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(54) Title: ANTIGEN BINDING PROTEINS THAT BIND PD-L1

(57) **Abstract**: There is disclosed compositions and methods relating to or derived from anti-PD-L1 antibodies. More specifically, there is disclosed fully human antibodies that bind PD-L1, PD- L1 -binding fragments and derivatives of such antibodies, and PD-L1 -binding polypeptides comprising such fragments. Further still, there is disclosed nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having PD-L1 related disorders or conditions, including various inflammatory disorders and various cancers.

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# Antigen Binding Proteins that Bind PD-L1

## Technical Field

The present disclosure provides compositions and methods relating to or derived from anti-PD-L1 antibodies. More specifically, the present disclosure provides human antibodies that bind PD-L1, PD-L1-binding fragments and derivatives of such antibodies, and PD-L1 -binding polypeptides comprising such fragments. Further still, the present disclosure provides nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having PD-L1 related disorders or conditions, including various inflammatory disorders and various cancers.

## Background

Programmed death ligand 1 (PD-L1) is a 40 kDa type 1 transmembrane protein. PD-L1 (human PD-L1 cDNA is composed of the base sequence shown by EMBL/GenBank Acc. No. NM_001267706 and mouse PD-L1 cDNA is composed of the base sequence shown by NM_021893) that is a ligand of PD-1is expressed in so-called antigen-presenting cells such as activated monocytes and dendritic cells. These cells present interaction molecules that induce a variety of immuno-inductive signals to T lymphocytes, and PD-L1 is one of these molecules that induce the inhibitory signal by ligating PD-1. It has been revealed that PD-L1 ligation suppressed the activation (cellular proliferation and induction of various cytokine productions) of PD-1 expressing T lymphocytes. PD-L1 expression has been confirmed in not only immunocompetent cells but also a certain kind of tumor cell lines (cell lines derived from monocytic leukemia, cell lines derived from mast cells, cell lines derived from hepatic carcinomas, cell lines derived from neuroblasts, and cell lines derived from breast carcinomas) (*Nature Immunology* (2001), vol. 2, issue 3, p. 261-267.).

Programmed death 1 (PD-1) is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-L1, and BTLA. The initial member of the family, CD28, was discovered by functional effect on augmenting T cell proliferation following the addition of monoclonal antibodies (Hutloff et al. (1999) *Nature* 397:263-266; Hansen et al. (1980) *Immunogenics* 10:247-260). Two cell surface glycoprotein ligands for PD-1 have been identified, PD-L1 and PDL-2, and have been shown to down-regulate T cell activation and cytokine secretion occur upon binding to PD-1 (Freeman et al. (2000) *J. Exp. Med.* 192:1027-

34; Latchman et al. (2001) *Nat. Immunol.* 2:261-8; Carter et al. (2002) *Eur. J. Immunol.* 32:634-43; Ohigashi et al. (2005) *Clin. Cancer Res.* 11:2947-53). Both PD-L1 (B7-H1) and PD-L2 (B7-DC) are B7 homologs that bind to PD-1. Expression of PD-L1 on the cell surface has also been shown to be upregulated through IFN-γ stimulation.

PD-L1 expression has been found in several murine and human cancers, including human lung, ovarian and colon carcinoma and various myelomas (Iwai et al. (2002) *Proc. Natl. Acad. Sci. USA* 99:12293-7; Ohigashi et al. (2005) *Clin. Cancer Res.* 11:2947-53). PD-L1 has been suggested to play a role in tumor immunity by increasing apoptosis of antigen-specific T-cell clones (Dong et al. (2002) *Nat. Med.* 8:793-800). It has also been suggested that PD-L1 might be involved in intestinal mucosal inflammation and inhibition of PD-L1 suppresses wasting disease associated with colitis (Kanai et al. (2003) *J. Immunol.* 171:4156-63).

**Summary**

The present disclosure provides a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least $10^{-6}$M, which has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO.

197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof. Preferably, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called E6 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called E7 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called E9 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called E11

herein), SEQ ID NO. 9/SEQ ID NO. 10 (called F1 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called F4 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called F7 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called F8 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called F11 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called G4 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called G9 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called G11 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called G12 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called H1 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called H3 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called H4 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called H5 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called H6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called H10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called H12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called PDL-D2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called PDL-D11 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called PDL-H1 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called RB4 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called RB11 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called RC5 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called RF5 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called RG9 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called RD1 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called RF11 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called RH11 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called RD9 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called RE10 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called RA3 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called RG1 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called RB1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called RG7 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called RA6 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called RA8 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called RA9 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called RB5 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called RB8 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called RC8 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called RC10 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called RD2 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called RE8 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called RE9 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called RG12 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called RSA1 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called R2A7 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called R2B12 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called R2C9 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called R2D5 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called R2D7 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called R2F4 herein), SEQ ID NO. 111/SEQ ID NO. 112 (called R2A10 herein), SEQ ID NO. 113/SEQ ID NO. 114 (called R2E2 herein), SEQ ID NO. 115/SEQ ID NO. 116 (called R3B8 herein), SEQ ID NO. 117/SEQ ID NO. 118 (called R3C3 herein), SEQ ID NO. 119/SEