be reversed. Thus, biotin, *e.g.*, can be incorporated into either a target antigen or a solid support and, conversely, avidin or other biotin binding moiety would be incorporated into the support or the target antigen, respectively. Other specific binding pairs contemplated for use herein include, but are not limited to, hormones and their receptors, enzyme, and their substrates, a nucleotide sequence and its complementary sequence, an antibody and the antigen to which it interacts specifically, and other such pairs known to those skilled in the art.

A. Diagnostic Uses

[00274] *General.* The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are useful in diagnostic methods. As such, the present technology provides methods using the antibodies in the diagnosis of activity of a molecule of interest in a subject. Heterodimeric trivalent/tetravalent multispecific antibodies of the present technology may be selected such that they have any level of epitope binding specificity and binding affinity to a target antigen. In general, the higher the binding affinity of an antibody, the more stringent wash conditions can be performed in an immunoassay to remove

nonspecifically bound material without removing the molecule of interest. Accordingly, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology useful in diagnostic assays usually have binding affinities of about 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1} or 10^{12} M^{-1}. Further, it is desirable that heterodimeric trivalent/tetravalent multispecific antibodies used as diagnostic reagents have a sufficient kinetic on-rate to reach equilibrium under standard conditions in at least 12 h, at least five (5) h, or at least one (1) hour.

[00275] Heterodimeric trivalent/tetravalent multispecific antibodies can be used to detect an immunoreactive target antigen in a variety of standard assay formats. Such formats include immunoprecipitation, Western blotting, ELISA, radioimmunoassay, and immunometric assays. *See* Harlow & Lane, *Antibodies, A Laboratory Manual* (Cold Spring Harbor Publications, New York, 1988); U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,879,262; 4,034,074, 3,791,932; 3,817,837; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; and 4,098,876. Biological samples can be obtained from any tissue or body fluid of a subject. In certain embodiments, the subject is at an early stage of cancer. In one embodiment, the early stage of cancer is determined by the level or expression pattern of a target antigen in a sample obtained from the subject. In certain embodiments, the sample is selected from the group consisting of urine, blood, serum, plasma, saliva, amniotic fluid, cerebrospinal fluid (CSF), and biopsied body tissue.

[00276] Immunometric or sandwich assays are one format for the diagnostic methods of the present technology. *See* U.S. Pat. No. 4,376,110, 4,486,530, 5,914,241, and 5,965,375. Such assays use one antibody, *e.g.*, a heterodimeric trivalent/tetravalent multispecific antibody or a population of heterodimeric trivalent/tetravalent multispecific antibodies immobilized to a solid phase, and another heterodimeric trivalent/tetravalent multispecific antibody or a population of heterodimeric trivalent/tetravalent multispecific antibodies in solution. Typically, the solution heterodimeric trivalent/tetravalent multispecific antibody or population of heterodimeric trivalent/tetravalent multispecific antibodies is labeled. If an antibody population is used, the population can contain antibodies binding to different epitope specificities within the target antigen. Accordingly, the same population can be used for both solid phase and solution antibody. If heterodimeric trivalent/tetravalent multispecific monoclonal antibodies are used, first and second monoclonal heterodimeric trivalent/tetravalent multispecific antibodies having different binding specificities are used

for the solid and solution phase. Solid phase (also referred to as "capture") and solution (also referred to as "detection") antibodies can be contacted with target antigen in either order or simultaneously. If the solid phase antibody is contacted first, the assay is referred to as being a forward assay. Conversely, if the solution antibody is contacted first, the assay is referred to as being a reverse assay. If the target is contacted with both antibodies simultaneously, the assay is referred to as a simultaneous assay. After contacting the target antigen with the heterodimeric trivalent/tetravalent multispecific antibody, a sample is incubated for a period that usually varies from about 10 min to about 24 hr and is usually about 1 hr. A wash step is then performed to remove components of the sample not specifically bound to the heterodimeric trivalent/tetravalent multispecific antibody being used as a diagnostic reagent. When solid phase and solution antibodies are bound in separate steps, a wash can be performed after either or both binding steps. After washing, binding is quantified, typically by detecting a label linked to the solid phase through binding of labeled solution antibody. Usually for a given pair of antibodies or populations of antibodies and given reaction conditions, a calibration curve is prepared from samples containing known concentrations of target antigen. Concentrations of the immunoreactive target antigen in samples being tested are then read by interpolation from the calibration curve (*i.e.*, standard curve). Analyte can be measured either from the amount of labeled solution antibody bound at equilibrium or by kinetic measurements of bound labeled solution antibody at a series of time points before equilibrium is reached. The slope of such a curve is a measure of the concentration of the target antigen in a sample.

[00277] Suitable supports for use in the above methods include, *e.g.*, nitrocellulose membranes, nylon membranes, and derivatized nylon membranes, and also particles, such as agarose, a dextran-based gel, dipsticks, particulates, microspheres, magnetic particles, test tubes, microtiter wells, SEPHADEX™ (Amersham Pharmacia Biotech, Piscataway N.J.), and the like. Immobilization can be by absorption or by covalent attachment. Optionally, heterodimeric trivalent/tetravalent multispecific antibodies can be joined to a linker molecule, such as biotin for attachment to a surface bound linker, such as avidin.

[00278] In some embodiments, the present disclosure provides a heterodimeric trivalent/tetravalent multispecific antibody of the present technology conjugated to a diagnostic agent. The diagnostic agent may comprise a radioactive or non-radioactive label, a contrast agent (such as for magnetic resonance imaging, computed tomography or

ultrasound), and the radioactive label can be a gamma-, beta-, alpha-, Auger electron-, or positron-emitting isotope. A diagnostic agent is a molecule which is administered conjugated to an antibody moiety, *i.e.*, antibody or antibody fragment, or subfragment, and is useful in diagnosing or detecting a disease by locating the cells containing the antigen. Radioactive levels emitted by the antibody may be detected using positron emission tomography or single photon emission computed tomography.

[00279] Useful diagnostic agents include, but are not limited to, radioisotopes, dyes (such as with the biotin-streptavidin complex), contrast agents, fluorescent compounds or molecules and enhancing agents (*e.g.*, paramagnetic ions) for magnetic resonance imaging (MRI). U.S. Pat. No. 6,331,175 describes MRI technique and the preparation of antibodies conjugated to a MRI enhancing agent and is incorporated in its entirety by reference. In some embodiments, the diagnostic agents are selected from the group consisting of radioisotopes, enhancing agents for use in magnetic resonance imaging, and fluorescent compounds. In order to load an antibody component with radioactive metals or paramagnetic ions, it may be necessary to react it with a reagent having a long tail to which are attached a multiplicity of chelating groups for binding the ions. Such a tail can be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which can be bound chelating groups such as, *e.g.*, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups known to be useful for this purpose. Chelates may be coupled to the antibodies of the present technology using standard chemistries. The chelate is normally linked to the antibody by a group which enables formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking. Other methods and reagents for conjugating chelates to antibodies are disclosed in U.S. Pat. No. 4,824,659. Particularly useful metal-chelate combinations include 2-benzyl-DTPA and its monomethyl and cyclohexyl analogs, used with diagnostic isotopes for radio-imaging. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and gadolinium are useful for MRI, when used along with the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology.

B. Therapeutic Uses

[00280] The immunoglobulin-related compositions (*e.g.*, heterodimeric trivalent/tetravalent multispecific antibodies) of the present technology are useful for the treatment of a disease or condition. Exemplary diseases or conditions include, but are not limited to cardiovascular disease, diabetes, autoimmune disease, dementia, Parkinson's disease, cancer or Alzheimer's disease. Such treatment can be used in patients identified as having pathological levels of a molecule of interest (*e.g.*, those diagnosed by the methods described herein) or in patients diagnosed with a disease known to be associated with such pathological levels. In one aspect, the present disclosure provides a method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a heterodimeric trivalent/tetravalent multispecific antibody of the present technology. Examples of cancers that can be treated by the antibodies of the present technology include, but are not limited to: lung cancer, colorectal cancer, skin cancer, breast cancer, ovarian cancer, leukemia, pancreatic cancer, and gastric cancer.

[00281] The compositions of the present technology may be employed in conjunction with other therapeutic agents useful in the treatment of cancer. For example, the antibodies of the present technology may be separately, sequentially or simultaneously administered with at least one additional therapeutic agent-selected from the group consisting of alkylating agents, platinum agents, taxanes, vinca agents, anti-estrogen drugs, aromatase inhibitors, ovarian suppression agents, VEGF/VEGFR inhibitors, EGF/EGFR inhibitors, PARP inhibitors, cytostatic alkaloids, cytotoxic antibiotics, antimetabolites, endocrine/hormonal agents, bisphosphonate therapy agents and targeted biological therapy agents (*e.g.*, therapeutic peptides described in US 6306832, WO 2012007137, WO 2005000889, WO 2010096603 *etc.*). In some embodiments, the at least one additional therapeutic agent is a chemotherapeutic agent. Specific chemotherapeutic agents include, but are not limited to, cyclophosphamide, fluorouracil (or 5-fluorouracil or 5-FU), methotrexate, edatrexate (10-ethyl-10-deaza-aminopterin), thiotepa, carboplatin, cisplatin, taxanes, paclitaxel, protein-bound paclitaxel, docetaxel, vinorelbine, tamoxifen, raloxifene, toremifene, fulvestrant, gemcitabine, irinotecan, ixabepilone, temozolmide, topotecan, vincristine, vinblastine, eribulin, mutamycin, capecitabine, anastrozole, exemestane, letrozole, leuprolide, abarelix, buserlin, goserelin, megestrol acetate, risedronate, pamidronate, ibandronate, alendronate, denosumab, zoledronate, trastuzumab, tykerb, anthracyclines (*e.g.*, daunorubicin and

doxorubicin), bevacizumab, oxaliplatin, melphalan, etoposide, mechlorethamine, bleomycin, microtubule poisons, annonaceous acetogenins, or combinations thereof.

[00282] In another aspect, the antibodies of the present technology may be separately, sequentially or simultaneously administered with one or more therapeutic agents useful in the treatment of Alzheimer's disease. Examples of such therapeutic agents include acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine), donepezil hydrochloride, and rivastigmine; gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; antioxidants such as Vitamin E and ginkolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454).

[00283] The compositions of the present technology may optionally be administered as a single bolus to a subject in need thereof. Alternatively, the dosing regimen may comprise multiple administrations performed at various times after the appearance of tumors or amyloid plaques.

[00284] Administration can be carried out by any suitable route, including orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), rectally, intracranially, intrathecally, or topically. Administration includes self-administration and the administration by another. It is also to be appreciated that the various modes of treatment of medical conditions as described are intended to mean "substantial", which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved.

[00285] In some embodiments, the antibodies of the present technology comprise pharmaceutical formulations which may be administered to subjects in need thereof in one or more doses. Dosage regimens can be adjusted to provide the desired response (*e.g.*, a therapeutic response).

[00286] Typically, an effective amount of the antibody compositions of the present technology, sufficient for achieving a therapeutic effect, range from about 0.000001 mg per kilogram body weight per day to about 10,000 mg per kilogram body weight per day. Typically, the dosage ranges are from about 0.0001 mg per kilogram body weight per day to about 100 mg per kilogram body weight per day. For administration of heterodimeric

trivalent/tetravalent multispecific antibodies, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg every week, every two weeks or every three weeks, of the subject body weight. For example, dosages can be 1 mg/kg body weight or 10 mg/kg body weight every week, every two weeks or every three weeks or within the range of 1-10 mg/kg every week, every two weeks or every three weeks. In one embodiment, a single dosage of antibody ranges from 0.1-10,000 micrograms per kg body weight. In one embodiment, antibody concentrations in a carrier range from 0.2 to 2000 micrograms per delivered milliliter. An exemplary treatment regime entails administration once per every two weeks or once a month or once every 3 to 6 months. Heterodimeric trivalent/tetravalent multispecific antibodies may be administered on multiple occasions. Intervals between single dosages can be hourly, daily, weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the antibody in the subject. In some methods, dosage is adjusted to achieve a serum antibody concentration in the subject of from about 75 μg/mL to about 125 μg/mL, 100 μg/mL to about 150 μg/mL, from about 125 μg/mL to about 175 μg/mL, or from about 150 μg/mL to about 200 μg/mL. Alternatively, heterodimeric trivalent/tetravalent multispecific antibodies can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the subject. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, or until the subject shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[00287] *Toxicity*. Optimally, an effective amount (*e.g.*, dose) of heterodimeric trivalent/tetravalent multispecific antibody described herein will provide therapeutic benefit without causing substantial toxicity to the subject. Toxicity of the heterodimeric trivalent/tetravalent multispecific antibody described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of the

heterodimeric trivalent/tetravalent multispecific antibody described herein lies within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the subject's condition. *See*, *e.g.*, Fingl *et al.*, In: *The Pharmacological Basis of Therapeutics*, Ch. 1 (1975).

Formulations of Pharmaceutical Compositions

[00288] *Formulations of Pharmaceutical Compositions.* According to the methods of the present technology, the heterodimeric trivalent/tetravalent multispecific antibodies can be incorporated into pharmaceutical compositions suitable for administration. The pharmaceutical compositions generally comprise recombinant or substantially purified antibody and a pharmaceutically-acceptable carrier in a form suitable for administration to a subject. Pharmaceutically-acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions for administering the antibody compositions (*See, e.g.*, *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA 18th ed., 1990). The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[00289] The terms "pharmaceutically-acceptable," "physiologically-tolerable," and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to a subject without the production of undesirable physiological effects to a degree that would prohibit administration of the composition. For example, "pharmaceutically-acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. "Pharmaceutically-acceptable salts and esters" means salts and esters that are pharmaceutically-acceptable and have the desired pharmacological properties. Such salts include salts that can be formed where acidic protons present in the composition are capable of reacting with inorganic or organic bases.

Suitable inorganic salts include those formed with the alkali metals, *e.g.*, sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, *e.g.*, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Such salts also include acid addition salts formed with inorganic acids (*e.g.*, hydrochloric and hydrobromic acids) and organic acids (*e.g.*, acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically-acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the heterodimeric trivalent/tetravalent multispecific antibody, *e.g.*, C_{1-6} alkyl esters. When there are two acidic groups present, a pharmaceutically-acceptable salt or ester can be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly where there are more than two acidic groups present, some or all of such groups can be salified or esterified. A heterodimeric trivalent/tetravalent multispecific antibody named in this technology can be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such heterodimeric trivalent/tetravalent multispecific antibody is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically-acceptable salts and esters. Also, certain embodiments of the present technology can be present in more than one stereoisomeric form, and the naming of such heterodimeric trivalent/tetravalent multispecific antibody is intended to include all single stereoisomers and all mixtures (whether racemic or otherwise) of such stereoisomers. A person of ordinary skill in the art, would have no difficulty determining the appropriate timing, sequence and dosages of administration for particular drugs and compositions of the present technology.

[00290] Examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and compounds for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or compound is incompatible with the heterodimeric trivalent/tetravalent multispecific antibody, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00291] A pharmaceutical composition of the present technology is formulated to be compatible with its intended route of administration. The heterodimeric trivalent/tetravalent multispecific antibody compositions of the present technology can be administered by

parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intradermal, transdermal, rectal, intracranial, intrathecal, intraperitoneal, intranasal; or intramuscular routes, or as inhalants. The heterodimeric trivalent/tetravalent multispecific antibody can optionally be administered in combination with other agents that are at least partly effective in treating a disease or medical condition described herein.

[00292] Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and compounds for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00293] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, *e.g.*, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, *e.g.*, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal compounds, *e.g.*, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be desirable to include isotonic compounds, *e.g.*, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the

injectable compositions can be brought about by including in the composition a compound which delays absorption, *e.g.*, aluminum monostearate and gelatin.

[00294] Sterile injectable solutions can be prepared by incorporating a heterodimeric trivalent/tetravalent multispecific antibody of the present technology in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the heterodimeric trivalent/tetravalent multispecific antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The antibodies of the present technology can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[00295] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the heterodimeric trivalent/tetravalent multispecific antibody can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding compounds, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating compound such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening compound such as sucrose or saccharin; or a flavoring compound such as peppermint, methyl salicylate, or orange flavoring.

[00296] For administration by inhalation, the heterodimeric trivalent/tetravalent multispecific antibody is delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[00297] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, *e.g.*, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the heterodimeric trivalent/tetravalent multispecific antibody is formulated into ointments, salves, gels, or creams as generally known in the art.

[00298] The heterodimeric trivalent/tetravalent multispecific antibody can also be prepared as pharmaceutical compositions in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00299] In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody is prepared with carriers that will protect the heterodimeric trivalent/tetravalent multispecific antibody against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically-acceptable carriers. These can be prepared according to methods known to those skilled in the art, *e.g.*, as described in U.S. Pat. No. 4,522,811.

Kits

[00300] The present technology provides kits for the detection and/or treatment of cancer, comprising at least one heterodimeric trivalent/tetravalent multispecific antibody composition described herein, or a functional variant (*e.g.*, substitutional variant) thereof. Optionally, the above described components of the kits of the present technology are packed in suitable containers and labeled for diagnosis and/or treatment of cancer. The above-mentioned components may be stored in unit or multi-dose containers, for example, sealed ampoules, vials, bottles, syringes, and test tubes, as an aqueous, preferably sterile, solution or as a

lyophilized, preferably sterile, formulation for reconstitution. The kit may further comprise a second container which holds a diluent suitable for diluting the pharmaceutical composition towards a higher volume. Suitable diluents include, but are not limited to, the pharmaceutically acceptable excipient of the pharmaceutical composition and a saline solution. Furthermore, the kit may comprise instructions for diluting the pharmaceutical composition and/or instructions for administering the pharmaceutical composition, whether diluted or not. The containers may be formed from a variety of materials such as glass or plastic and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper which may be pierced by a hypodermic injection needle). The kit may further comprise more containers comprising a pharmaceutically acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, culture medium for one or more of the suitable hosts. The kits may optionally include instructions customarily included in commercial packages of therapeutic or diagnostic products, that contain information about, for example, the indications, usage, dosage, manufacture, administration, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[00301] The kits are useful for detecting the presence of a target antigen in a biological sample, *e.g.*, any body fluid including, but not limited to, *e.g.*, serum, plasma, lymph, cystic fluid, urine, stool, cerebrospinal fluid, ascitic fluid or blood and including biopsy samples of body tissue. For example, the kit can comprise: one or more heterodimeric trivalent/tetravalent multispecific antibodies of the present technology capable of binding a target antigen in a biological sample; means for determining the amount of the target antigen in the sample; and means for comparing the amount of the immunoreactive target antigen in the sample with a standard. One or more of the heterodimeric trivalent/tetravalent multispecific antibodies may be labeled. The kit components, (*e.g.*, reagents) can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect the immunoreactive target antigen.

[00302] For antibody-based kits, the kit can comprise, *e.g.*, 1) a first antibody, *e.g.* a humanized, or chimeric heterodimeric trivalent/tetravalent multispecific antibody of the present technology, attached to a solid support, which binds to a target antigen; and,

optionally; 2) a second, different antibody which binds to either the target antigen or to the first antibody, and is conjugated to a detectable label.

[00303] The kit can also comprise, *e.g.*, a buffering agent, a preservative or a protein-stabilizing agent. The kit can further comprise components necessary for detecting the detectable-label, *e.g.*, an enzyme or a substrate. The kit can also contain a control sample or a series of control samples, which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit. The kits of the present technology may contain a written product on or in the kit container. The written product describes how to use the reagents contained in the kit, *e.g.*, for detection of a target antigen *in vitro* or *in vivo*, or for treatment of cancer in a subject in need thereof. In certain embodiments, the use of the reagents can be according to the methods of the present technology.

EXAMPLES

[00304] The present technology is further illustrated by the following Examples, which should not be construed as limiting in any way.

Example 1: Materials and Methods

[00305] *Protein production.* All proteins were expressed using the expi293 expression system (Thermo Fisher Scientific, Waltham MA) according to manufacturer's instructions. Briefly, maxiprepped plasmids containing each antibody were diluted and incubated with expifectamine for 20min before being added to expi293s in shaker flasks. Cells were incubated for 4 days or until cell viability dropped <70%, whichever came first. IgG-based proteins were purified over a protein A column using a GE P920 AKTA FPLC and eluted using 50mM Citric acid. The BiTE was purified using prepacked Ni^{2+}NTA columns (GE) and eluted using a 250mM imidazole buffer. All proteins were run on SEC-HPLC to validate their size and quantify their purity.

[00306] *Heterodimerization.* Heterodimerization was achieved using Fab Arm Exchange (FAE). Briefly, K409R and F405L mutations were placed in the Fc regions of each reciprocal pair of IgG or IgG-[L]-scFv bispecific antibodies to be heterodimerized. Paired homodimers were then mixed at 3 different molar rations (1:1, 1.2:1 and 1:1.2) and incubated

in reducing conditions for 5hrs at 30°C before being dialyzed overnight at room temperature in sodium citrate buffer (pH 8.2). After an initial overnight dialysis, samples were moved to 4°C for another 24hrs before being analyzed by SEC-HPLC and CZE chromatography to assess heterodimerization yields. In all experiments the 1:1 ratio was used, after validating its purity was optimal.

[00307] *Cell lines*. EL.4 cells were obtained from ATCC. M14 cells were obtained from ATCC and transfected with luciferase prior to use in all assays. IMR32 cells were obtained from ATCC and transfected with luciferase prior to use in all assays. Molm13-fluc cells were a gift from the Brentjens lab. Naïve T-cells were purified from PBMCs using the Dynabeads™ Untouched™ human T cells kit, according to manufacturer's protocol. Activated T cells were generated by using CD3/CD28 dynabeads and 30U/ml of human IL-2. T-cells were stimulated twice, at day 0 and day 7, and used in cytotoxicity, cell binding or conjugate assays day 15-18 of culture.

[00308] *Cell binding FACS*. For cell binding assays, 1M cells were incubated with 5pmol of antibody for 30min at 4°C, followed by either an anti-human Fc secondary or an anti-3F8 or anti-OKT3 idiotype antibody (5pmol) and the corresponding anti-Fc secondary (anti-rat APC or anti-mouse PE, respectively). Samples were acquired using a FACSCalibur and analyzed by FlowJo.

[00309] *Affinity Measurements*. Binding kinetics were evaluated using SPR (GE, Biacore T200). Briefly, chips were coated with GD2, CD33 or huCD3de antigen and a titration series of each bispecific antibody were flowed over them. Binding affinities were calculated using a two-state reaction model.

[00310] *Cytotoxicity measurements*. Cytotoxicity was evaluated using a 4hr ^{51}Cr release assay. Briefly, 1M target cells were incubated with 100 μCi of activity and incubated with activated human T cells (10:1 E:T) and serially titrated bispecific antibody. Released ^{51}Cr was measured using a gamma counter.

[00311] *Animal Models*. All experiments have been conducted in accordance with and approved by the Institutional Animal Care and Use Committee in MSKCC. Two mouse models were used: (1) a humanized immunodeficient xenograft model (huDKO) and (2) a transgenic huCD3e-expressing syngeneic model (huCD3e-tg). Briefly, huDKO (Balb/C IL2rg$^{-/-}$, Rag2$^{-/-}$) mice were implanted subcutaneously with 2M M14 melanoma cells. After

5-15 days, mice were treated with intravenous activated human T cells (20-40M/dose), intravenous bispecific antibody (25pmol/dose) and subcutaneous IL-2 (100U/dose) for three weeks. For huCD3e-tg (C57BL/6) mice were implanted subcutaneously with EL.4 lymphoma cells. After 7 days, mice were treated intravenous bispecific antibody (25pmol/dose) for three weeks. For BiTEs, either 7 pmol or 350 pmol were administered daily for 3 weeks. Weights and tumor volumes were measured once per week and overall mouse health was evaluated at least 3-times per week. Mice were sacrificed if tumor volumes reached 1.5-2.0cm^3 volumes. No toxicities were seen during treatment of any mice.

[00312] *Conjugate formation*. For conjugate assays, T cells were labeled with CFSE (2.5 μM) and M14 melanoma cells were labeled with CTV (2.5 μM). 50M/ml cells were incubated with dye for 5min at room temperature, followed by the addition of 30ml of complete RPMI (supplemented with 10% fetal calf serum (heat inactivated), 2mM glutamine and 1% P/S) and incubated at 37°C for 20min. Cells were pelleted and washed with complete medium twice before being added antibodies or cells. Labeled cells were mixed at a 1:5 ratio (E:T) along with serially titrated bispecific antibody, in duplicate. After 30min, cells were fixed with a final concentration of 2% PFA (10min, RT) and washed in 5ml of PBS. Cells were acquired using a BD LSR Fortessa and analyzed using Flowjo.

[00313] *Activation assay*. Purified naïve T cells were incubated with M14 melanoma cells (10:1 E:T) and serially titrated bispecific antibody, in duplicate. After 24hrs supernatant was collected and frozen at -80°C. Cells were then stained with antibodies against CD4, CD8, CD45, and CD69 to assess the CD69 upregulation. For the 96hr assay, T cells were first labeled with 2.5μM of CTV. After 96hrs cells were stained with antibodies against CD4, CD8, CD45 and CD25 to assess CD25 upregulation and CTV dilution.

[00314] *Cytokine Assay*. Frozen supernatant from the activation assay (24hr) was used to quantify cytokine production after 24hrs of coculture. IL-2, IFNγ, IL-10, IL-6 and TNFα were measured with the 5-plex legend plex system according to manufacturer guidelines.

[00315] **Figure 23** provides a summary of the various HDTVS antibodies tested in the Examples disclosed herein. The table summarizes all successfully produced HDTVS formatted multi-specific antibodies across a variety of antigen models. All clones were expressed in Expi293 cells and heterodimerized using the controlled Fab Arm Exchange method. HDTVS type displays the category of each clone. Fab 1 and scFv 1 (and

corresponding Ag1 and Ag3) are attached in a cis-orientation on one heavy chain (linked by the light chain of Fab) while Fab 2 and scFv 2 (and corresponding Ag2 and Ag4) are on a separate heavy chain molecule in a cis-orientation (linked by the light chain of Fab).

[00316] *Sequences. The amino acid sequences utilized in the Examples are provided below:*

Anti-HER2

LC (VL-CL-scFv):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTSGGGGSGGGGSGGG
GSQVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGYINPS
RGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYW
GQGTPVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVG
DRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDYTFTI
SSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR (SEQ ID NO: 2353)

HC (VH-CH1-CH2-CH3, N297A, K322A):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 2354)

HC (VH-CH1-CH2-CH3, N297A, K322A, F405L):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW

GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 2355)

HC (VH-CH1-CH2-CH3, N297A, K322A, K409R):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 2356)

Anti-GD2

LC (VL-CL-scFv):

EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAPRLLIYSASNRYSG
VPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTSGGGGSGGGGSGGGGS
QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRG
YTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQ
GTPVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDR
VTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDYTFTISS
LQPEDIATYYCQQWSSNPFTFGCGTKLQITR (SEQ ID NO: 2357)

LC (VL-CL):

EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAPRLLIYSASNRYSG
VPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 2358)

HC (VH-CH1-CH2-CH3, N297A, K322A):

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGVIWAGGI
TNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGGHYGYALDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 2359)

HC (VH-CH1-CH2-CH3, N297A, K322A, F405L):

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGVIWAGGI
TNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGGHYGYALDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 2360)

HC (VH-CH1-CH2-CH3, N297A, K322A, K409R):

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGVIWAGGI
TNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGGHYGYALDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG

VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 2361)

Anti-GD2(2)

LC (VL-CL-scFv):

KIVMTQTPATLSVSAGERVTITCKASQSVSNHVTWYQQKPGQAPRLLIYSASNRYSG
VPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTSGGGGSGGGGSGGGGS
QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRG
YTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQ
GTPVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDR
VTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDYTFTISS
LQPEDIATYYCQQWSSNPFTFGCGTKLQITR (SEQ ID NO: 2362)

LC (VL-CL):

KIVMTQTPATLSVSAGERVTITCKASQSVSNHVTWYQQKPGQAPRLLIYSASNRYSG
VPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 2363)

HC (VH-CH1-CH2-CH3, N297A, K322A):

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGVIWAGGI
TNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGGHYGYALDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT

PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2364)

HC (VH-CH1-CH2-CH3, N297A, K322A, F405L):

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGVIWAGGI
TNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGGHYGYALDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2365)

HC (VH-CH1-CH2-CH3, N297A, K322A, K409R):

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGVIWAGGI
TNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGGHYGYALDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2366)

Anti-GD2(3)

LC (VL-CL-scFv):

EIVMTQSPATLSVSPGERATLSCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIHKVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPPLTFGAGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTSGGGGSGG
GGSGGGGSQVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEW

IGYINPSRGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHY SLDYWGQGTPVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSL SASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGT DYTFTISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR (SEQ ID NO: 2367)

LC (VL-CL):

EIVMTQSPATLSVSPGERATLSCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIHKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPPLTFGAGTKLELKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 2368)

HC (VH-CH1-CH2-CH3, N297A, K322A):

EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGAIDPYYGG TSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGMEYWGQGTSVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2369)

HC (VH-CH1-CH2-CH3, N297A, K322A, F405L):

EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGAIDPYYGG TSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGMEYWGQGTSVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2370)

HC (VH-CH1-CH2-CH3, N297A, K322A, K409R):

EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGAIDPYYGG
TSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGMEYWGQGTSVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2371)

Anti-CD33

LC (VL-CL-scFv):

EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPGQPPRLLIYAASNQ
GSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPWTFGGGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTSGGGGSGGGG
SGGGGSQVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIG
YINPSRGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSL
DYWGQGTPVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLS
ASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGTD
YTFTISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR (SEQ ID NO: 2372)

LC (VL-CL):

EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPGQPPRLLIYAASNQ
GSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPWTFGGGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:
2373)

HC (VH-CH1-CH2-CH3, N297A, K322A):

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGYIYPYNG
GTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGRPAMDYWGQGTL

VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID
NO: 2374)

HC (VH-CH1-CH2-CH3, N297A, K322A, F405L):

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGYIYPYNG
GTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGRPAMDYWGQGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID
NO: 2375)

HC (VH-CH1-CH2-CH3, N297A, K322A, K409R):

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGYIYPYNG
GTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGRPAMDYWGQGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID
NO: 2376)

Anti-CD3

LC (VL-CL):

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGV
PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGQGTKLQITRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 2377)

HC (VH-CH1-CH2-CH3, N297A, K322A):

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRG
YTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQ
GTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 2378)

HC (VH-CH1-CH2-CH3, N297A, K322A, F405L):

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRG
YTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQ
GTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 2379)

HC (VH-CH1-CH2-CH3, N297A, K322A, K409R):

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRG
YTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQ
GTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV

EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2380)

huOKT3-VL (SEQ ID NO: 2390)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGV PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGCGTKLQIT

huOKT3-VH (SEQ ID NO: 2391)

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRG YTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQ GTPVTVSS

huA33-VL (SEQ ID NO: 2392)

DIQMTQSQSSLSTSVGDRVTITCKASQNVRTVVAWYQQKPGKSPKTLIYLASNRHTG VPSRFSGSGSGTEFTLTISNVQPEDFADYFCLQHWSYPLTFGSGTKLEIK

huA33-VH (SEQ ID NO: 2393)

EVQLVESGGGLVKPGGSLRLSCAASGFAFSTYDMSWVRQAPGKRLEWVATISSGGS YTYYLDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAPTTVVPFAYWGQGTL VTVSS

huM195-VL (SEQ ID NO: 2394)

EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPGQPPRLLIYAASNQ GSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPWTFGGGTKLEIK

huM195-VH (SEQ ID NO: 2395)

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGYIYPYNG GTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGRPAMDYWGQGTL VTVSS

Example 2: Functionality of Lo1+1+2, Hi1+1+1 and 2+1+1 HDTVS Variants

[00317] **Figure 1a** shows the basic design strategy of each HDTVS variant compared with the parental 2+2 IgG-[L]-scFv. **Figures 1b-1g** describe each of the three designs in more detail.

[00318] The Lo1+1+2 utilizes two different Fab domains that (a) target two distinct antigens within a tumor and (b) have moderate to low binding affinities (*e.g.* K_D 100 nM – 100 pM), and two identical scFvs that target an immune cell so as to improve tumor cell specificity. As illustrated in **Figure 1b**, this design targets tumors more specifically due to its unexpectedly poor activity when only one of the two Fab domains is engaged with the tumor target (such as when only one of the two Fab domain-specific antigens is expressed). Importantly, when both Fab domains bind their respective tumor targets, normal cytotoxic potency is restored. This allows for improved therapeutic index (or safety) when the target antigens are not unique to the tumor, where each target antigen (but never both) is shared to some extent by normal cells. While a standard BsAb or 2+2 design would harm normal tissues, this Lo1+1+2 design should spare normal tissues that express only one of the two targeted antigens, while maintaining the full potency against a tumor cell that expresses both antigens.

[00319] As illustrated in **Figure 1c**, the Hi1+1+2 design is capable of recognizing two distinct antigens with equal potency, regardless of simultaneous binding. Since Fab domains of appropriately high affinity (*e.g.*, K_D <100 pM) are sufficient to induce potent cytotoxicity even monovalently, two different Fab domains can be used to broaden the tumor cell selectivity and permits targeting of heterogeneous tumors with a single drug.

[00320] The 2+1+1 design is capable of improved immune cell interactions by virtue of its dual specificity toward the immune cell, either improving activation or providing more selective activation. As demonstrated herein, the second scFv domain is somewhat dispensable due to the biophysical properties of the IgG-[L]-scFv platform. Thus, using two different scFv domains can provide a greater diversity of interactions than a normal bivalent approach. As illustrated in **Figure 1d**, the 2+1+1 design can be used to both improve signaling in a more selective population of immune cells (B1(+)B2(+)) or to enhance activation through colocalization of complementary pairs of receptors. Importantly, the 2+1+1 design can be used to interact with activating receptors and/or inhibitory receptors or

antagonistic antibodies that specifically inhibit signaling of certain immune cell pathways, such as blocking PD-1 on T cells while activating through CD3.

[00321] The 2+1+1 design takes advantage of the two anti-immune cell binding domains to recruit a broader selection of immune cells (*e.g.*, anti-CD3 for T cells + anti-CD16 for NK cells) or for combinatorial recruitment of payloads with immune cells as theranostics (*e.g.*, anti-CD3 for T cells and anti-BnDOTA for imaging). As illustrated in **Figure 1e**, the 2+1+1 design takes advantage of the minimal differences in therapeutic activity between a 2+1 design and a 2+2 design to add a new function, thus broadening the selection of delivered anti-tumor activity to multiple types of immune cells or to chemical or radiological payloads.

[00322] The 1+1+1+1 format combines the previous 4 designs to take advantage of all possible combinations. As shown in **Figure 1f**, this allows for the combinatorial properties of the 2+1+1 design to be combined with the specificity or selectivity improvements from the Hi1+1+2 and Lo1+1+2 designs.

Example 3: – Superiority of 2+2 IgG-[L]-scFv Design over BiTE and IgG-Het

[00323] **Figure 2a-2b** show the unexpected benefits of the IgG-[L]-scFv (2+2 BsAb) over other common designs such as IgG-Het and BiTE, highlighting both the benefit of having a valency >1 and the structural properties imparted by a Fab/scFv combination. As shown in **Figure 2a**, the top panels compare cytotoxicity, cell binding and antigen affinity properties between the IgG-[L]-scFv, IgG-Het and BiTE formats.

[00324] The left most panel shows that the 2+2 BsAb achieved nearly 1,000-fold improved cytotoxicity over the 1+1 IgG-Het and >20-fold than the 1+1 BiTE. Measurements were made using a standard four hour ^{51}Cr release assay using activated human T cells and GD2(+) M14-luciferase cells, with each antibody diluted over 7-logs. The center panel shows the varying levels of antigen binding (GD2 or CD3) between these three formats using GD2(+) M14-luciferase cells or CD3(+) activated human T cells. Cells were stained with each of the three formats and detected using either anti-hu3F8 or anti-huOKT3 idiotypic antibodies. As with the cytotoxicity, the cell binding to both antigens was superior for the 2+2 BsAb due to increased valency. The right panel displays the binding kinetics against the antigen GD2 for each of the three platforms. The 2+2 BsAb exhibited stronger antigen binding over either 1+1 design (BITE or IgG-Het). The bottom panels compare these three constructs in two separate animal models: a huCD3(+) transgenic syngeneic mouse model

(left panel) or a humanized immunodeficient xenograft mouse model (right panel). Both models had antibodies injected twice per week and began approximately one week after tumor implantation. Only the 2+2 BsAb was capable of delaying subcutaneous GD2(+) EL.4 tumor growth in the syngeneic model. The 1+1 IgG-Het and the 1+1 BiTE were just as ineffective as the inactive negative control BsAb. Administering the BiTE format daily or at a 10x higher dose level ("hi dose" group, syngeneic mice, **Figure 2a**) did not result in any anti-tumor effect. In the xenograft model, where human ATCs and IL-2 were added to support T cell survival in all groups, the 1+1 IgG-Het still failed to show any benefit compared to the control, while the 2+2 BsAb strongly inhibited subcutaneous GD2(+) M14Luc tumors. As show in **Figure 2b**, these striking differences in cytotoxicity between the IgG-[L]-scFv and IgG-Het formats were reproducible using two additional anti-GD2 antibodies, suggesting that the effects were not specific to any one GD2 epitope.

[00325] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 4: Characterization of IgG-[L]-scFv HDTVS Variants

[00326] **Figure 3** describes the characterization of the IgG-[L]-scFv platform to identify the necessity and sufficiency of each binding domain as well as their relative impact on overall functional activity. Unexpectedly, the changes in valency did not entirely correlate with changes in functional output, suggesting a preference for tumor binding by the Fab domain over immune cell binding by the scFv domain, as well as a preference for cis-oriented domains over trans-oriented domains.

[00327] As illustrated in **Figure 3**, the four IgG-[L]-scFv variants display potencies somewhere between the parental 2+2 IgG-[L]-scFv (top left) and the IgG-Het (bottom right). The 2+1 BsAb (second from left) used heterodimerization to remove one of the two immune cell binding scFv domains yet functioned quite similarly to the parental 2+2 BsAb. Neutralization of the second tumor cell binding Fab domain to create a 1+2 BsAb (third from right) reduced the potency further, but unexpectedly additional removal of an scFv domain did not significantly change the potency, as long as the two remaining domains were in a Cis orientation (1+1C, third from left). Neutralization of the second tumor cell binding Fab was achieved by replacing it with a Fab that binds CD33, an antigen not found on tumor cells or T cells. Neutralization/removal of both the tumor binding Fab domain and the T cell engaging

scFv domain in a Trans orientation (1+1T, second from right) caused the biggest drop in potency (equivalent to the IgG-Het), even lower than the 1+1C despite equivalent valency. These results demonstrate that orientation or spatial arrangements of the antigen binding domains are important determinants of therapeutic potency.

[00328] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 5: Modifications of the 2+2 IgG-[L]-scFv and Their Relative Binding Activities

[00329] **Figure 4** describes the binding activities of each IgG-[L]-scFv variant, compared to the parental 2(GD2)+2(CD3) BsAb and the IgG-Het. Monovalency towards tumor (*e.g.* 1+2), was created by changing one of the 2 Fab domains to an irrelevant binder (*i.e.*, a huCD33 targeting Fab). Monovalency (*e.g.* 2+1) towards T cells is created by removing one of the two scFv domains. As illustrated in **Figure 4**, bivalency improves antigen binding over monovalency (upper panels). Surface Plasmon Resonance was used to measure antigen binding kinetics against both GD2 coated chips (upper left) and CD3 coated chips (upper right). Briefly, each BsAb was serially titrated and flowed against each chip. Against GD2, the 2+2 BsAb and 2(GD2)+1(CD3) BsAb showed equivalent binding activities whereas the 1+1C, 1+1T, 1+2 and 1+1 IgG-Het all displayed inferior GD2 binding. Against CD3, the pattern was similar, with bivalency being superior over monovalency, but to a lesser extent (which may be attributable in part to the spatial restrictions of bivalent scFv binding compared to Fab binding). The 2+2 and 1+2 BsAb showed the strongest binding, while the 2+1, 1+1T and 1+1C exhibited inferior binding kinetics. The Fab binding domain of the IgG-Het appeared to show some benefit over a monovalent scFv, but this may result from the more stable sequence of a Fab domain compared with an scFv domain, where CH1/CL interactions are lacking. Compared to SPR, cell binding (measured as described in **Figure 2** but using a standard anti-Fc secondary antibody instead of using anti-idiotypic antibodies) showed similar results (bottom left). GD2 binding (left Y-axis) was the strongest in constructs with bivalency (2+2, 2+1), and less for constructs with monovalency (1+1T, 1+1C, 1+2 and IgG-Het). The same pattern was observed with CD3-specific cell binding (right Y-axis), with 2+2 and 1+2 binding being more effective than 2+1, 1+1T and 1+1C.

[00330] Similar to the CD3-specific SPR readings, the IgG-Het showed stronger Fab binding than scFv binding. Conjugate formation between targets and effector cells when

mixed together with titrated BsAb (bottom right), showed much smaller differences between IgG-[L]-scFv variants. The 2+2 BsAb showed the most efficient conjugate formation activity, followed by the 2+1 BsAb and then all others (except control). These results demonstrate that after the removal of the second anti-effector cell scFv, all other changes to the IgG-[L]-scFv do not markedly reduce its capacity to conjugate effector target cells together, or that the small differences in cell binding activities do not impact conjugate formation or the stability of conjugate formation.

[00331] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 6: Modifications of the 2+2 IgG-[L]-scFv and their Relative Cytotoxicity

[00332] **Figure 5** describes the anti-tumor cytotoxicity of each IgG-[L]-scFv variant *in vitro*, across two GD2(+) cell lines. As illustrated in **Figure 5** and summarized in **TABLE 2**, the variants showed a wide range of cytotoxic potency (assays were performed as described in **Figure 2**).

TABLE 2

	K_D				Cytotoxic EC50	
	GD2	**Fold Change**	**CD3**	**Fold Change**	**EC50**	**Fold Change**
2+2	2.8 nM	-	10 nM	-	17 fM	-
2+1	2.5 nM	0.9	310 nM	30.1	106 fM	6.2
1+1C	30 nM	10.9	110 nM	11.0	292 fM	17.2
1+2	31 nM	11.3	11 nM	1.0	454 fM	26.7
1+1H	31 nM	11.4	70 nM	6.8	14 pM	823.5
1+1T	21 nM	7.7	88 nM	8.5	13 pM	764.7

[00333] Against both tumor cell lines, the 2+2 BsAb displayed the highest cytotoxic effect, followed by the 2+1 and then both 1+1C and 1+2. Interestingly, the 1+1T and IgG-Het (nearly 1,000-fold worse than 2+2) were nearly identical to each other, suggesting that: the cis-oriented binding domains provide superior killing activity compared to trans-oriented binding domains, and that a 2+1 interaction is superior to a 1+2 interaction. Despite the similarities of both the trans and cis oriented 1+1 variants having identical tumor cell binding, effector cell binding capacities, antigen binding kinetics, and conjugate formation activity, the cis-trans orientations of these two constructs differ substantially in the functional output (50-fold) as measured by *in vitro* cytotoxicity. This unexpected observation may account for why the 1+2 fails to kill as potently as the 2+1. Without wishing to be bound by theory, it is believed that the 1+2 interaction may be caught between a cis and trans interaction at all times, while the 2+1 is more often in a cis interaction. An alternative possibility is that the tumor-binding Fab domains may be more critical for driving anti-tumor potency.

[00334] Additionally, the value of each domain and its orientation was quantified. While the 2+2 was about 1,000-fold more potent than the IgG-Het (or 1+1T), it was only 6-fold more potent than the 2+1, and 20-25 fold more potent than the 1+2 or 1+1C. These data

demonstrate that the second scFv imparts about 6-fold change in activity (2+2 is 6-fold better than 2+1), the bivalent Fab imparts about 25-fold change (2+2 is up to 25-fold better than 1+2 domain) and the Cis/Trans orientation imparts another 50-fold change (1+1C is 50-fold better than 1+1T).

[00335] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 7: Modifications of the 2+2 IgG-[L]-scFv and Their Relative Immune Cell Activation

[00336] **Figure 6** describes the cell activation properties of each IgG-[L]-scFv variant *in vitro*. As illustrated in **Figure 6**, the variations made to the IgG-[L]-scFv variants significantly influence their capacity to activate immune cells. The upper panels show upregulation of CD69 expression on T cells after 24 hours of *in vitro* coculture with varying concentrations of each BsAb and GD2(+) M14Luc tumor cells. As in **Figure 5**, valency and cis/trans orientation appear to play an important role, suggesting that the activation potency and cytotoxicity are correlated. The 2+2 BsAb again displayed its superiority over all other variants tested, at both the level of expression level of CD69 (left) and the frequency of CD69(+) cells (right). Removal of a single domain (2+1 or 1+2) markedly lowered activation, and was made worse with the transition to 1+1C, 1+1T and finally IgG-Het. A similar pattern emerged after 96 hr of coculture (bottom panel). CD25 expression remained the highest for the 2+2, both in terms of expression level (left) and frequency of CD25(+) (center) cells. All other variants showed reduced activation of effector T cells. Proliferation was also measured using Cell Trace Violet (CTV) dilution. T cells were labeled with the cell penetrating dye CTV and incubated with target cells (M14Luc) and titrated with BsAb for 96hrs. The frequency of cells fluorescing with less remaining CTV than an unstimulated control was considered to have divided at least once. As such, proliferation was the greatest for the 2+2 and reduced for all other IgG-[L]-scFv variants (right). No activation or proliferation was observed with any construct in the absence of tumor cells (data not shown) indicating that there is minimal activation without target antigen. These results demonstrate that a cis interaction is considerably more potent than a trans interaction (1+1C vs 1+1T) and furthermore that two cis interactions are more potent than one (2+2 vs 1+1C or 1+2 or 2+1) (two cis interactions are only possible in a dual bivalent approach, such as the 2+2 IgG-[L]-scFv).

[00337] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 8: Modifications of the 2+2 IgG-[L]-scFv and Their Relative In Vivo Tumor Clearance

[00338] **Figure 7** describes the *in vivo* anti-tumor activity of each IgG-[L]-scFv variant in two different tumor models. As illustrated in **Figure 7**, the *in vivo* anti-tumor activity of each variant largely correlated with *in vitro* cytotoxicity. In the xenograft model (right) the strongest anti-tumor activity was imparted by the 2+2 BsAb. Surprisingly, the 2+1 was very similar, with only a slight difference in tumor recurrence (5/5 CR for both). As with the cytotoxicity data, the next most effective were the 1+1C and 1+2, validating both *in vitro* findings that the cis orientation is superior to the trans and the 2+1 was superior to the 1+2. All other variants (1+1T, IgG-Het, control BsAb) failed to show any effect on tumor growth. In the more aggressive syngeneic model using EL.4 tumors (as done in **Figure 1**), no IgG-[L]-scFv variant aside from the 2+2 showed an anti-tumor effect. As opposed to the xenograft model where activated T-cells are directly administered to the mouse, the syngeneic model requires activation *in situ*, suggesting that the *in vitro* cell activation differences may manifest *in vivo* leading to diminished capacity to shrink tumors. Taken together, these results suggest that the optimal BsAb platform is capable of strong cell activation in the presence of antigen, and that bivalency toward both cell populations, target cells and effector cells, is critical. In addition, these results confirm the importance of two cis-interactions in a bispecific antibody (2+2) over all single cis-interacting variants (2+1, 1+1C, 1+2) or non-cis interacting variants (1+1T, 1+1H).

[00339] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 9: 2+2 IgG-[L]-scFv is Superior to Other Bivalent Antibody Designs

[00340] **Figure 8** shows cytotoxicity and conjugate formation activity from 3 additional 2+2 designs, thus demonstrating the overall superiority of the IgG-[L]-scFv format. The 2+2 IgG-[L]-scFv format was more demonstrably more potent than other conventional 2+2 formats. The IgG-chemical conjugate (Yankelevich *et al.*, *Pediatr Blood Cancer* 59:1198-1205 (2012)) the IgG-[H]-scFv (with scFv attached at the C-terminus of the HC instead of the LC of the IgG; Coloma & Morrison, *Nat Biotechnol* 15:159-163 (1997)) and the BITE-Fc, all

failed to kill cells as potently *in vitro*, compared with the IgG-[L]-scFv design. The poor cytotoxic effects were observed despite apparently improved conjugate formation activity (bottom left) and cell binding activity (bottom right). These results demonstrate that the structural features of the IgG-[L]-scFv format (unique flexibility, orientations and arrangements of the four antigen binding domains) may be correlated with effects on T-cell recruitment, activation and cytotoxicity. **Figures 12a-12c** show the *in vivo* anti-tumor activity from two additional 2+2 designs, thus confirming the overall superiority of the IgG-[L]-scFv format (2+2). Using an *in vivo* T-cell arming model, only the IgG-[L]-scFv format (2+2) of the present technology was able to inhibit tumor growth. Strikingly, despite the dual bivalency of the dimeric BiTE-Fc and the IgG-[H]-scFv, both failed to display any anti-tumor activity compard to the control BsAb. These results confirm the *in vitro* findings, that the superiority of the IgG-[L]-scFv design is not strictly due to decreased distance between binding domains, but instead suggests that the potency of the IgG-[L]-scFv is not simply a function of minimization of intermembrane distance. Rather, the exceptional *in vitro* and *in vivo* potency of the IgG-[L]-scFv may be attributed at least in part to the properties of cis-configured Fab and scFv domains, spaced apart with a single Ig domain (C_L), such as stiffness or flexibility.

[00341] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 10: 2+2 IgG-[L]-scFv and Subset of Variants Against Alternative Antigens

[00342] **Figure 9** describes some of the differences in activity observed with different tumor antigens. As illustrated in **Figure 9**, the IgG-[L]-scFv platform does depend in part on the tumor antigen. When targeted to CD33 (top panels) a similar pattern of cell binding and cytotoxicity was found. CD33(+) MOLM13-fluc cells were assayed as described in **Figure 4** (left). As with GD2, reduction in valency (1+1T, 1+1C, or 1+2) significantly decreased binding activity. In terms of cytotoxicity, the Cis/Trans orientation appeared to play less of a role (both 1+1T and 1+C are most inferior, and equivalent to IgG-Het), and therefore the difference between the 2+1 and 1+2 was diminished. The lack of cis/trans difference may also explain the overall worse EC50 against CD33(+) MOLM-13fluc as compared to GD2(+) M14Luc or IMR32Luc. When the tumor antigen was changed to HER2 (lower panels), and the antigen binding domains possessed significantly higher binding affinity, a different pattern was observed. 2+2 and 1+2 variants appeared identical, with similar tumor binding

levels despite the monovalency. This suggests that with sufficiently high affinities, the second tumor binding domain is dispensable, as predicated in the Hi1+1+2 HDTVS design.

[00343] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 11: Hi1+1+2 and Lo1+1+2 Proof of Concept Studies

[00344] As depicted in **Figure 10a** (left side), the 2(HER2)+2(CD3) functions similarly to the 1(HER2) + 2(CD3), where only one Fab domain binds the tumor and the second Fab recognizes an irrelevant antigen, due to the very high affinity interaction between HER2 and the anti-HER2 Fab used (Herceptin). In both FACS binding (top) and an *in vitro* cytotoxicity assay (bottom) with U2OS cells, the 2(HER2)+2(CD3) and the 1(HER2)+2(CD3) were indistinguishable, highlighting the possibility of using the second Fab arm to target a separate antigen. Conversely, the Lo1(GD2) +1(GD2) +2(CD3) (right side), shows the utility of two separate tumor antigen specificities when binding affinities are sufficiently low. Here the 2(GD2)+2(CD3), the 1(GD2) +2(CD3) and Lo1(GD2)+1(GD2) +2(CD3) showed major differences that are explained by the differences in valency between constructs. In both FACS binding (top) and *in vitro* cytotoxicity (bottom) with U2OS cells, the 2(GD2) +2(CD3) displayed superior activity over a 1(GD2) +2(CD3) format having an irrelevant second specificity (thus limiting binding to monovalency). However, adding a second relevant Fab binding specificity (*e.g.* HER2) in Lo1(GD2) +1(HER2) +2(CD3) was able to rescue this defect and even improve binding and killing. These results highlight the utility of targeting two separate antigens on the same cell when the Fab affinity for each individual antigen is sufficiently low (*e.g.*, 100 pM to 100 nM K_D). Additionally, the approximately 100-fold difference in EC50 between the Lo1(GD2) +1(HER2)+2(CD3) and 1(GD2)+2(CD3) validates the improved therapeutic index between monovalent and bivalent binding of a Lo1(GD2)+1(HER2)+2(CD3) construct. Had the second specificity (*i.e.* HER2) of the Lo1+1+2(GD2) been irrelevant (no binding to tumor or T cells), it would have functioned as the 1(GD2) +2(CD3) with 100-fold less activity. This is in contrast to the 2+2 which would not be able to distinguish a dual-antigen positive tumor from a GD2(+) normal tissue (such as peripheral nerves).

[00345] As shown in **Figure 10b**, when these two sets of constructs were presented to tumor cells expressing high levels of only one antigen (HER2 and GD2, left and right sides

respectively), the same patterns were observed. With the 2(HER2) +2(CD3) and 1(HER2) +2(CD3), similar FACS binding and cytotoxicity were observed against the HCC1954 cell line which shows high expression of HER2(+). However, stronger binding and cytotoxicity was observed with the 2(GD2)+2(CD3) compared to the 1(GD2)+2(CD3) and a Lo1(GD2)+1(HER2)+2(CD3) having an irrelevant second specificity (second Fab domain did not recognize the tumor cell line IMR32Luc).

[00346] Taken together, with a sufficiently high effective affinity interaction a 1+2 IgG-[L]-scFv functions identically to a 2+2, suggesting the Hi1+1+2 can be used to target two separate antigens instead of just one. However, with a sufficiently low effective affinity interaction, a Lo1+1+2 can provide an improved therapeutic index to distinguish between single antigen positive normal tissue and double antigen positive tumor cells.

[00347] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 12: Binding Affinity and Cytotoxic Selectivity of the Low Affinity 1+1+2 Format Antibodies of the Present Technology

[00348] The binding affinity of L1CAM/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody, which can bind ganglioside GD2 and adhesion protein L1CAM simultaneously, was compared with homodimeric formats against GD2 and L1CAM. Neuroblastoma cells (IMR32) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in **Figure 13**, the binding of the low affinity 1+1+2 HDTVS antibody was stronger than that of the anti-L1CAM homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody, thus showing improved targeting specificity for tumors expressing both GD2 and L1CAM.

[00349] The combined binding effect of GD2/B7H3 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody, which can bind both GD2 and B7H3 simultaneously was also compared with the homodimeric format antibodies against GD2 and B7H3, and monovalent control antibodies against GD2 or B7H3. Osteosarcoma cells (U2OS) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in **Figure 15**, the binding of the low affinity 1+1+2 heterodimer antibody was similar

to the anti-B7H3 homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody. Importantly, the GD2/B7H3 1+1+2 Lo HDTVS antibody also shows improved binding over monovalent control antibodies, thus demonstrating cooperative binding of the heterodimeric GD2/B7H3 1+1+2 Lo antibody.

[00350] To assess the cytotoxic selectivity of the low affinity 1+1+2Lo format antibodies of the present technology, HER2/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody, which can bind both GD2 and HER2 simultaneously, was studied. In this format, a low affinity HER2 sequence was used. Homodimeric formats against GD2 and HER2, and monovalent control antibodies against GD2 or HER2 were included for reference. Osteosarcoma cells (U2OS) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the antibodies and activated human T-cells for four hours at 37°C. After four hours, supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. As shown in **Figure 16**, the low affinity 1+1+2 heterodimer antibody killed U2OS cells as effectively as the anti-GD2 and anti-HER2 homodimeric antibodies and showed clear superiority over the monovalent control formats. Therefore, the 1+1+2Lo design exhibited 10-100-fold lower cytotoxic potency in cells expressing each individual antigen compared to target cells expressing both antigens simultaneously. A homodimeric design for either GD2 or HER2 would not be expected to exhibit such selectivity.

[00351] These results demonstrate the selective cytotoxicity could be attained with the 1+1+2Lo design by targeting cells expressing each individual antigen with 10-100-fold lower cytotoxic potency than targets expressing both antigens simultaneously.

[00352] Accordingly, the 1+1+2Lo format antibodies of the present technology are useful in methods for treating a disease or condition, such as cancer.

Example 13: Binding Affinity and Cytotoxic Dual Specificity of the 1+1+2Hi Format Antibodies of the Present Technology

[00353] To assess the binding affinity of the heterodimeric 1+1+2Hi format antibodies of the present technology, the combined binding effect of HER2/EGFR 1+1+2Hi, a heterodimeric 1+1+2Hi format antibody, which can bind both HER2 and EGFR, either simultaneously or separately, was analyzed. Homodimeric formats against HER2 and EGFR were included for reference. Desmoplastic Small Cell Round Tumor cells (JN-DSRCT1)

were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. As shown in **Figure 14**, the binding of the high affinity 1+1+2 heterodimer antibody was stronger than that of either anti-HER2 or anti-EGFR homodimeric antibodies, while maintaining specificity for both antigens, thus demonstrating cooperative binding.

[00354] HER2/GPA33 1+1+2 Hi, a heterodimeric 1+1+2Hi format antibody, which can bind both GPA33 and HER2 either simultaneously or separately, was compared with the homodimeric format antibodies against GPA33 and HER2, and monovalent control antibodies against GPA33 or HER2. To compare the combined binding effect, colon cancer cells (Colo205) were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. HER2/GPA33 1+1+2 Hi antibody bound both HER2 and GPA33 on Colo205 cells, either simultaneously or separately (**Figure 17b**). As shown in **Figure 17b**, the binding affinity of the 1+1+2Hi heterodimer antibody was stronger than either anti-HER2 or anti-GPA33 homodimeric and monovalent control antibodies, while maintaining specificity for both antigens, thus demonstrating cooperative binding.

[00355] To evaluate the cytotoxic specificity of the HER2/GPA33 1+1+2Hi format antibody, colon cancer cells (Colo205) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the indicated antibody and activated human T-cells for four hours at 37°C. After four hours, the supernatant was harvested and read on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. As shown in **Figure 17a**, the high affinity 1+1+2 heterodimer antibody killed Colo205 cells as effectively as the anti-GPA33 homodimeric antibody, but with greather potency than the anti-HER2 homodimeric antibody and monovalent control antibodies. These results demonstrate functional cooperativity between the HER2 and GPA33 antigen binding domains, and illustrate that the dual specificity of a 1+1+2Hi format does not significantly compromise its cytotoxicity against either antigen individually.

[00356] Accordingly, the 1+1+2Hi format antibodies of the present technology are useful in methods for treating a disease or condition, such as cancer.

Example 14: Combined Binding Effects and Cytokine Release Induced by the 2+1+1 Format Antibodies of the Present Technology

[00357] To evaluate the combined binding effects of the heterodimeric 2+1+1 format antibodies of the present technology, several heterodimeric 2+1+1 format antibodies were compared with their corresponding homodimeric format antibodies and monovalent control antibodies. For example, CD3/CD4 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and CD4 simultaneously was compared with its corresponding bivalent format antibodies against CD3 and CD4, and a monomeric CD3 binder (2+1). For this binding assay, active human T cells were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in **Figure 19**, the binding of CD3/CD4 2+1+1 antibodies showed enhanced binding compared to the bivalent CD4 antibody and monomeric CD3 binder (2+1), thus demonstrating cooperative binding.

[00358] Similarly, binding of CD3/PD-1 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and PD-1 simultaneously, was compared with homodimeric anti-PD-1 and anti-CD3 antibodies, and with an anti-CD3 monomeric (2+1) binder. For this binding assay active human T cells were incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in **Figure 20**, the 2+1+1 heterodimer antibody bound cells better than either anti-PD-1 homodimeric antibody or anti-CD3 monomeric (2+1) binder, thus demonstrating cooperative binding. Collectively, these data demonstrate that a heterodimeric 2+1+1 format antibody of the present technology binds its target better than the corresponding weaker-binding homodimeric antibody and its corresponding monomeric (2+1) binder, thus demonstrating cooperative binding.

[00359] Next, cytokine release induced by CD3/CD28 2+1+1, a heterodimeric 2+1+1 format antibody, was analyzed. The homodimeric format antibodies against CD3 and CD28 were included for reference. Naïve human T-cells and melanoma tumor cells (M14) were co-cultured along with the indicated BsAb for 20 hours. Culture supernatants were harvested following the incubation and analyzed for secreted cytokine IL-2 by FACS. Data were normalized to T-cell cytokine release after 20 hours without target cells or antibody. As shown in **Figure 18**, the CD3/CD28 2+1+1 antibody showed more potent cytokine release activity compared to either CD3 or CD28 engagement alone, illustrating cooperative activity

from dual CD3/CD28 engagement. These results demonstrate the utility of a heterodimeric 2+1+1 design that can bind both CD3 and CD28 on T-cells.

[00360] Accordingly, the 2+1+1 format antibodies of the present technology are useful in methods for treating a disease or condition, such as cancer.

Example 15: Comparison of the IgG-L-scFv Format of the Present Technology with BiTE-Fc and IgG-H-scFv Formats

[00361] The IgG-L-scFv design was next compared with two other common dual bivalent design strategies: the BiTE-Fc and the IgG-H-scFv formats. First, to compare cytokine release induced by IgG-L-scFv design compared to BiTE-Fc and the IgG-H-scFv, naïve T-cells and melanoma tumor cells (M14) were co-cultured along with each BsAb for 20 hours. Culture supernatants were harvested and analyzed for secreted cytokine IL-2. Data were normalized to T-cell cytokine release after 20 hours without target cells or antibody. As shown in **Figure 21a**, the IgG-L-scFv design (2+2) exhibited unusually potent T-cell functional activity compared to other dual bivalent T-cell bispecific antibody formats.

[00362] To compare binding intensity, T-cells and melanoma tumor cells (M14) were separately incubated with each antibody for 30 minutes at 4°C, washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in **Figure 21b** (upper panel), IgG-L-scFv design showed unusually weak T-cell binding activity compared to other dual bivalent T-cell bispecific antibody formats. In contrast to their GD2 binding activity (**Figure 21b** (middle panel)), each BsAb demonstrated quite different T-cell binding activities. These data demonstrated how the IgG-L-scFv design is uniquely different than other dual-bivalent designs, with each scFv showing incomplete bivalent binding. Although the inclusion of two scFv domains in the IgG-L-scFv did result in an improvement over monovalent designs, it still did not compare to the binding activity of the 2+2 IgG-H-scFv or 2+2 BiTE-Fc designs, illustrating the sterically hindered binding of this format.

[00363] The effect of the observed binding and cytokine release profiles on the *in vivo* antitumor activity was explored next. Immunodeficient mice (Balb/c IL-2Rgc-/-, Rag2-/-) were implanted with neuroblastoma cells (IMR32) subcutaneously and treated with intravenous activated T-cells and antibody (2-times per week). Tumors sizes were measured by caliper. As shown in **Figure 21c**, the IgG-L-scFv design antibodies inhibited tumor

growth. In comparison, the IgG-H-scFv and BiTE-Fc design antibodies showed a borderline *in vivo* effect. Therefore, in contrast to the IgG-H-scFv (2+2HC) and the BiTE-Fc (2+2B) designs, the IgG-L-scFv format (2+2) demonstrated significant cytokine IL-2 responses *in vitro* (**Figure 21a**), which correlated with stronger *in vivo* activity (**Figure 21c**).

[00364] Collectively, these data demonstrate the *in vivo* superiority of the IgG-L-scFv format antibodies in that only the IgG-L-scFv format antibodies were capable of inhibiting tumor growth in animals in contrast to other dual bivalent designs.

[00365] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 16: Importance of Cis-Oriented Binding Domains With Respect to In vitro Properties of an Anti-IgG-[L]-scFv Antibody

[00366] To further understand the *in vitro* properties of antibodies of various designs, a anti-CD33 IgG-[L]-scFv panel was created, and the *in vitro* cytotoxicity EC_{50}, fold-difference in EC_{50}, antigen valency, heterodimer design and protein purity were examined. **Figure 22** summarizes the data. Fold change was based on the EC_{50} of 2+2. Purity was calculated as the fraction of protein at correct elution time out of the total protein by area under the curve of the SEC-HPLC chromatogram. For the cytotoxicity assays, CD33-transfected cells (Nalm6) were first incubated with ^{51}Cr for one hour. Afterwards, ^{51}Cr labeled target cells were mixed with serial titrations of the indicated antibody and activated human T-cells for four hours at 37°C. The supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. These results shown in **Figure 22** confirm the relative importance of cis-oriented binding domains in an additional antigen system (CD33) which is much more membrane distal than GD2 (see **Figure 5**).

[00367] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

EQUIVALENTS

[00368] The present technology is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects

of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the present technology. It is to be understood that this present technology is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[00369] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[00370] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, *etc.* As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, *etc.* As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

[00371] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

CLAIMS

1. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;

ii. a light chain constant domain of the first immunoglobulin (CL-1);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and

iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment;

b. the second polypeptide comprises in the N-terminal to C-terminal direction:

i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;

ii. a first CH1 domain of the first immunoglobulin (CH1-1); and

iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;

c. the third polypeptide comprises in the N-terminal to C-terminal direction:

i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope;

ii. a second CH1 domain of the third immunoglobulin (CH1-3); and

iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid

sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope;

ii. a light chain constant domain of the third immunoglobulin (CL-3);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and

iv. a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment, and

wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713,

1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or

wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349.

2. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;

ii. a light chain constant domain of the first immunoglobulin (CL-1);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and

iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein the VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment;

b. the second polypeptide comprises in the N-terminal to C-terminal direction:

i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;

ii. a first CH1 domain of the first immunoglobulin (CH1-1); and

iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;

c. the third polypeptide comprises in the N-terminal to C-terminal direction:

i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope;

ii. a second CH1 domain of the third immunoglobulin (CH1-3); and

iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope;

ii. a light chain constant domain of the third immunoglobulin (CL-3);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and

iv. a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein the VL-4 and VH-4 are capable of specifically binding to a third epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment, and

wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein each of V-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

3. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;
   ii. a light chain constant domain of the first immunoglobulin (CL-1);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and
   iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment;
b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;
c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and
   iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope;

ii. a light chain constant domain of the third immunoglobulin (CL-3);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and

iv. a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the fourth epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment; and

wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or

wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein each of V-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909,

917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

4. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;
   ii. a light chain constant domain of the first immunoglobulin (CL-1);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and
   iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment;
b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;
c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and

iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; and

ii. a light chain constant domain of the third immunoglobulin (CL-3); and wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein V-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

5. The heterodimeric multispecific antibody of claim 4, wherein both VH-1 and VH-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85,

93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein both VL-1 and VL-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

6. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;
   ii. a light chain constant domain of the first immunoglobulin (CL-1);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$; and
   iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ to form a single-chain variable fragment;
b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;
c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and
   iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid

sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; and

ii. a light chain constant domain of the third immunoglobulin (CL-3); and

wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or

wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157,

165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein V-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

7. The heterodimeric multispecific antibody of any one of claims 1-6, wherein VH-1 or VH-3 comprise a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein the VL-1 or VL-3 comprise a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113,

2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

8. The heterodimeric multispecific antibody of any one of claims 1-7, wherein VH-2 or VH-4 comprise a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349; and/or
wherein VL-2 or VL-4 comprise a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345.

9. The heterodimeric multispecific antibody of any one of claims 1-8, wherein each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301

respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029

respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629

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respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

10. The heterodimeric multispecific antibody of any one of claims 1-9, wherein each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485

respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237

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respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

11. The heterodimeric multispecific antibody of any one of claims 1-8, wherein each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53

respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469

respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

12. The heterodimeric multispecific antibody of any one of claims 1-8 or 11, wherein each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301

respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565

respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

13. The heterodimeric multispecific antibody of any one of claims 1-12, wherein each of VL-2 and VH-2 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397

respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925

respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

14. The heterodimeric multispecific antibody of any one of claims 1-3 or 7-12, wherein each of VL-4 and VH-4 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757

respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

15. The heterodimeric multispecific antibody of any one of claims 1-14, wherein the first immunoglobulin or the third immunoglobulin binds to a cell surface antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7 +aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NT5E), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR- HER3, EGFRvIII, EphA3, ERGT(GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis

X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin 5AC, NaPi2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC[MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC[MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B.

16. The heterodimeric multispecific antibody of any one of claims 1-15, wherein the first immunoglobulin and the third immunoglobulin bind to two different epitopes on a target cell.

17. The heterodimeric multispecific antibody of claim 16, wherein the target cell is a cancer cell.

18. The heterodimeric multispecific antibody of any one of claims 1-17, wherein the second immunoglobulin or the fourth immunoglobulin bind to an epitope on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

19, The heterodimeric multispecific antibody of any one of claims 1-3 or 7-18, wherein the second immunoglobulin or the fourth immunoglobulin bind to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7 +aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2.

20. The heterodimeric multispecific antibody of any one of claims 1-3 or 7-19, wherein the second immunoglobulin and the fourth immunoglobulin bind to two different epitopes on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

21. The heterodimeric multispecific antibody of any one of claims 1-3 or 7-19, wherein the second immunoglobulin binds CD3 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD4, CD8, CD25, CD28, CTLA4, OX40, ICOS, PD-1, PD-L1, 41BB, CD2, CD69, and CD45.

22. The heterodimeric multispecific antibody of any one of claims 1-3 or 7-19, wherein the second immunoglobulin binds CD16 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD56, NKG2D, and KIRDL1/2/3.

23. The heterodimeric multispecific antibody of any one of claims 1-22, wherein the fourth immunoglobulin binds to an agent selected from the group consisting of a cytokine, a nucleic acid, a hapten, a small molecule, a radionuclide, an immunotoxin, a vitamin, a peptide, a lipid, a carbohydrate, biotin, digoxin, or any conjugated variants thereof.

24. The heterodimeric multispecific antibody of any one of claims 1-23, wherein the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity between about 100 nM to about 100 pM.

25. The heterodimeric multispecific antibody of claim 24, wherein the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are between 60 and 120 angstroms apart.

26. The heterodimeric multispecific antibody of any one of claims 1-25, wherein the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity that is less than 100 pM.

27. The heterodimeric multispecific antibody of claim 26, wherein the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are up to 180 angstroms apart.

28. The heterodimeric multispecific antibody of any one of claims 1-27, wherein the first heterodimerization domain and/or the second heterodimerization domain is a CH2-CH3 domain and has an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE.

29. The heterodimeric multispecific antibody of claim 28, wherein the first heterodimerization domain and/or the second heterodimerization domain is an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A.

30. The heterodimeric multispecific antibody of claim 28 or 29, wherein the first heterodimerization domain is a CH2-CH3 domain comprising a K409R mutation and the second heterodimerization domain is a CH2-CH3 domain comprising a F405L mutation.

31. The heterodimeric multispecific antibody of any one of claims 1-30, wherein the antibody is a monoclonal antibody, a chimeric antibody, or a humanized antibody.

32. A recombinant nucleic acid sequence encoding the heterodimeric multispecific antibody of any one of claims 1-31.

33. A host cell or vector comprising the recombinant nucleic acid sequence of claim 32.

34. A composition comprising the heterodimeric multispecific antibody of any one of claims 1-31 and a pharmaceutically-acceptable carrier, wherein the antibody is optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof.

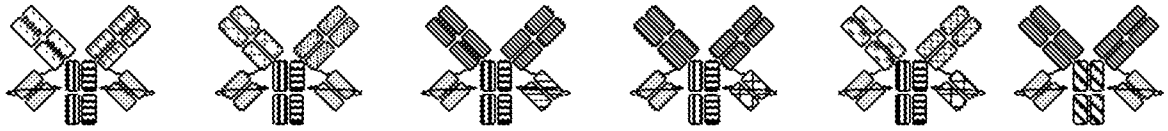
35. A method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of the heterodimeric multispecific antibody of any one of claims 1-31.

36. The method of claim 35, wherein the cancer is selected from the group consisting of lung cancer, colorectal cancer, skin cancer, breast cancer, ovarian cancer, leukemia, pancreatic cancer, and gastric cancer.

37. The method of claim 35 or 36, wherein the heterodimeric multispecific antibody is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent.

38. A kit comprising the heterodimeric multispecific antibody of any one of claims 1-31, and instructions for use.

Figure 1a



Monovalent A1 Monovalent A2 Bivalent B 3 Specificities 4 Domains	Monovalent A1 Monovalent A2 Bivalent B 3 Specificities 4 Domains	Bivalent A Monovalent B1 Monovalent B2 3 Specificities 4 Domains	Bivalent A Monovalent B1 Monovalent B2 3 Specificities 4 Domains	Monovalent A1 Monovalent A2 Monovalent B1 Monovalent B2 4 Specificities 4 Domains	Bivalent A Bivalent B 2 Specificities 4 Domains
1+1+2 Lo Affinity Improved Specificity	**1+1+2 Hi Affinity Broader Selectivity**	**2+1+1 More Immune Activation**	**2+1+1 Combo Combinatorial Recruitment**	**1+1+1+1 More Immune Activation Improved Specificity or Broader Selectivity**	**2+2 Standard Functions**

Figure 1b

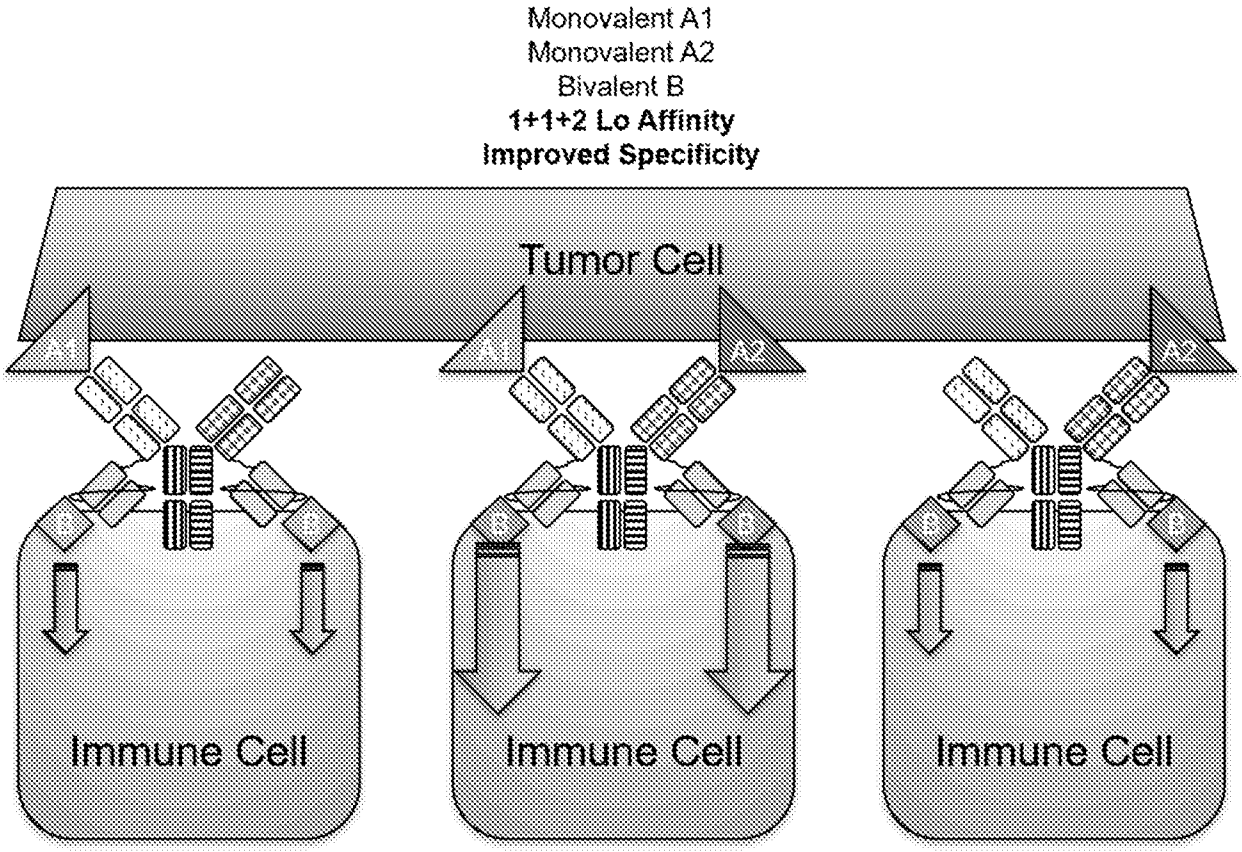


Figure 1c

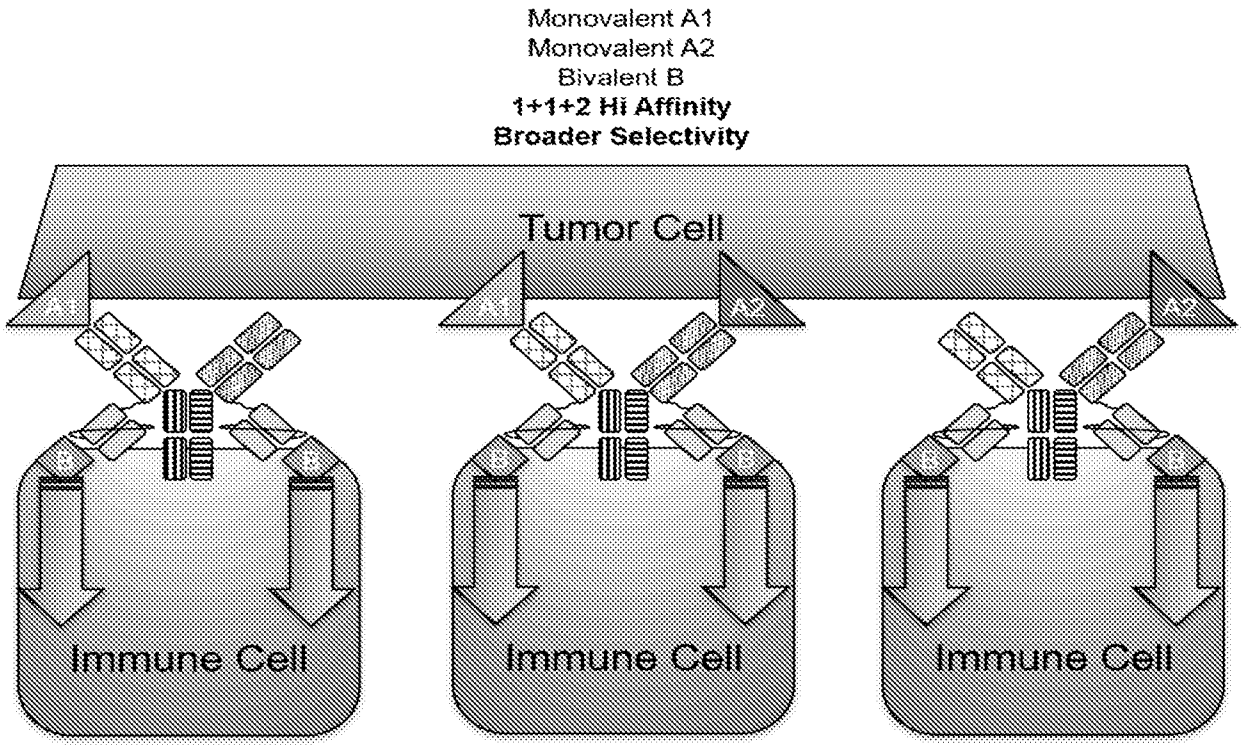

Monovalent A1
Monovalent A2
Bivalent B
1+1+2 Hi Affinity
Broader Selectivity
Tumor Cell
A1
A2
A2
B
B
B
B
B
B
Immune Cell
Immune Cell
Immune Cell

Figure 1d

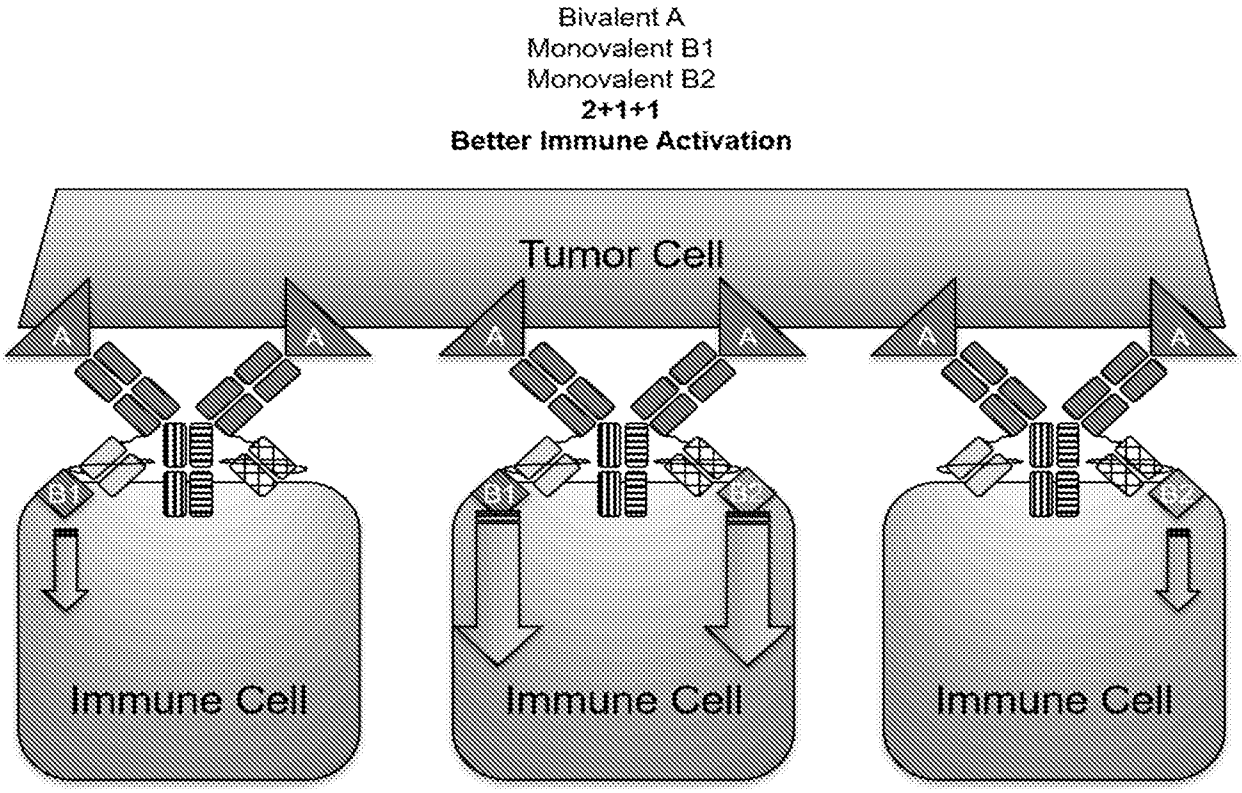

Bivalent A
Monovalent B1
Monovalent B2
2+1+1
Better Immune Activation
Tumor Cell
A
A
A
A
A
A
B1
B1
B2
B2
Immune Cell
Immune Cell
Immune Cell

Figure 1e

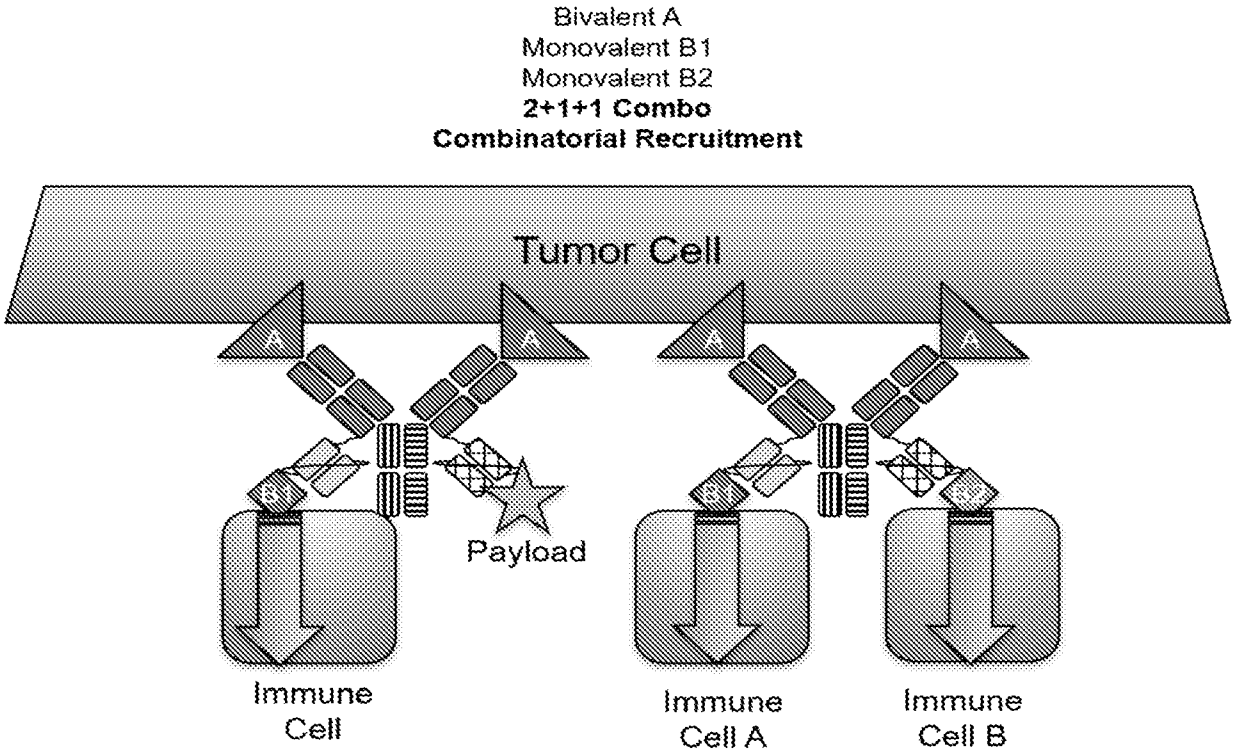

Bivalent A
Monovalent B1
Monovalent B2
2+1+1 Combo
Combinatorial Recruitment
Tumor Cell
A
A
A
A
B1
B2
Payload
Immune Cell
Immune Cell A
Immune Cell B

Figure 1f

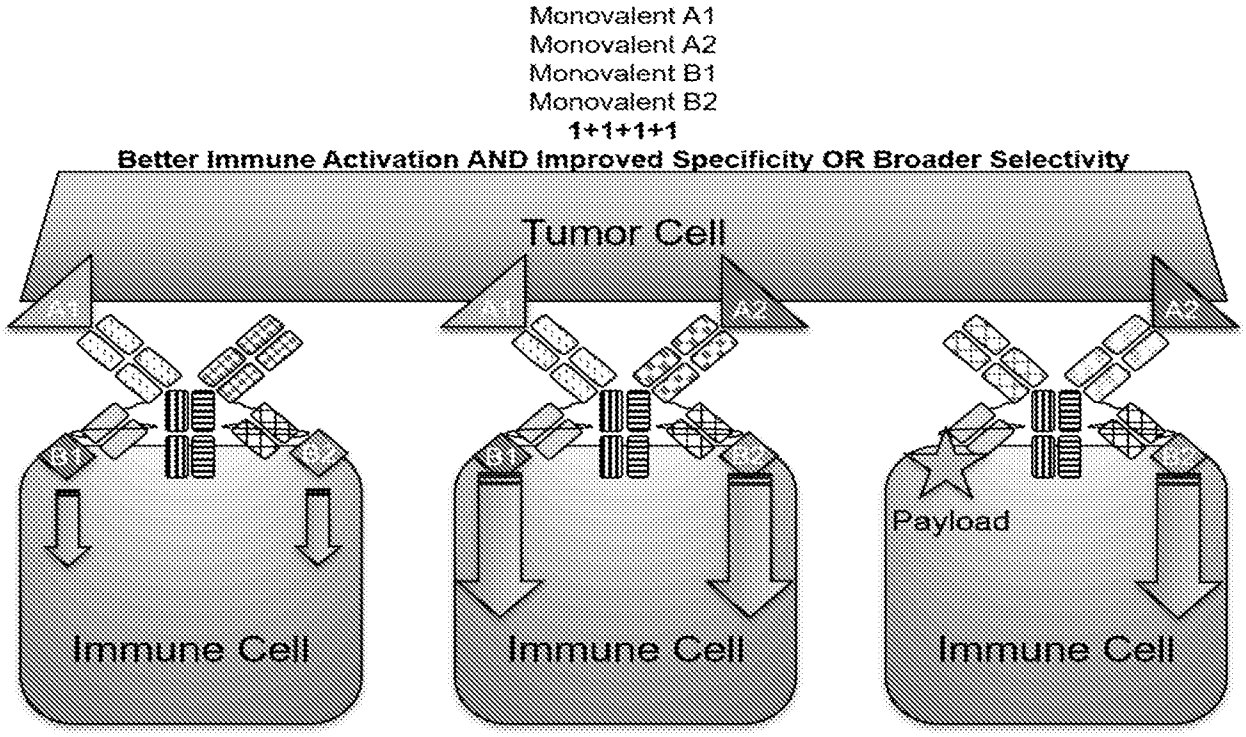

Monovalent A1
Monovalent A2
Monovalent B1
Monovalent B2
1+1+1+1
Better Immune Activation AND Improved Specificity OR Broader Selectivity
Tumor Cell
A1
A2
B1
B2
Payload
Immune Cell
Immune Cell
Immune Cell

Figure 2a

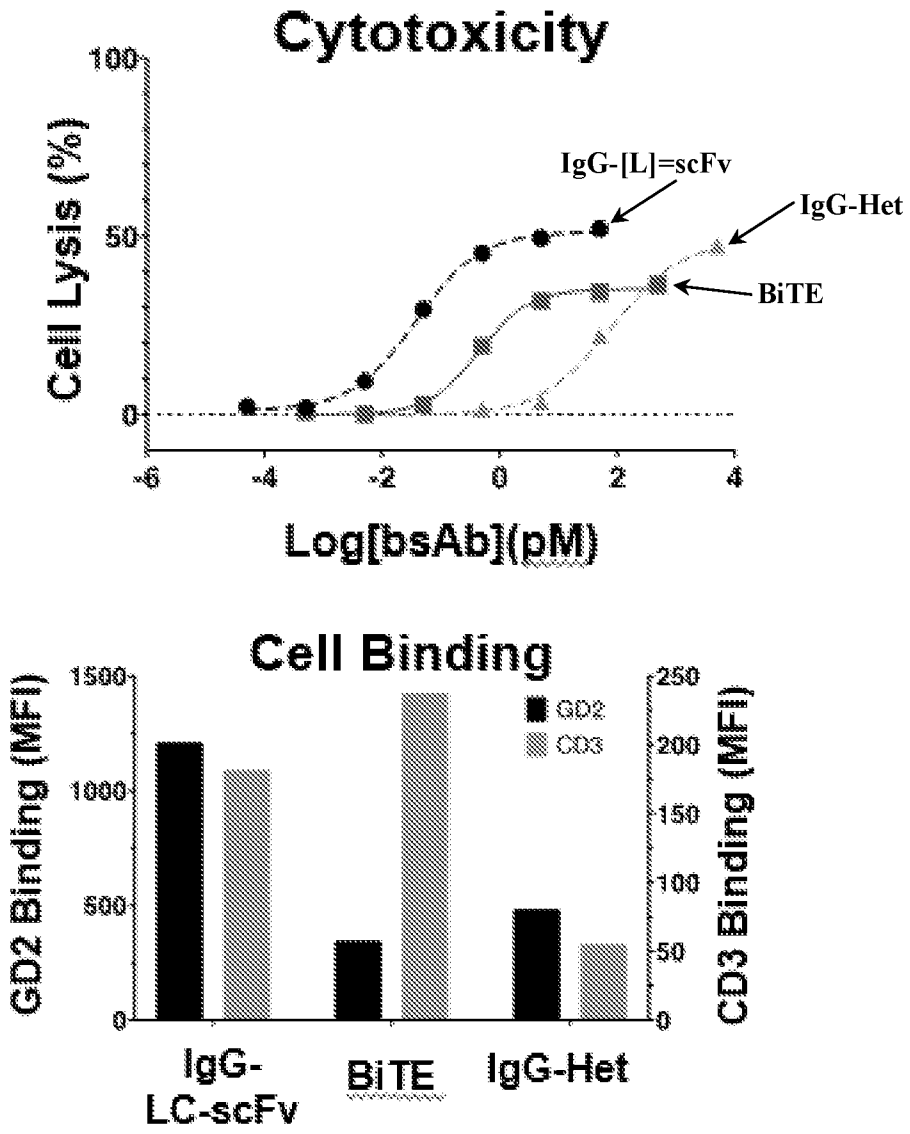

Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
IgG-[L]=scFv
IgG-Het
BiTE
Cell Binding
GD2 Binding (MFI)
1500
1000
500
0
CD3 Binding (MFI)
250
200
150
100
50
0
GD2
CD3
IgG-LC-scFv
BiTE
IgG-Het

Figure 2a (cont.)

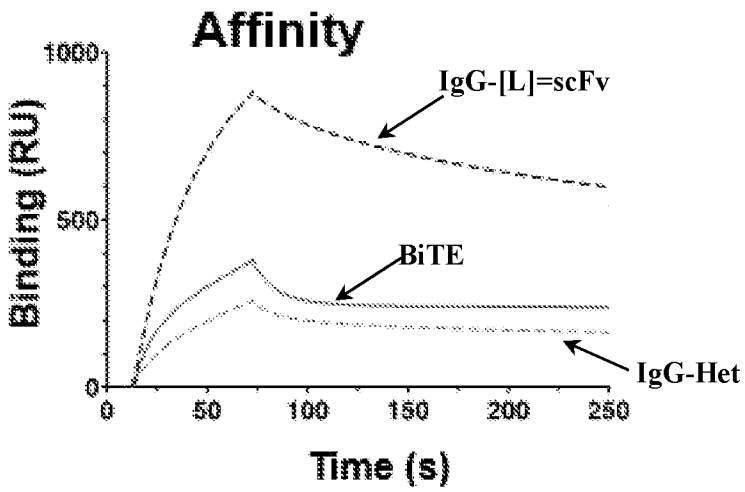


Figure 2a (cont.)

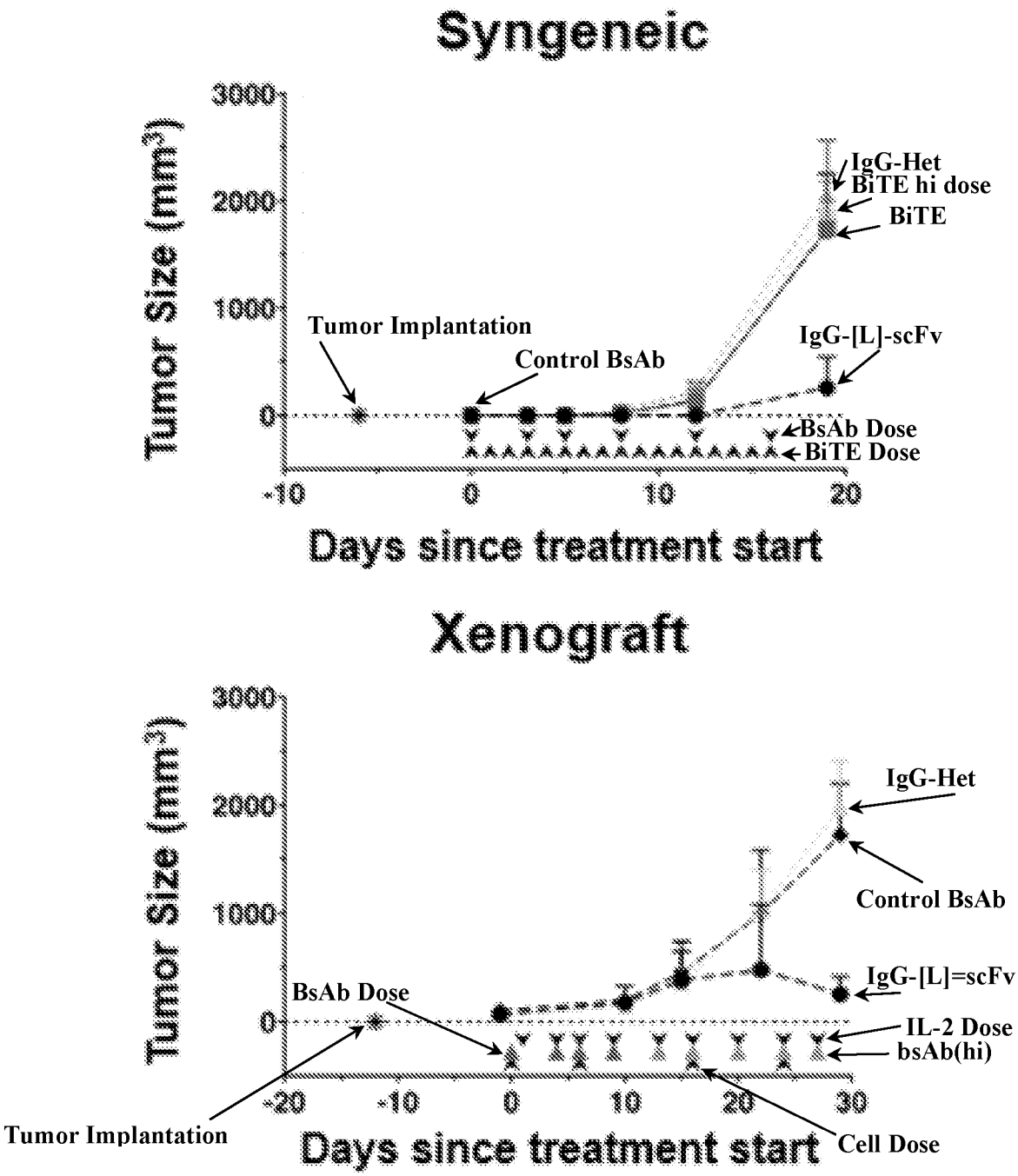


Figure 2b

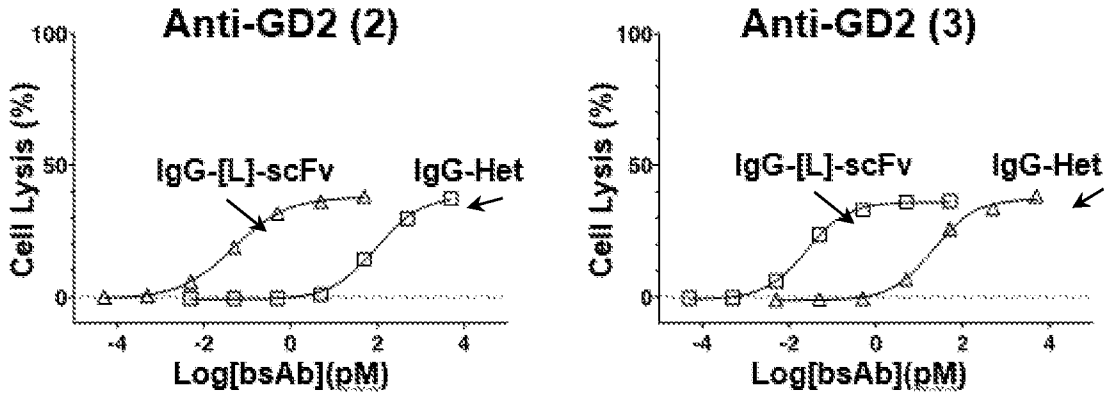

Anti-GD2 (2)
Cell Lysis (%)
100
50
0
IgG-[L]-scFv
IgG-Het
-4
-2
0
2
4
Log[bsAb](pM)
Anti-GD2 (3)
Cell Lysis (%)
100
50
0
IgG-[L]-scFv
IgG-Het
-4
-2
0
2
4
Log[bsAb](pM)

Figure 3

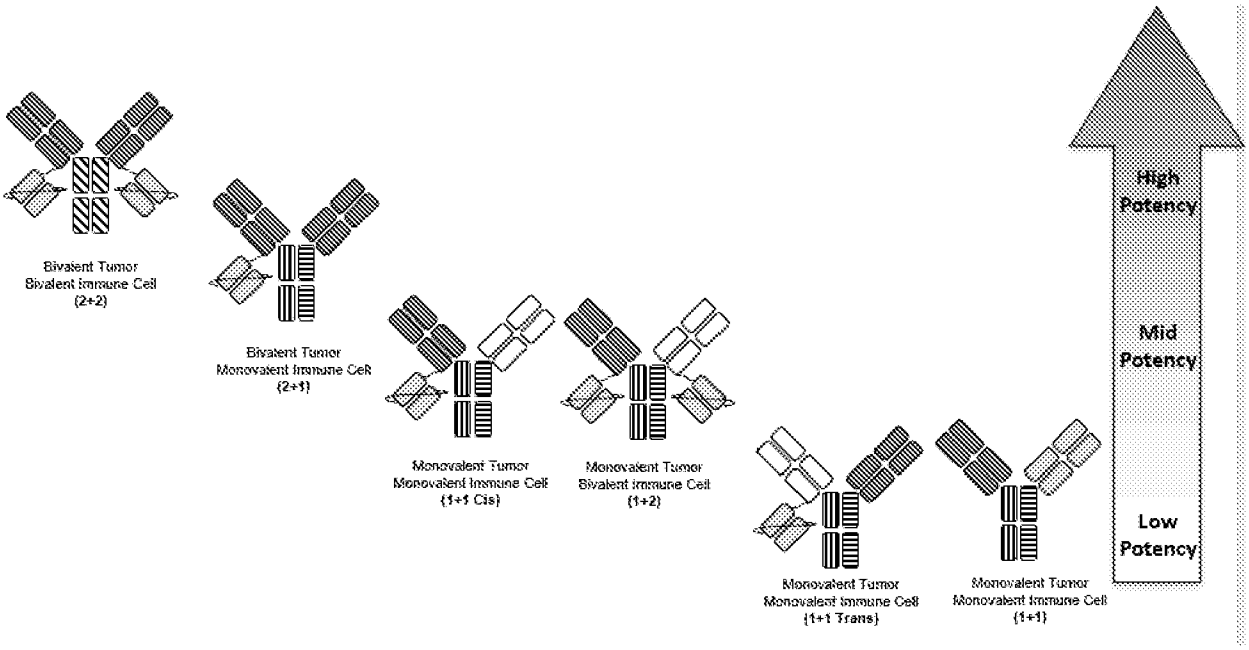
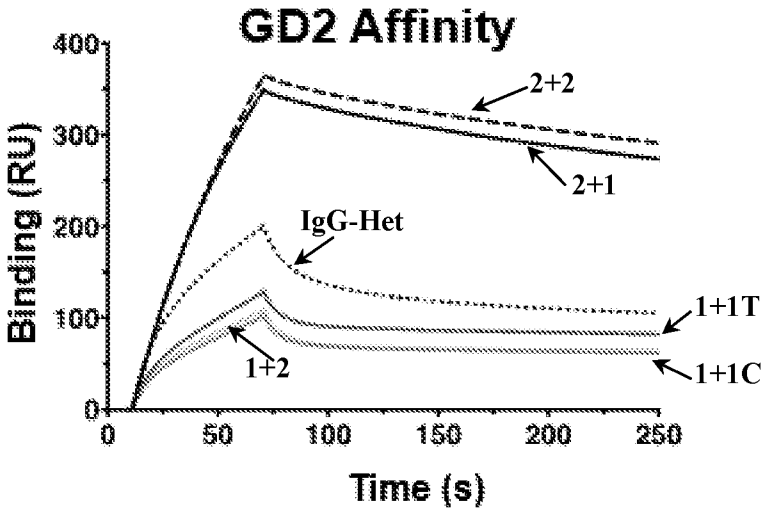

Bivalent Tumor
Bivalent Immune Cell
(2+2)
Bivalent Tumor
Monovalent Immune Cell
(2+1)
Monovalent Tumor
Monovalent Immune Cell
(1+1 Cis)
Monovalent Tumor
Bivalent Immune Cell
(1+2)
Monovalent Tumor
Monovalent Immune Cell
(1+1 Trans)
Monovalent Tumor
Monovalent Immune Cell
(1+1)
High Potency
Mid Potency
Low Potency

Figure 4


GD2 Affinity
Binding (RU)
400
300
200
100
0
0
50
100
150
200
250
Time (s)
2+2
2+1
IgG-Het
1+1T
1+2
1+1C

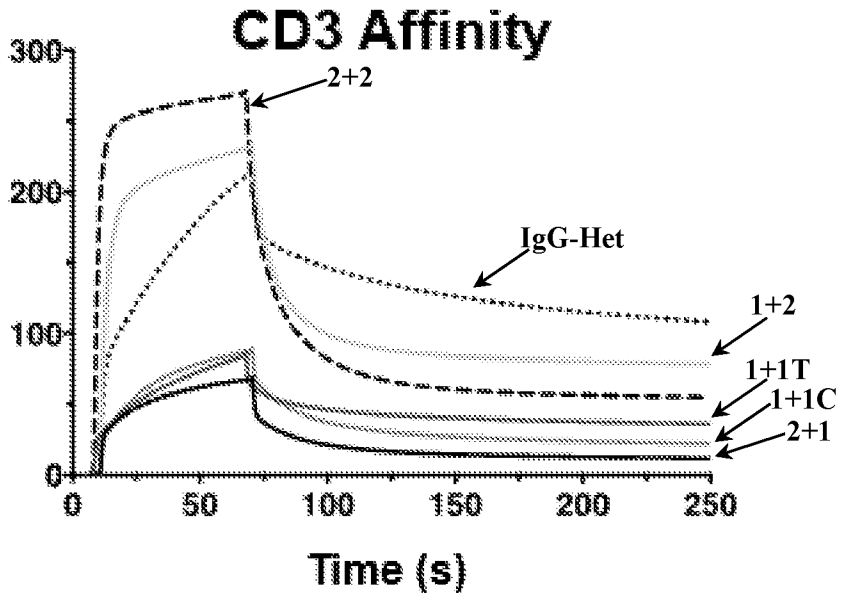

CD3 Affinity
300
200
100
0
0
50
100
150
200
250
Time (s)
2+2
IgG-Het
1+2
1+1T
1+1C
2+1

Figure 4 (cont.)

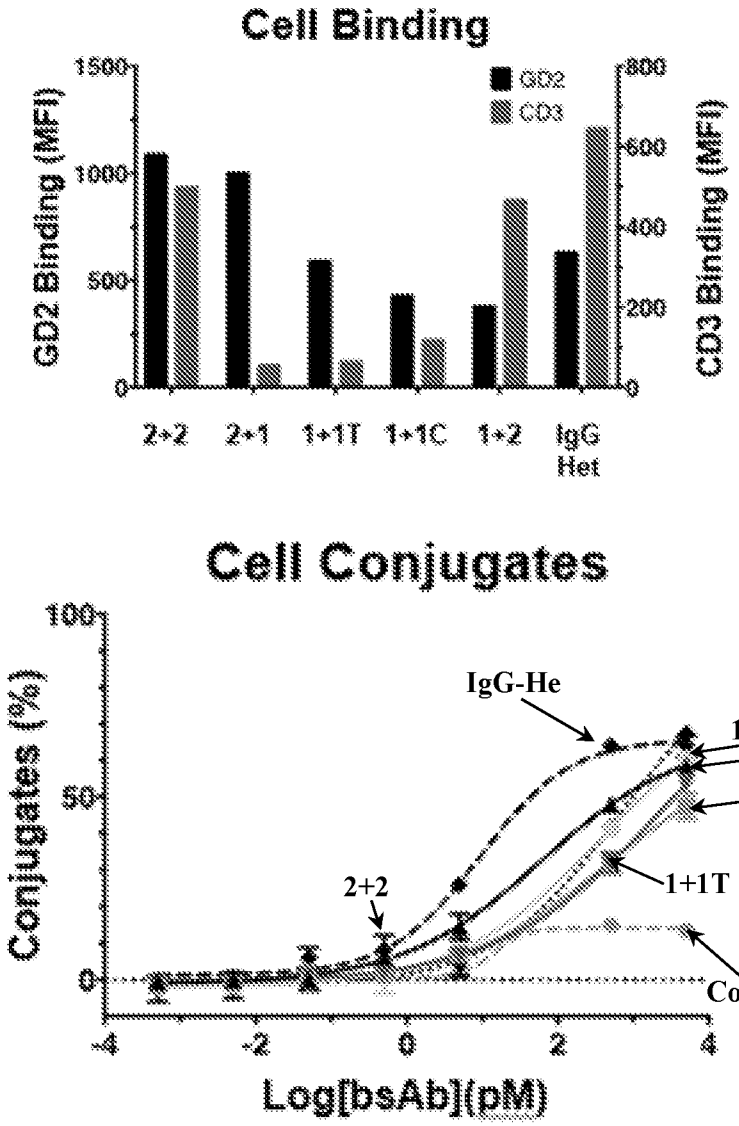


Figure 5

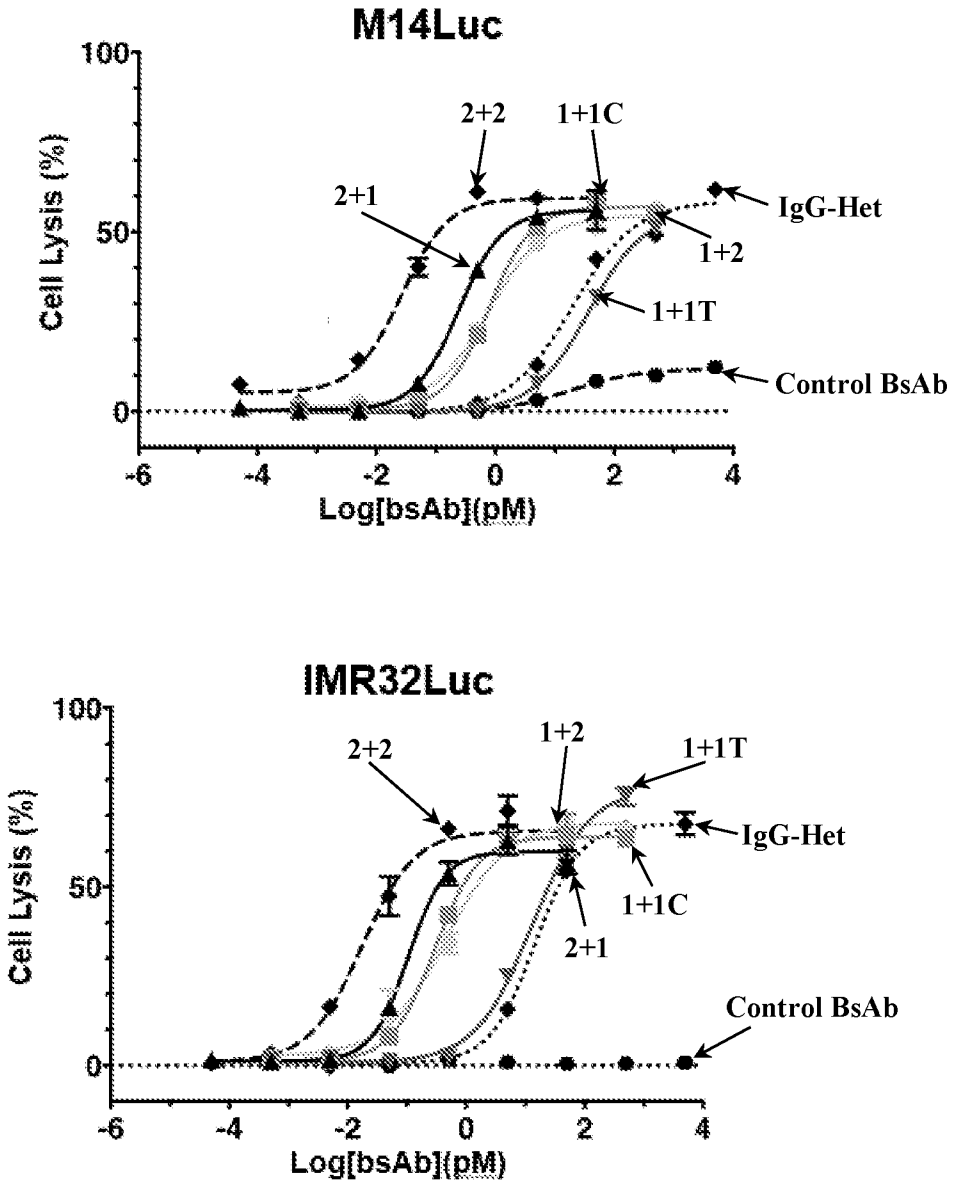
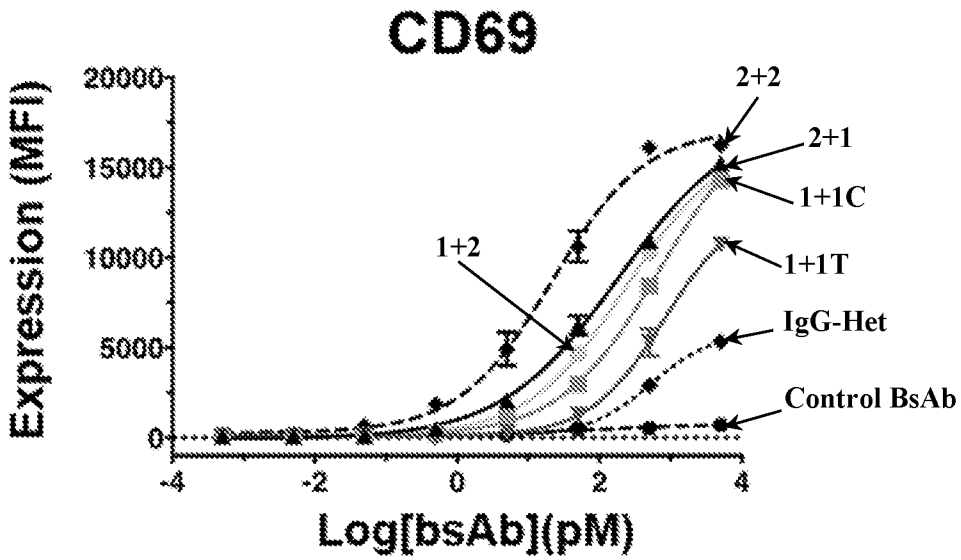

M14Luc
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
1+1C
2+1
IgG-Het
1+2
1+1T
Control BsAb
IMR32Luc
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
1+2
1+1T
IgG-Het
1+1C
2+1
Control BsAb

Figure 6


CD69
Expression (MFI)
20000
15000
10000
5000
0
-4
-2
0
2
4
Log[bsAb](pM)
2+2
2+1
1+1C
1+2
1+1T
IgG-Het
Control BsAb

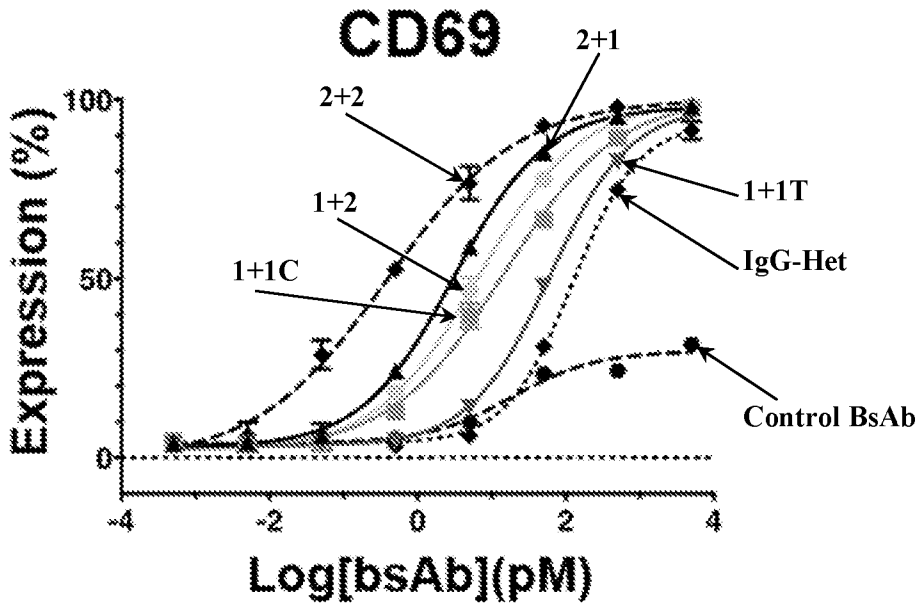
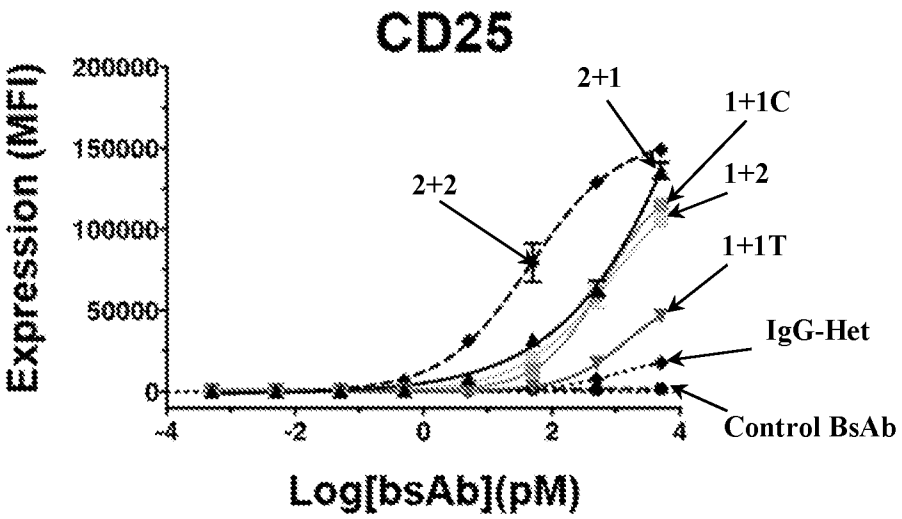

CD69
Expression (%)
100
50
0
-4
-2
0
2
4
Log[bsAb](pM)
2+1
2+2
1+2
1+1C
1+1T
IgG-Het
Control BsAb

Figure 6 (cont.)



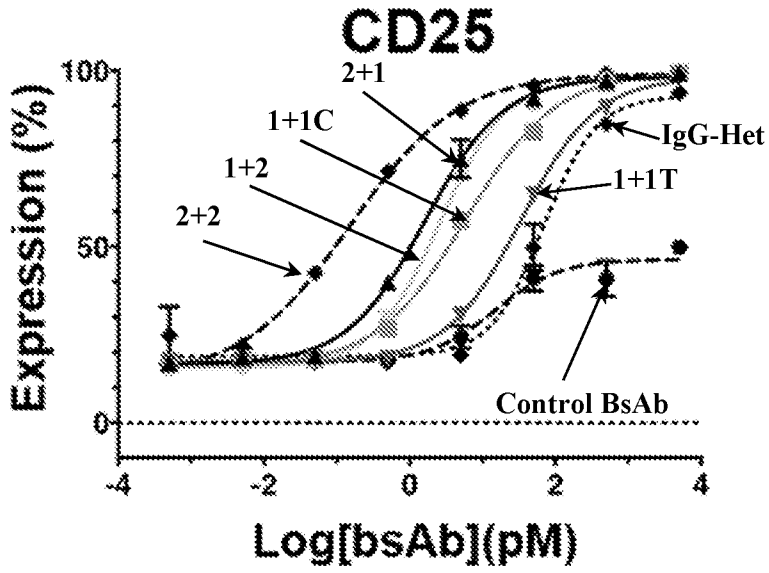


Figure 6 (cont.)

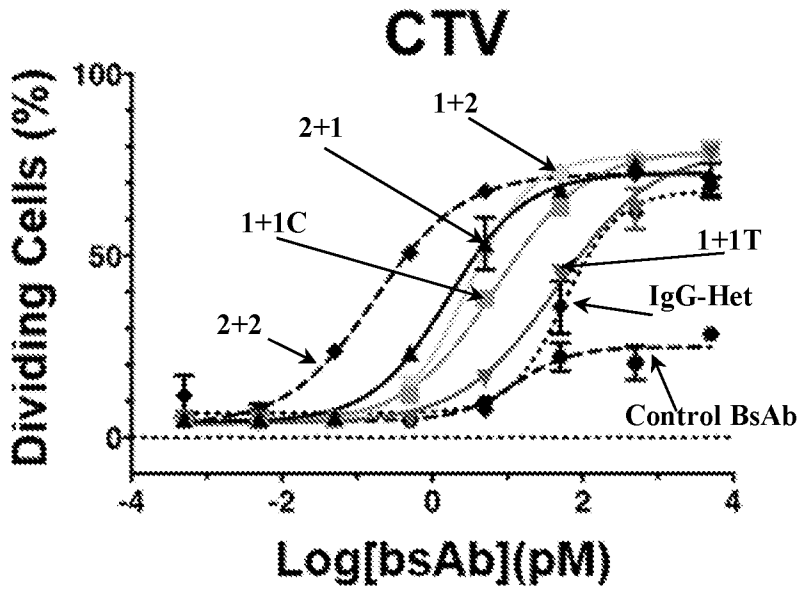


Figure 7

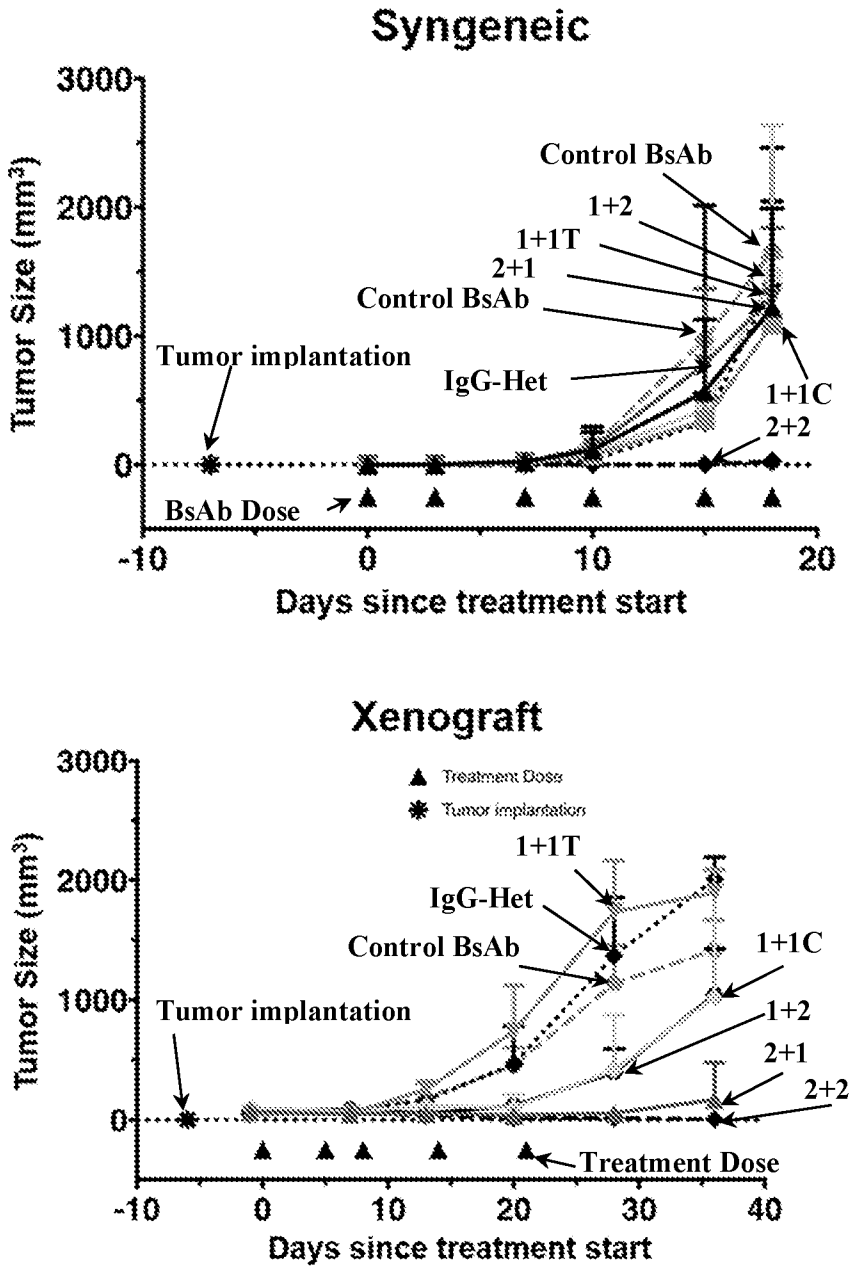

Syngeneic
Tumor Size (mm³)
3000
2000
1000
0
Control BsAb
1+2
1+1T
2+1
Control BsAb
Tumor implantation
IgG-Het
1+1C
2+2
BsAb Dose
-10
0
10
20
Days since treatment start
Xenograft
Treatment Dose
Tumor implantation
Tumor Size (mm³)
3000
2000
1000
0
1+1T
IgG-Het
Control BsAb
1+1C
Tumor implantation
1+2
2+1
2+2
Treatment Dose
-10
0
10
20
30
40
Days since treatment start

Figure 8

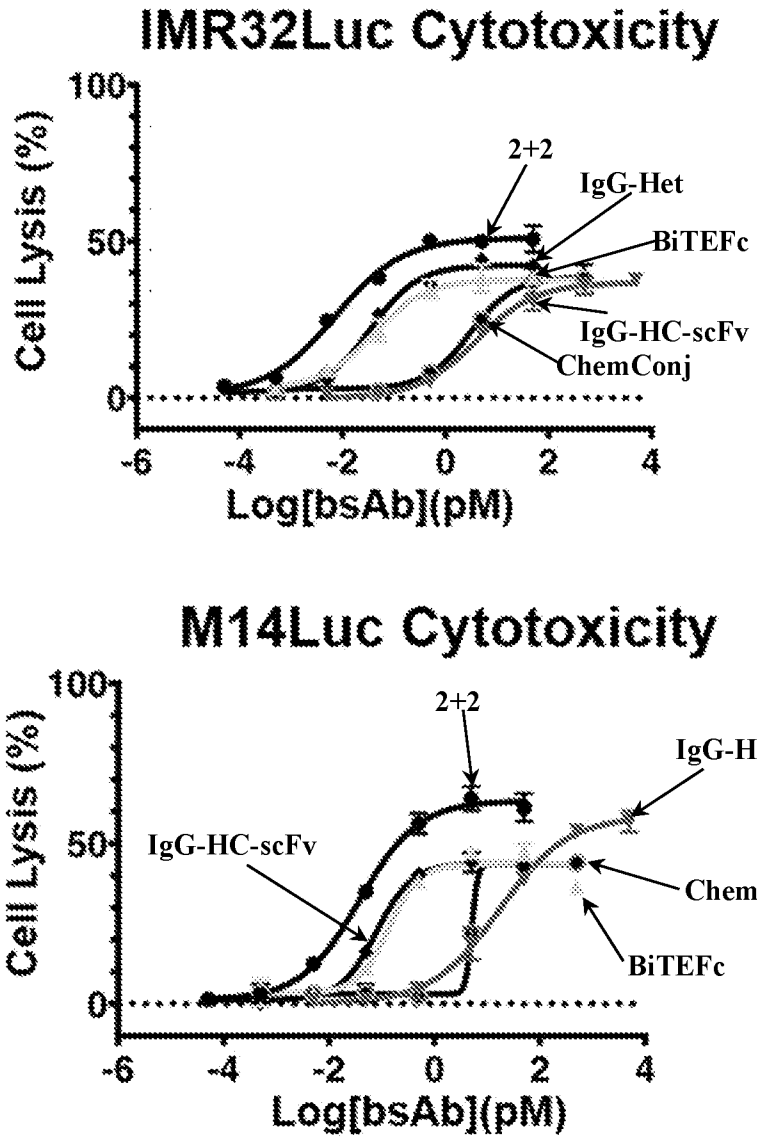
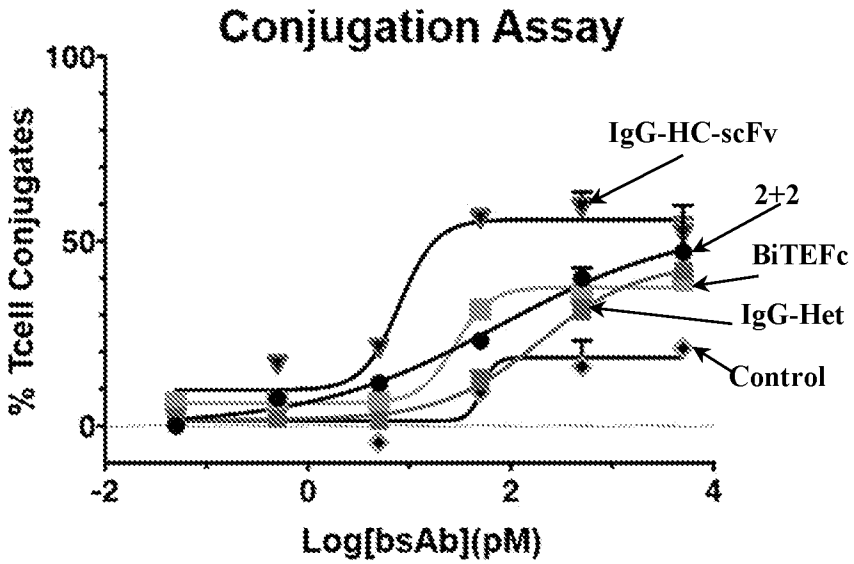

IMR32Luc Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
IgG-Het
BiTEFc
IgG-HC-scFv
ChemConj
M14Luc Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
IgG-Het
IgG-HC-scFv
ChemConj
BiTEFc

Figure 8 (cont.)



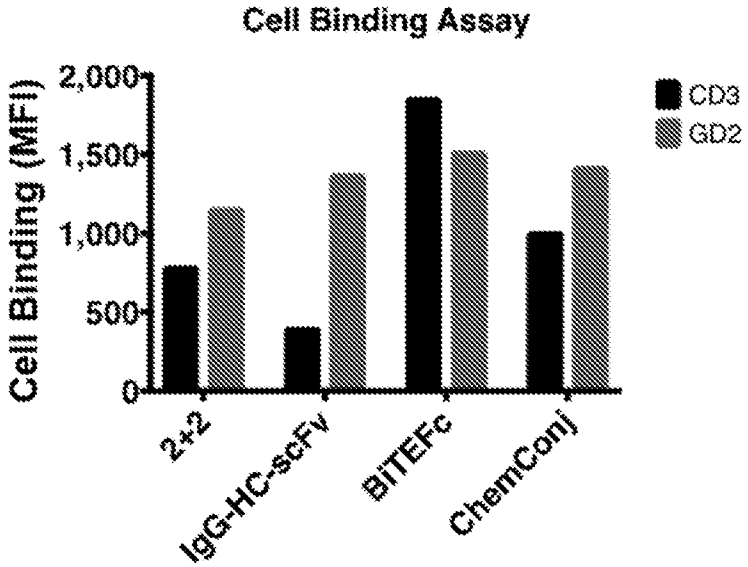


Figure 9

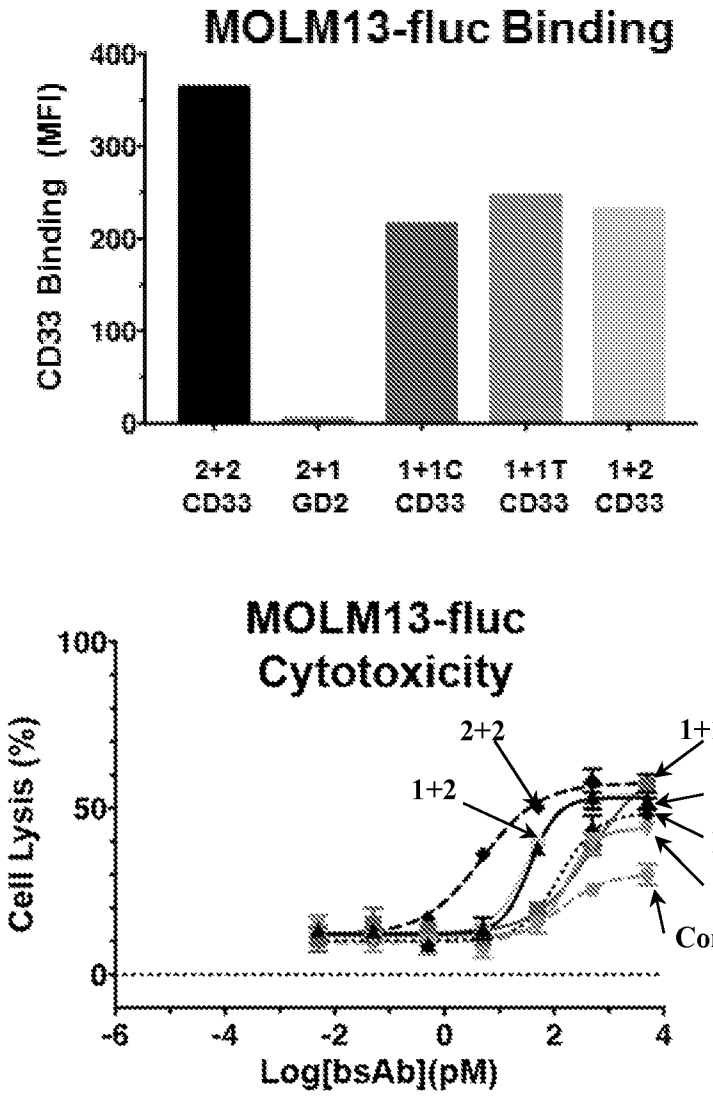

MOLM13-fluc Binding
CD33 Binding (MFI)
400
300
200
100
0
2+2 CD33
2+1 GD2
1+1C CD33
1+1T CD33
1+2 CD33
MOLM13-fluc Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
1+1C
1+2
2+1
IgG-Het
1+1T
Control BsAb

Figure 9 (cont.)

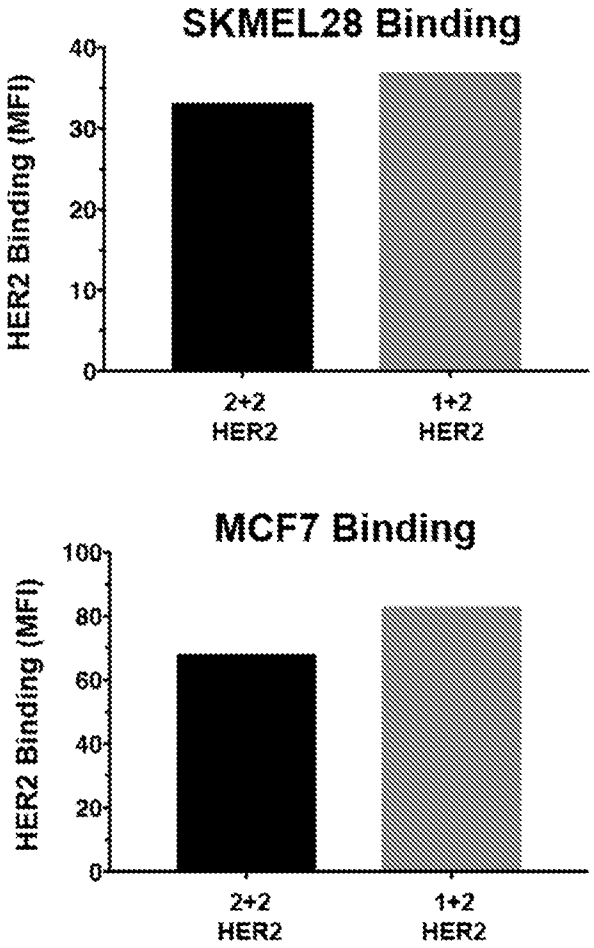


Figure 10a

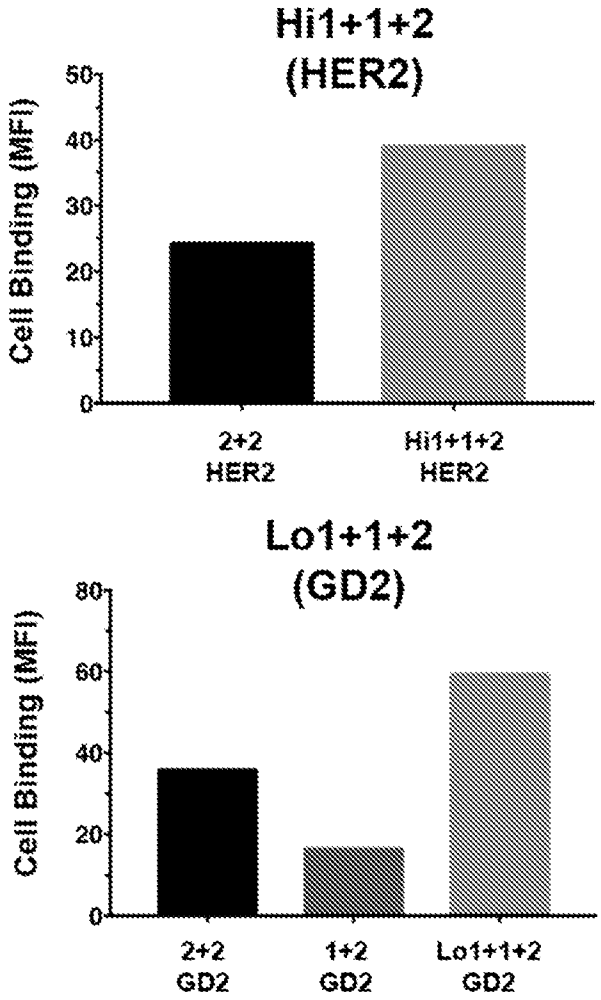

Hi1+1+2
(HER2)
Cell Binding (MFI)
50
40
30
20
10
0
2+2
HER2
Hi1+1+2
HER2
Lo1+1+2
(GD2)
Cell Binding (MFI)
80
60
40
20
0
2+2
GD2
1+2
GD2
Lo1+1+2
GD2

Figure 10a (cont.)

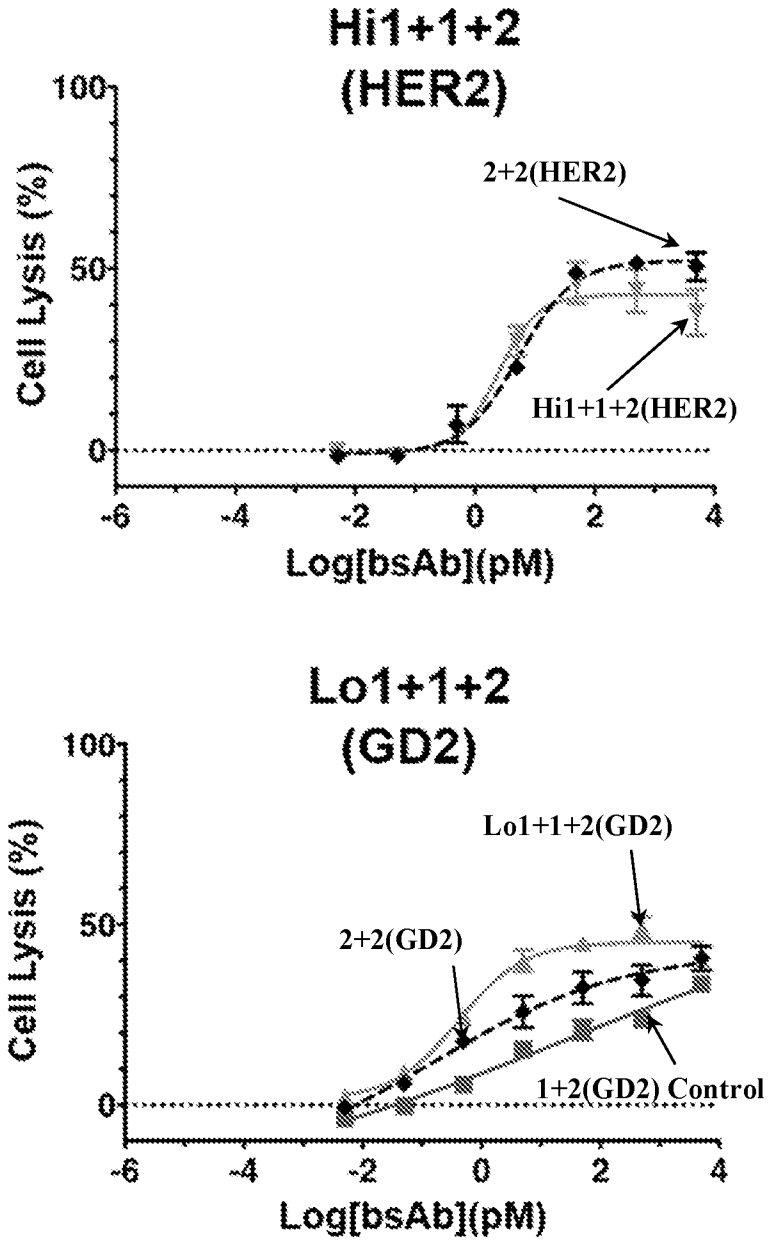


Figure 10b

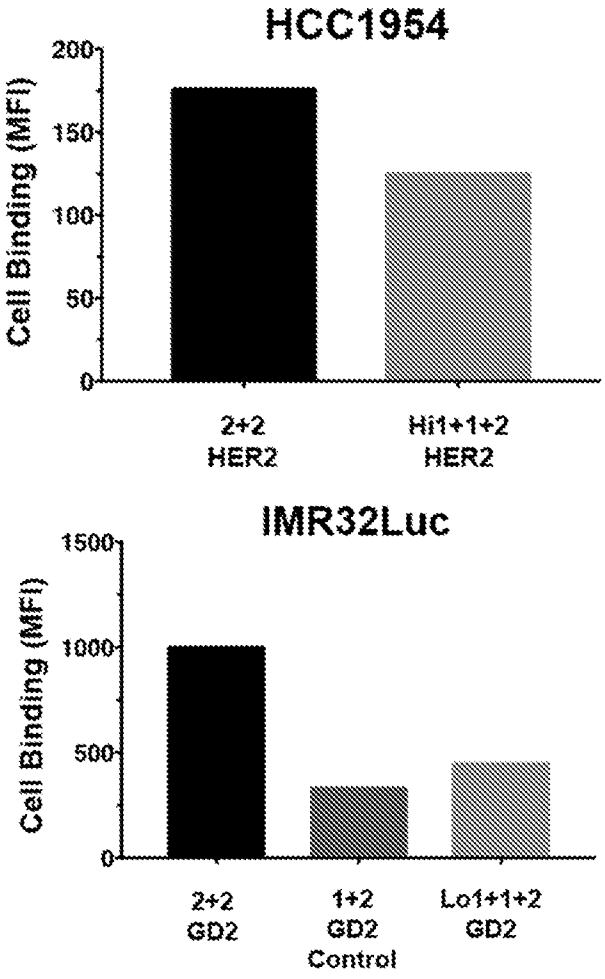

HCC1954
Cell Binding (MFI)
200
150
100
50
0
2+2
HER2
Hi1+1+2
HER2
IMR32Luc
Cell Binding (MFI)
1500
1000
500
0
2+2
GD2
1+2
GD2
Control
Lo1+1+2
GD2

Figure 10b (cont.)

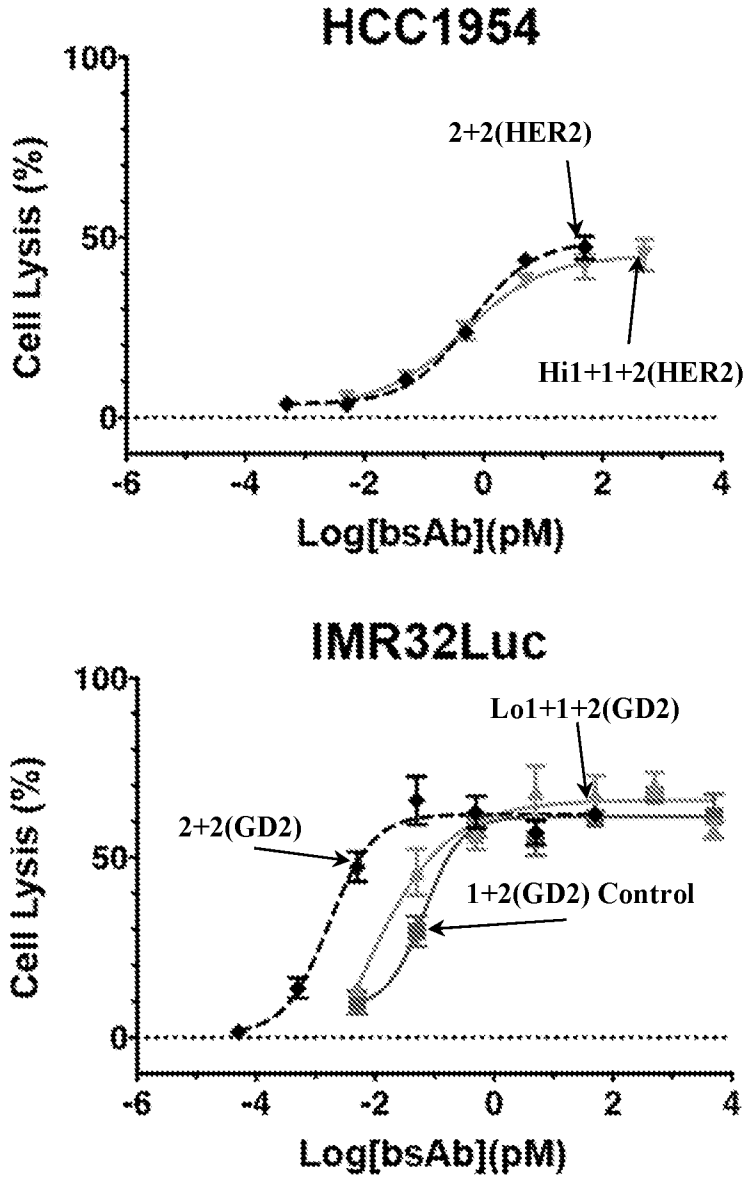


Figure 11a

First CH2-CH3 domain	Second CH2-CH3 domain
F405A	T394F
S364D	Y349K
S364E	L368K
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370N/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S354K
L368E/D401N	S364K
L368E	S357R/S364K
L368E	S354K/K409E
L368E	S364K/E409V
L368D	S364K

Figure 11b

First CH2-CH3 domain	Second CH2-CH3 domain
F405A	T394F
S364D	Y349K
S364E	Y349K
S364H	Y349T
L351K	L351E
D401K	T411E
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
L351K/S364H/D401K	Y349T/L351E/T411E
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

Figure 11c

First CH2-CH3 domain	Second CH2-CH3 domain
Y407T	T366Y
F405A	T394W
T366Y/F405A	T394W/Y407T
Y407A	T366W
T366S/L368A/Y407V	T366W
T366S/L368A/Y407V/Y349C	T366W/S354C
K392D/K409D	E356K/D399K
K370D/K392D/K409D	E356K/E357K/D399K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
I199T/N203D/K247Q/R355Q/N384S/ K392N/V397M/Q419E/K447_ (deletion of K447)	Q196K/I199T/P217R/P228R/N276K
I199T/N203D/K247Q/R355Q/N384S /K392N/V397M/Q419E/K447_	Q196K/I199T/N276K
N384S/K392N/V397M/Q419E	N276K
D221E/P228E/L368E	D221R/P228R/K409R
C220E/P228E/L368E	C220R/E224R/P228R/K409R
F405L	K409R
T366I/K392M/T394W	F405A/Y407V
T366V/K409F	L351Y/Y407A
T366A/K392E/K409F/T411E	D399R/S400R/Y407A
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R

Figure 11d

First CH2-CH3 domain	Second CH2-CH3 domain
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

Figure 11e

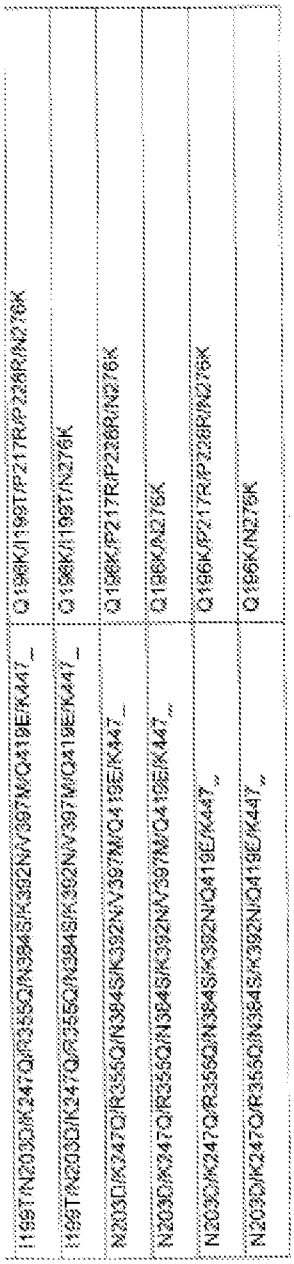

First CH2-CH3 domain
Second CH2-CH3 domain
I199T/N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
Q196K/I199T/P217R/P228R/N276K
I199T/N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
Q196K/I199T/N276K
N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
Q196K/P217R/P228R/N276K
N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
Q196K/N276K
N203D/K247Q/R355Q/N384S/K392N/Q419E/K447_
Q196K/P217R/P228R/N276K
N203D/K247Q/R355Q/N384S/K392N/Q419E/K447_
Q196K/N276K

Figure 12a

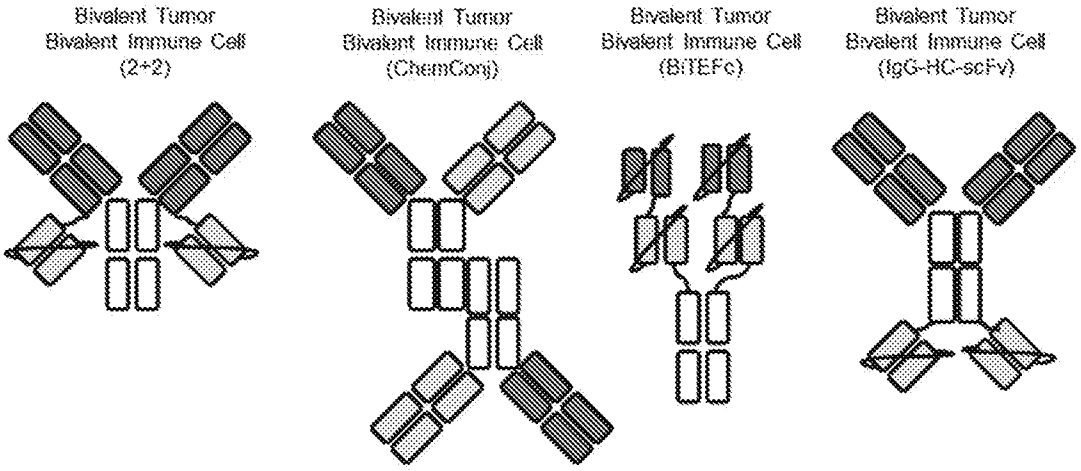


Figure 12b

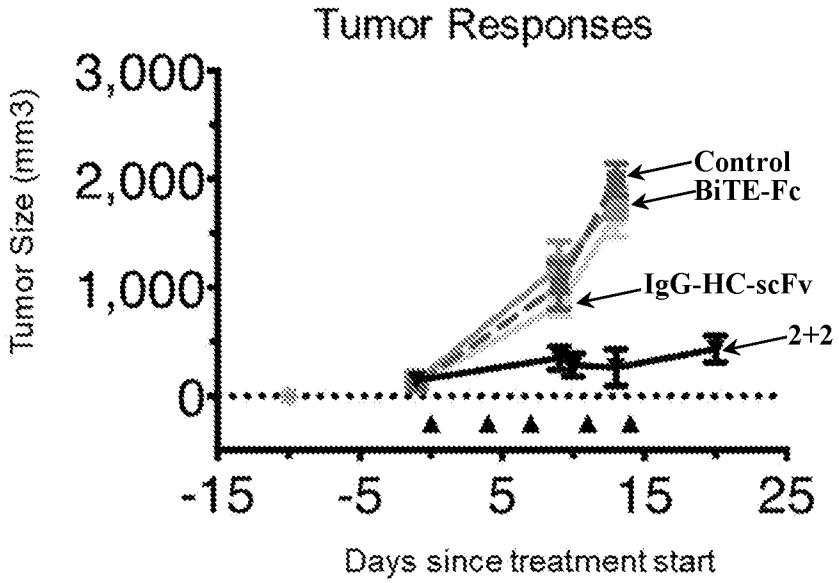


Figure 12c

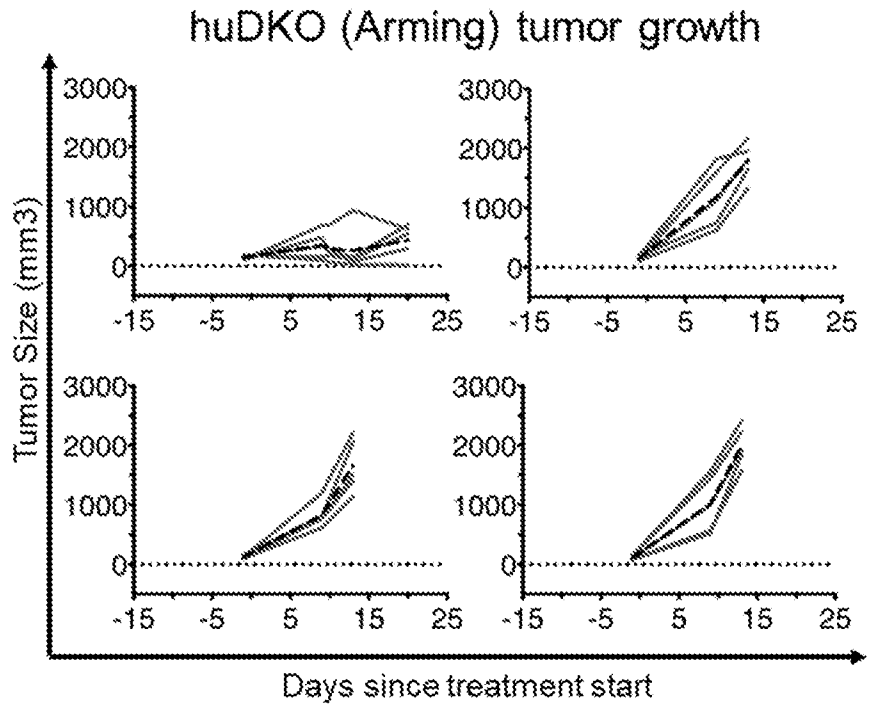
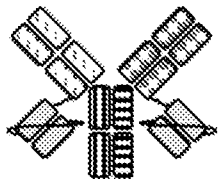

huDKO (Arming) tumor growth
Tumor Size (mm3)
3000
2000
1000
0
-15
-5
5
15
25
Days since treatment start

Figure 13



Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains

1+1+2 Lo Affinity
Improved Specificity

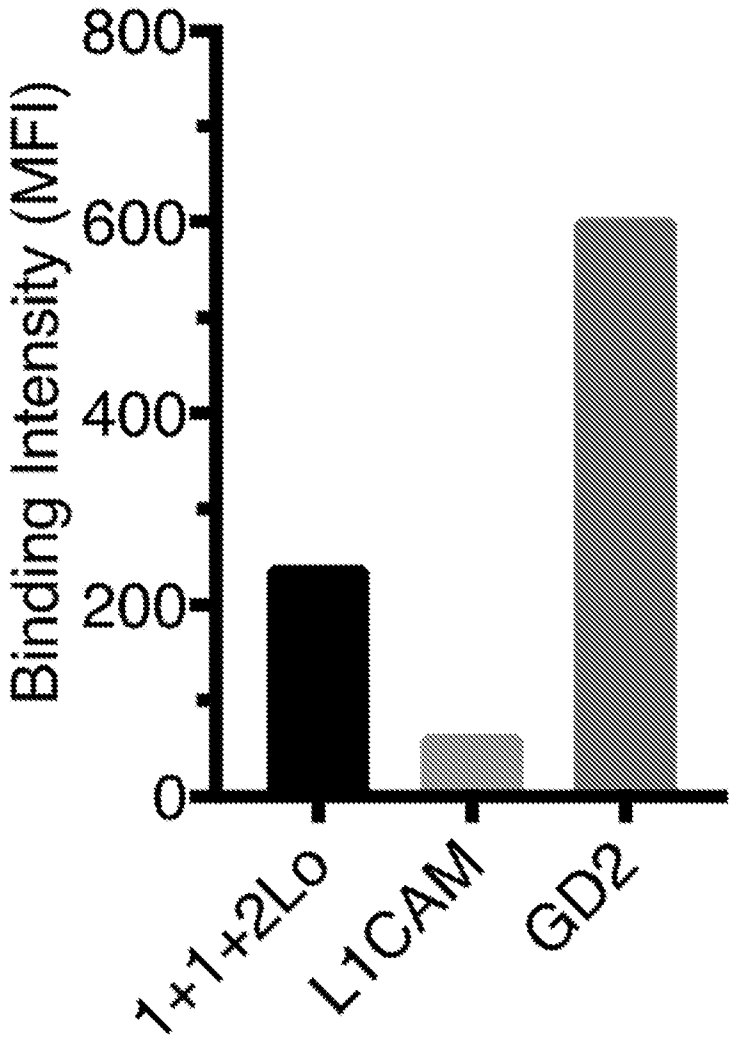


Figure 14

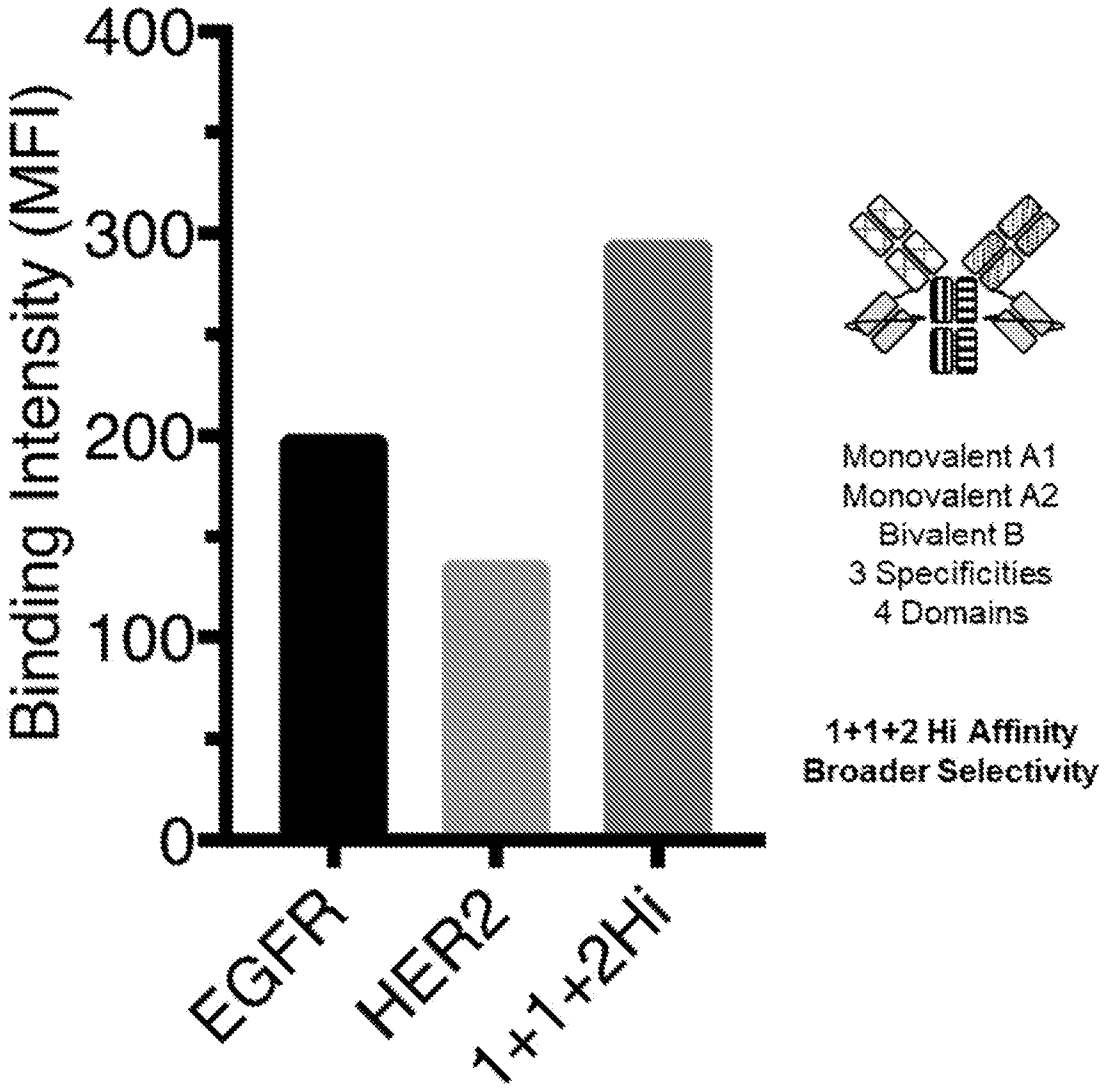

Binding Intensity (MFI)
400
300
200
100
0
EGFR
HER2
1+1+2Hi
Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains
1+1+2 Hi Affinity
Broader Selectivity

Figure 15

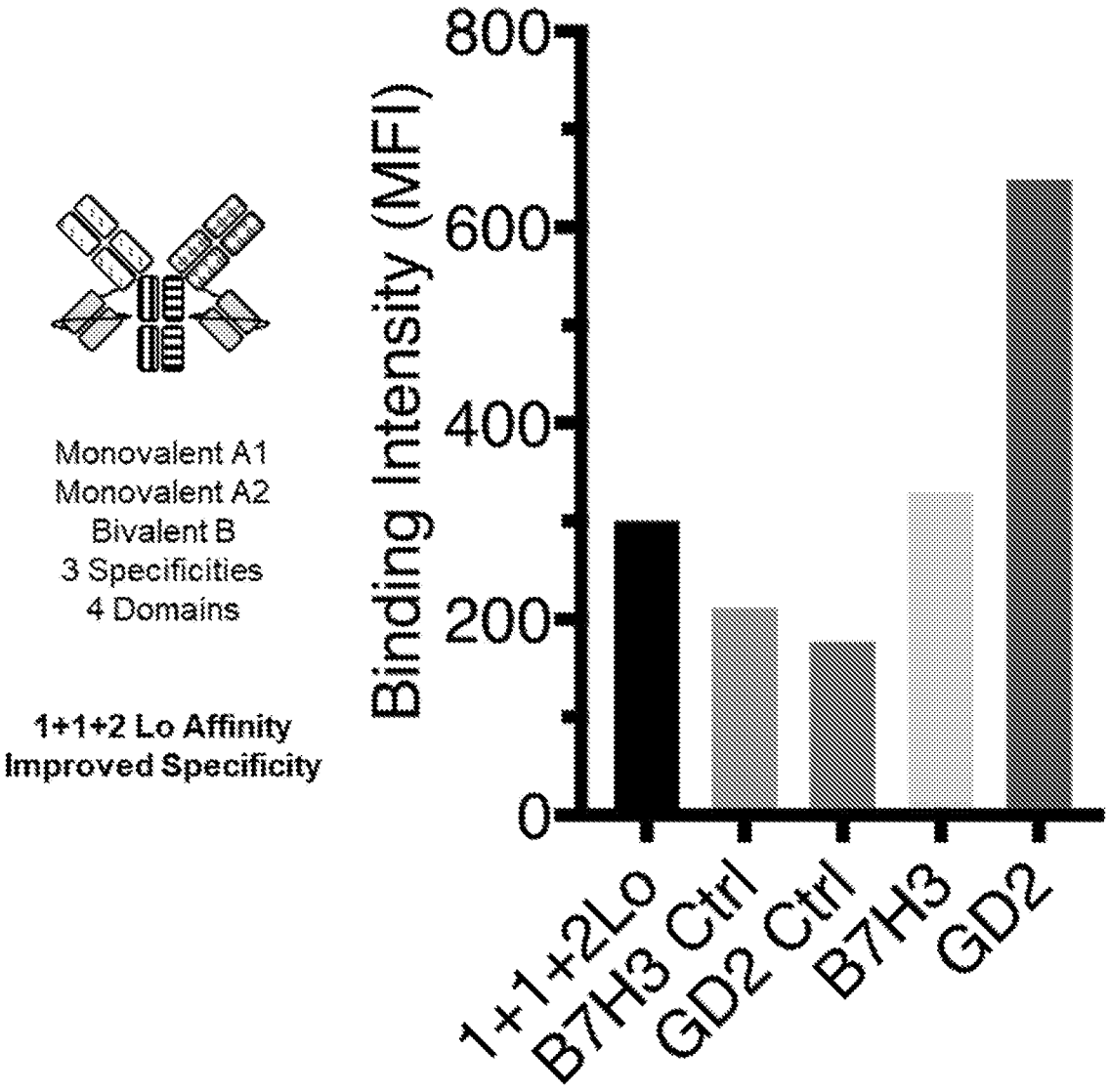
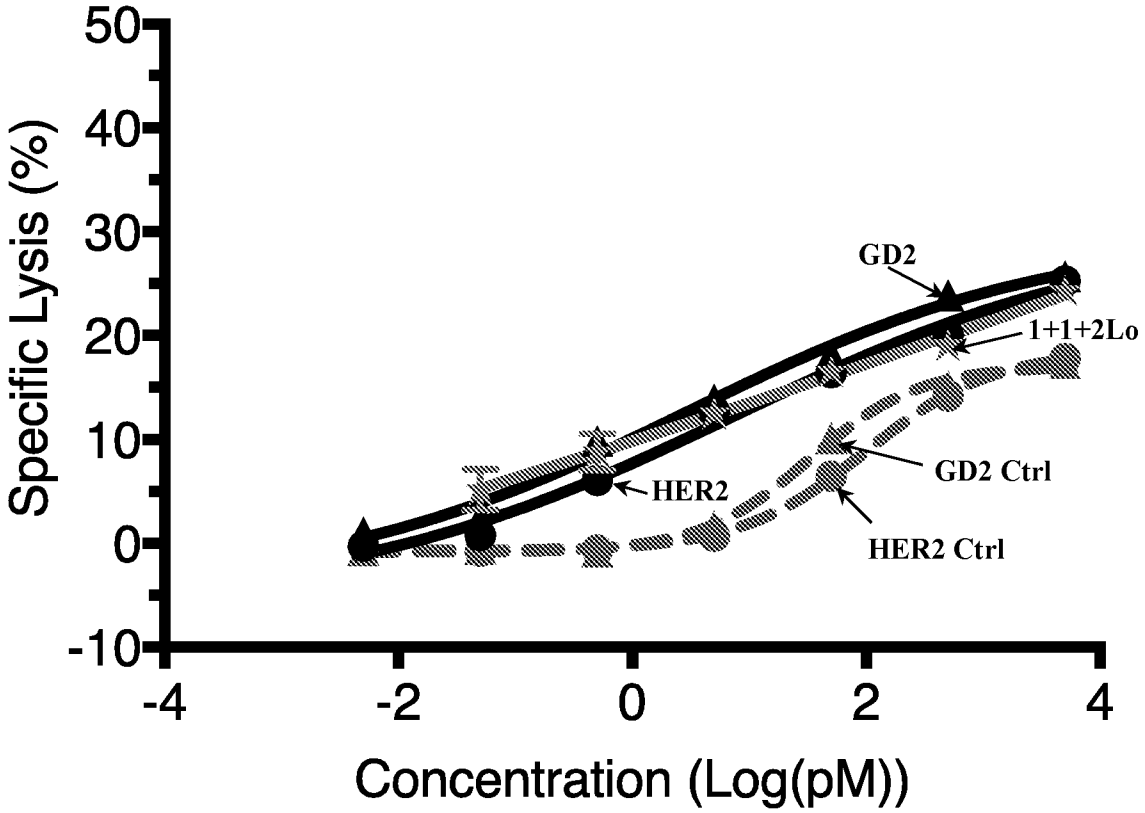
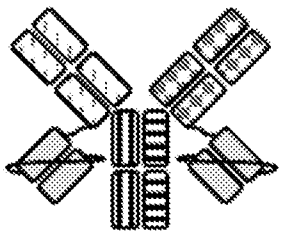

Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains
1+1+2 Lo Affinity
Improved Specificity
Binding Intensity (MFI)
800
600
400
200
0
1+1+2Lo
B7H3 Ctrl
GD2 Ctrl
B7H3
GD2

Figure 16

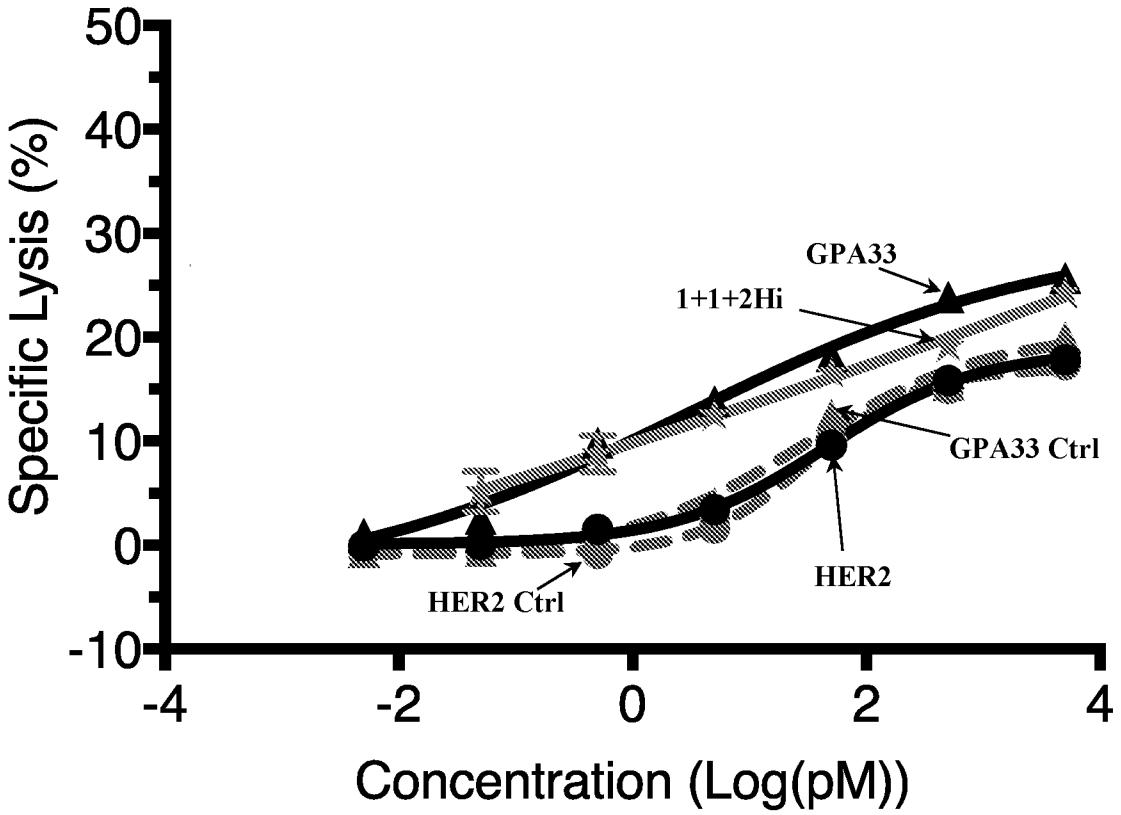


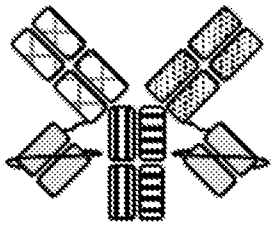


Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains

1+1+2 Lo Affinity
Improved Specificity

Figure 17a





Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains

1+1+2 Hi Affinity
Broader Selectivity

Figure 17b

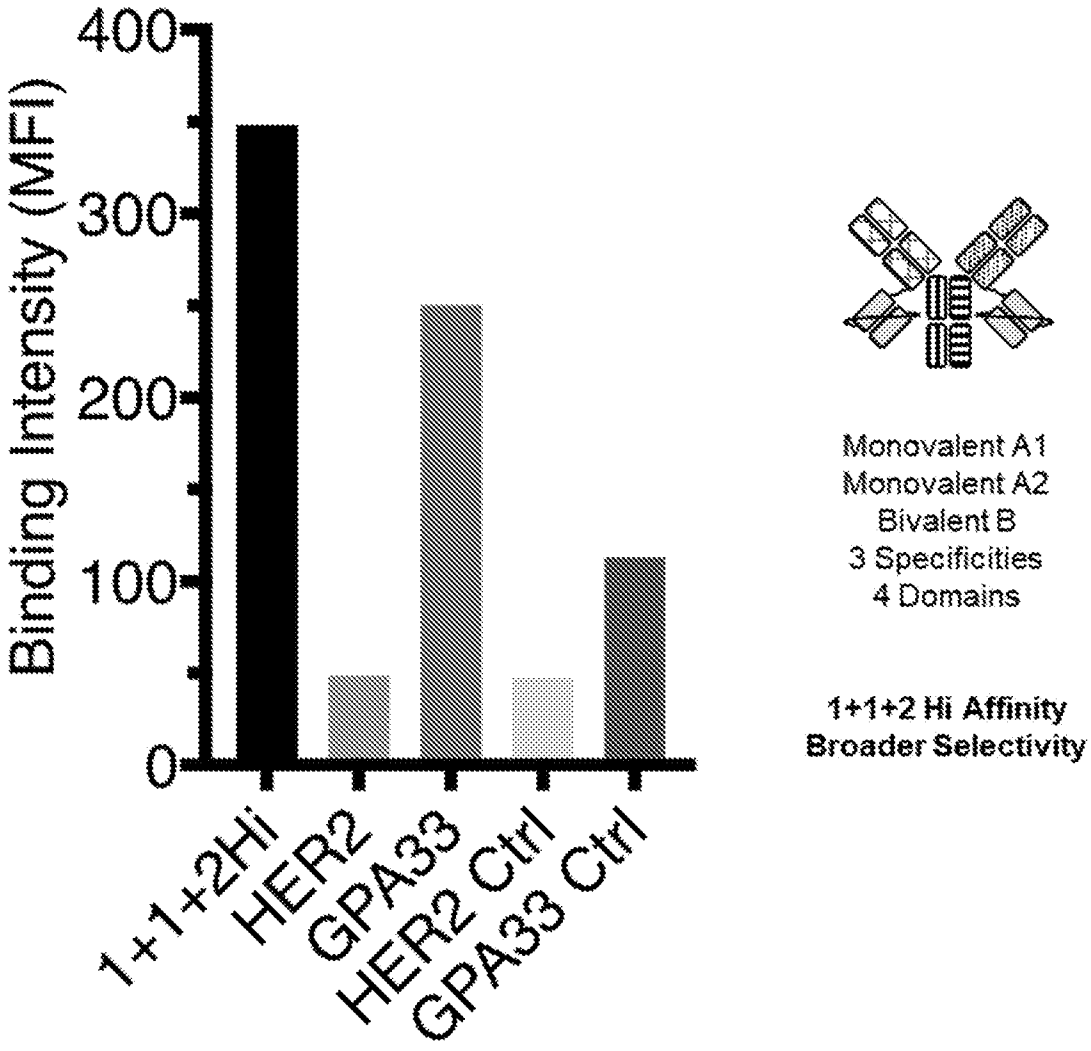
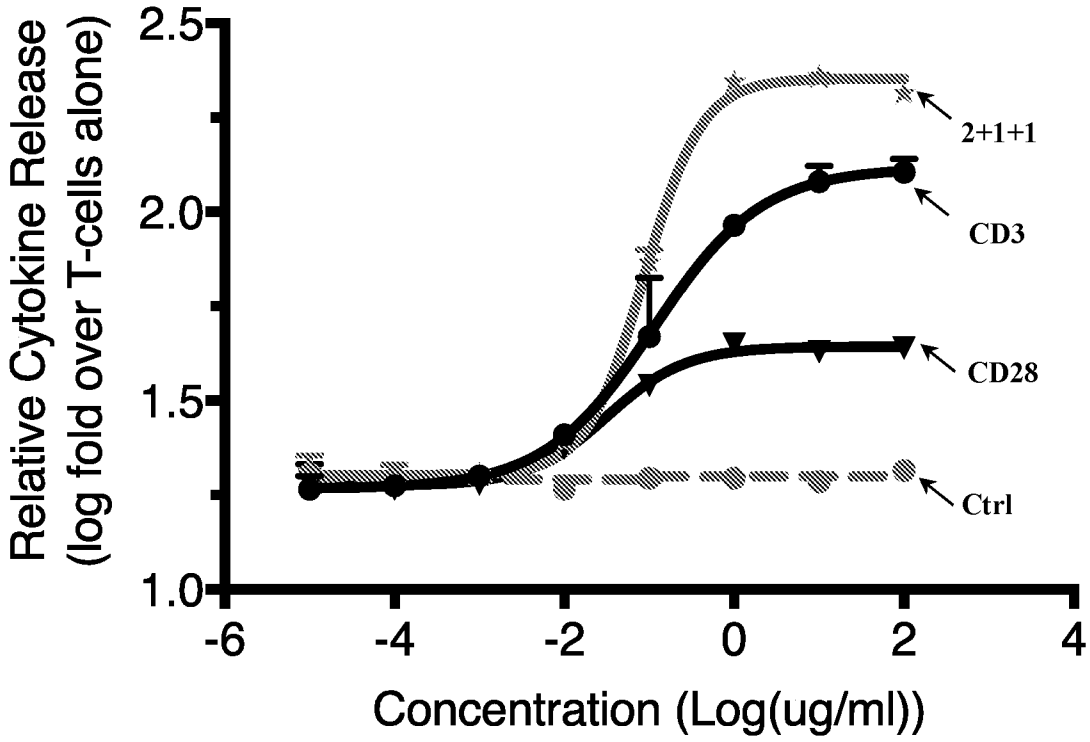
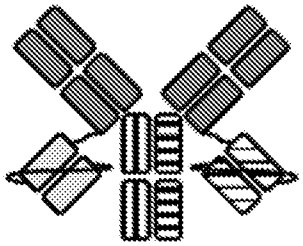

Binding Intensity (MFI)
400
300
200
100
0
1+1+2Hi
HER2
GPA33
HER2 Ctrl
GPA33 Ctrl
Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains
1+1+2 Hi Affinity
Broader Selectivity

Figure 18





Bivalent A
Monovalent B1
Monovalent B2
3 Specificities
4 Domains

2+1+1
More Immune
Activation

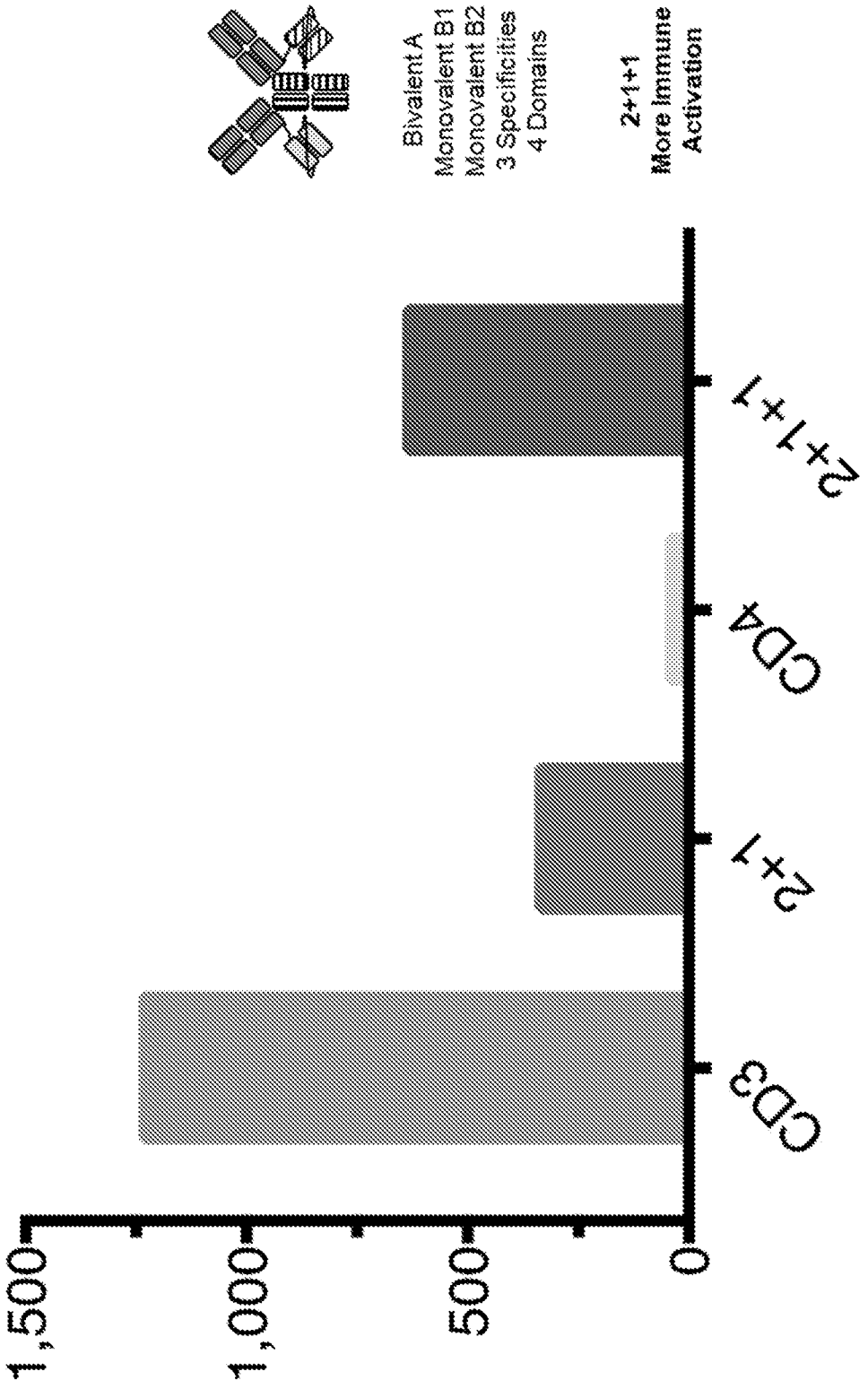

Bivalent A
Monovalent B1
Monovalent B2
3 Specificities
4 Domains
2+1+1
More Immune
Activation
1,500
1,000
500
0
CD3
2+1
CD4
2+1+1

Figure 19

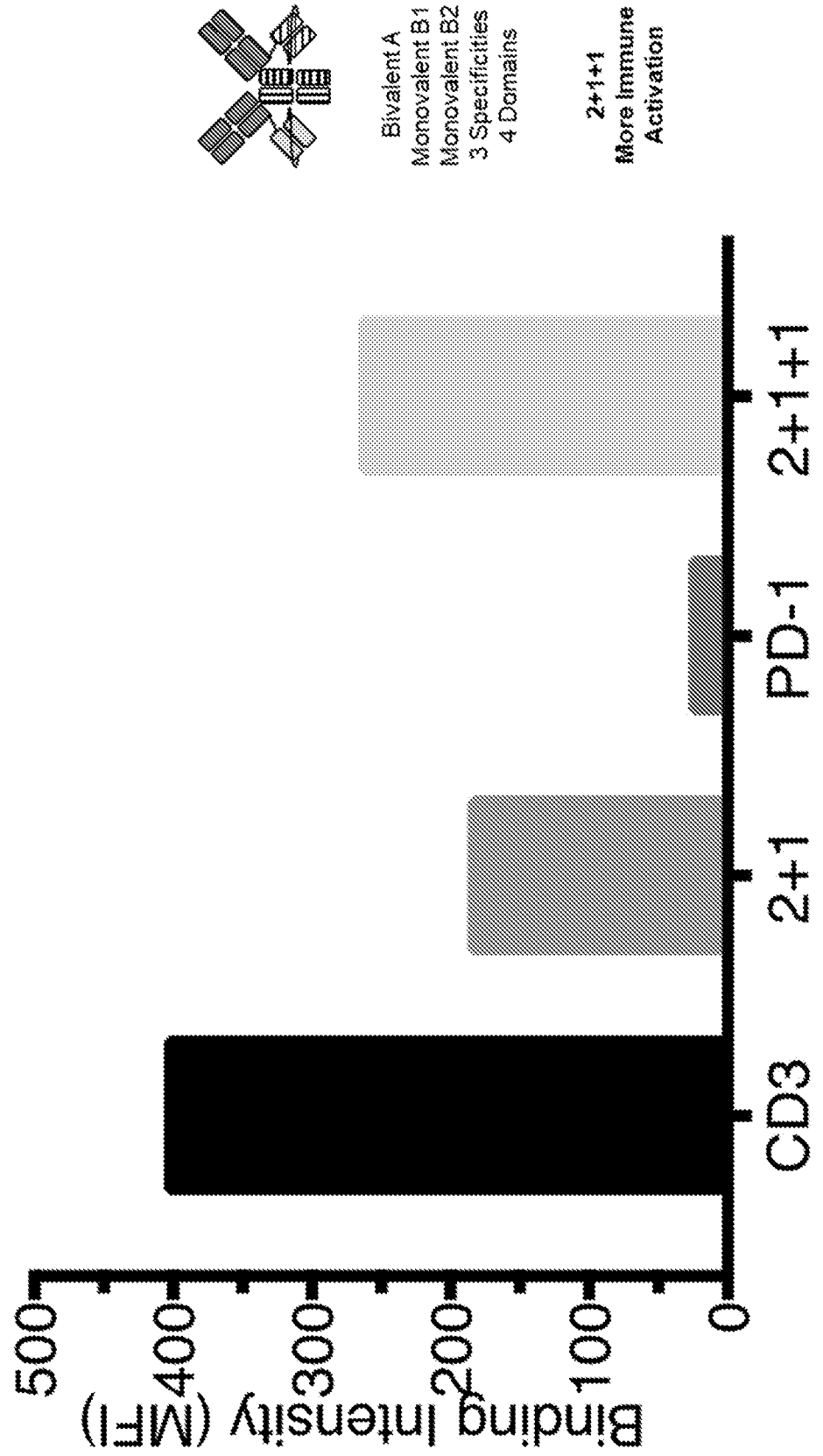

Bivalent A
Monovalent B1
Monovalent B2
3 Specificities
4 Domains
2+1+1
More Immune
Activation
Binding Intensity (MFI)
500
400
300
200
100
0
CD3
2+1
PD-1
2+1+1

Figure 20

Figure 21a

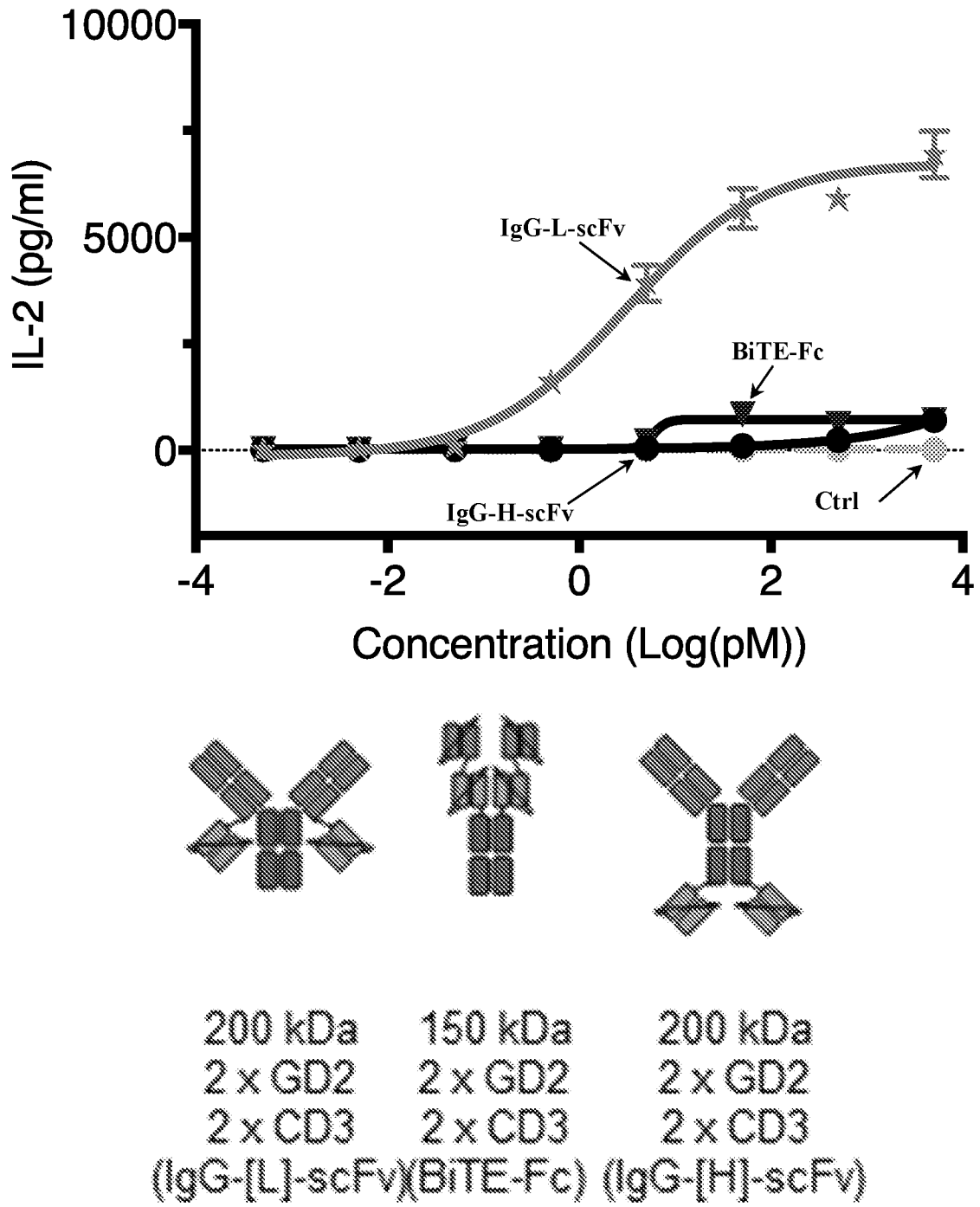

10000
5000
0
IL-2 (pg/ml)
IgG-L-scFv
BiTE-Fc
IgG-H-scFv
Ctrl
-4
-2
0
2
4
Concentration (Log(pM))
200 kDa
2 x GD2
2 x CD3
(IgG-[L]-scFv)
150 kDa
2 x GD2
2 x CD3
(BiTE-Fc)
200 kDa
2 x GD2
2 x CD3
(IgG-[H]-scFv)

Figure 21b

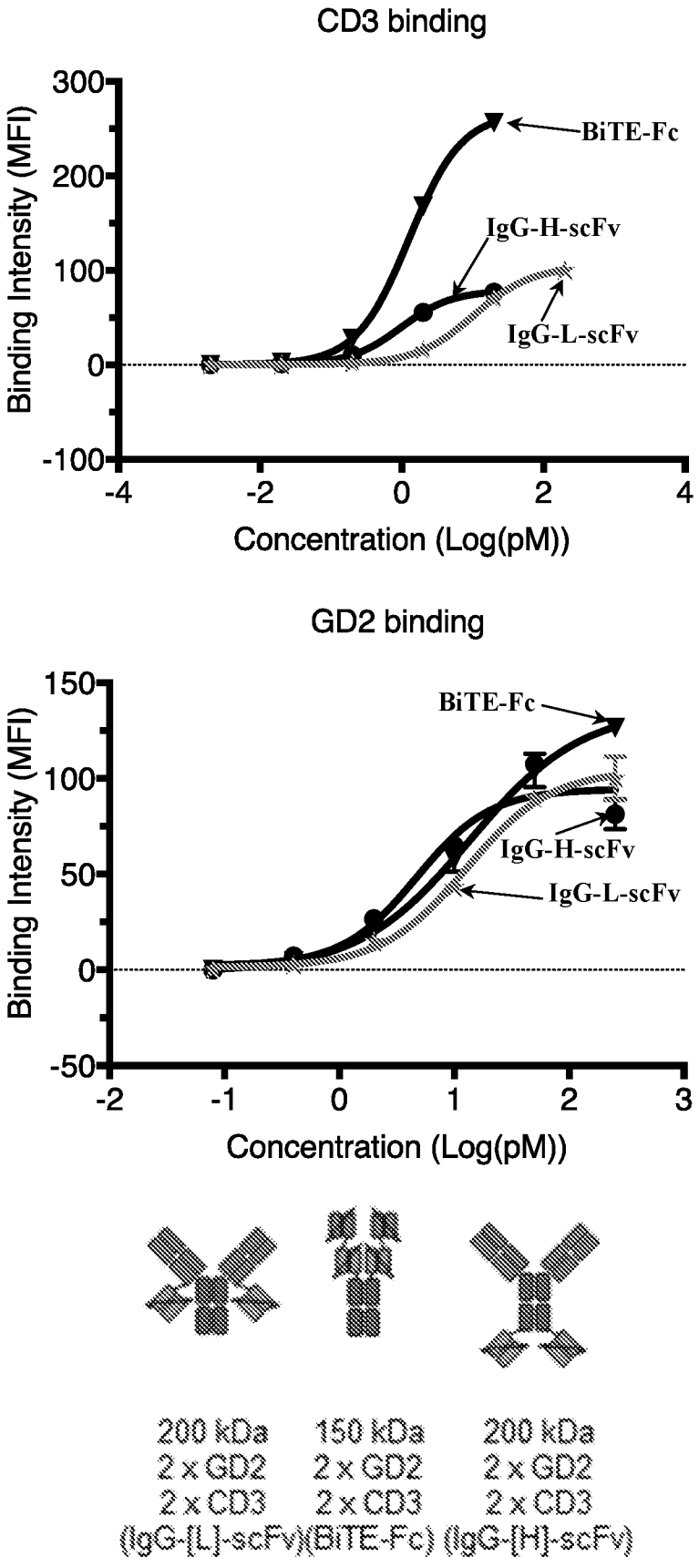

CD3 binding
Binding Intensity (MFI)
300
200
100
0
-100
-4
-2
0
2
4
Concentration (Log(pM))
BiTE-Fc
IgG-H-scFv
IgG-L-scFv
GD2 binding
Binding Intensity (MFI)
150
100
50
0
-50
-2
-1
0
1
2
3
Concentration (Log(pM))
BiTE-Fc
IgG-H-scFv
IgG-L-scFv
200 kDa
2 x GD2
2 x CD3
(IgG-[L]-scFv)
150 kDa
2 x GD2
2 x CD3
(BiTE-Fc)
200 kDa
2 x GD2
2 x CD3
(IgG-[H]-scFv)

Figure 21c

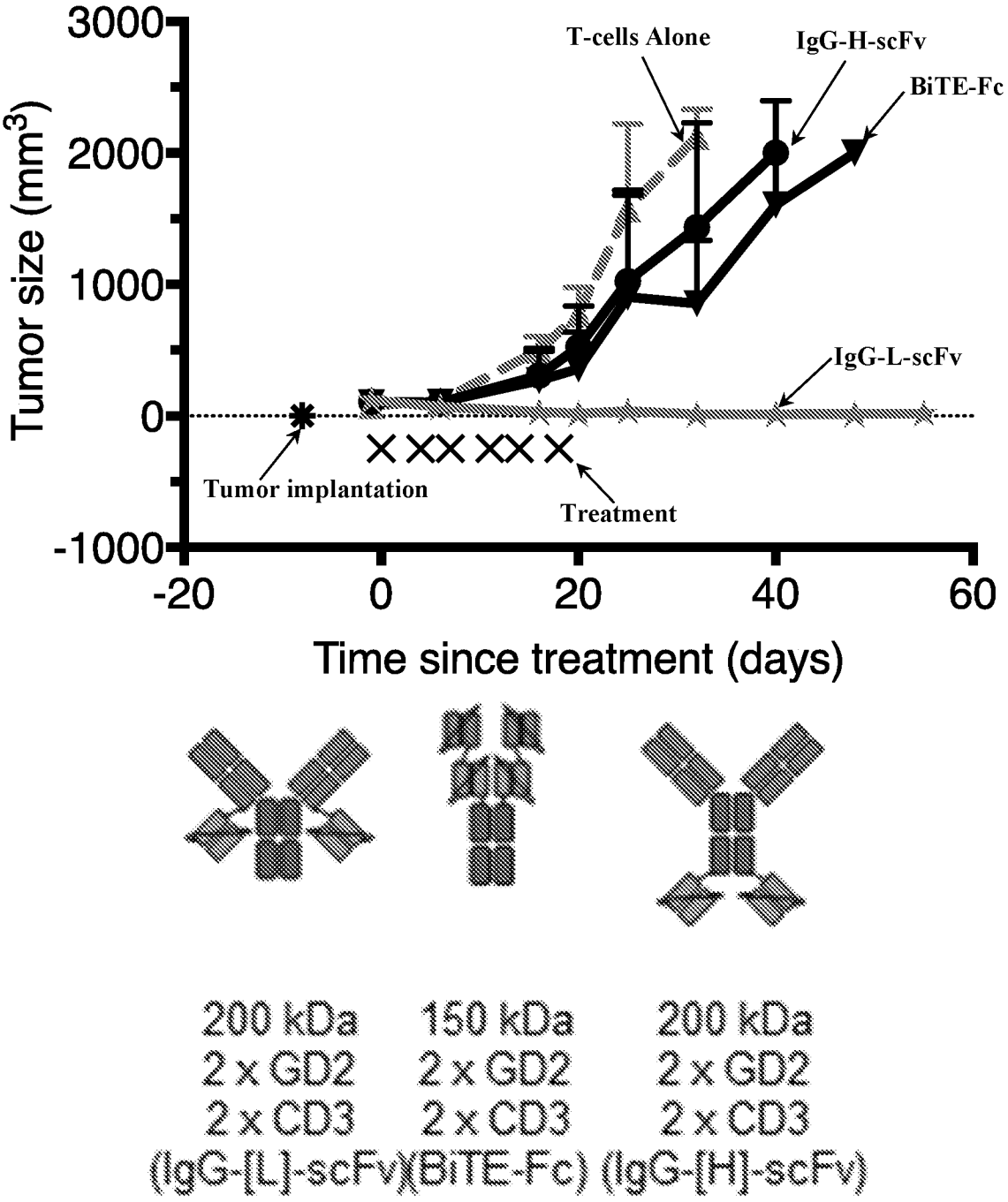

3000
2000
1000
0
-1000
Tumor size (mm3)
-20
0
20
40
60
Time since treatment (days)
T-cells Alone
IgG-H-scFv
BiTE-Fc
IgG-L-scFv
Tumor implantation
Treatment
200 kDa
2 x GD2
2 x CD3
(IgG-[L]-scFv)
150 kDa
2 x GD2
2 x CD3
(BiTE-Fc)
200 kDa
2 x GD2
2 x CD3
(IgG-[H]-scFv)

Figure 22

BsAb	EC_{50} (pM)	Fold Change	CD33 Valency	CD3 Valency	K409R mAb	F405L mAb	SEC-HPLC Purity (%)
2+2	0.9		2	2	-	-	92%
1+1H	134.4	149	1	1	IgG(huM195)	IgG(huOKT3)	94%
2+1	4.5	5	2	1	IgG(huM195)	IgG(huM195)-[L]-scFv(huOKT3)	97%
1+2	6.0	6.7	1	2	IgG(huM195)-[L]-scFv(huOKT3)	IgG(hu3F8)-[L]-scFv(huOKT3)	92%
1+1T	500	555	1	1	IgG(huM195)	IgG(hu3F8)-[L]-scFv(huOKT3)	94%
1+1C	11.5	12.3	1	1	IgG(hu3F8)	IgG(huM195)-[L]-scFv(huOKT3)	94%

Figure 23

HDTVS Type	Fab1	VH & VL SEQ ID NOs	Fab2	VH & VL SEQ ID NOs	scFv 1	VH & VL SEQ ID NOs	ScF v2	VH & VL SEQ ID NOs	Ag1	Ag2	Ag3	Ag4
2+1	hu3F8	1325 1321	hu3F8	1325 1321	huO KT3	2391 2390	-	-	GD2	GD2	CD3	-
1+1+2Lo	hu3F8	1325 1321	huM195	2395 2394	huO KT3	2391 2390	huO KT3	2391 2390	GD2	CD33	CD3	CD3
1+1+1	huM195	2395 2394	hu3F8	1325 1321	huO KT3	2391 2390	-	-	CD33	GD2	CD3	-
1+1+1	hu3F8	1325 1321	huM195	2395 2394	huO KT3	2391 2390	-	-	GD2	CD33	CD3	-
1+1+2Hi	hu3F8	1325 1321	hu4D5	1425 1421	huO KT3	2391 2390	huO KT3	2391 2390	GD2	HER2	CD3	CD3
1+1+2Hi	hu4D5	1425 1421	huM195	2395 2394	huO KT3	2391 2390	huO KT3	2391 2390	HER2	CD33	CD3	CD3
2+1	huM195	2395 2394	huM195	2395 2394	huO KT3	2391 2390	-	-	CD33	CD33	CD3	-
1+1+2Lo	hu3F8	1325 1321	hu4D5H 91A	1421 1417	huO KT3	2391 2390	huO KT3	2391 2390	GD2	HER2	CD3	CD3
1+1+2Lo	ch14.18	1309 1305	hu4D5H 91A	1421 1417	huO KT3	2391 2390	huO KT3	2391 2390	GD2	HER2	CD3	CD3
1+1+2Lo	hu4D5 H91A	1421 1417	huM195	2395 2394	huO KT3	2391 2390	huO KT3	2391 2390	HER2	CD33	CD3	CD3
1+1+2Hi	hu4D5	1425 1421	huA33	2393 2392	huO KT3	2391 2390	huO KT3	2391 2390	HER2	A33	CD3	CD3
1+1+2Lo	hu3F8	1325 1321	hu8H9	621 617	huO KT3	2391 2390	huO KT3	2391 2390	GD2	B7H3	CD3	CD3
1+1+2Lo	huM195	2395 2394	hu8H9	621 617	huO KT3	2391 2390	huO KT3	725 721	CD33	B7H3	CD3	CD3
1+1+2Hi	chC225	1101 1097	hu4D5	1425 1421	huO KT3	2391 2390	huO KT3	2391 2390	EGF R	HER2	CD3	CD3
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huO KT3	2391 2390	hu1 D6E 10	669 665	GD2	GD2	CD3	PD-1
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huO KT3	2391 2390	huM AB9 928	245 241	GD2	GD2	CD3	CTL A4

HDTVS Type	Fab1	VH & VL SEQ ID NOs	Fab2	VH & VL SEQ ID NOs	scFv 1	VH & VL SEQ ID NOs	ScF v2	VH & VL SEQ ID NOs	Ag1	Ag2	Ag3	Ag4
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huOKT3	2391 2390	TNX-355	893 889	GD2	GD2	CD3	CD4
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huOKT3	2391 2390	TGN1412	1901 1897	GD2	GD2	CD3	CD28

Figure 23 (contd.)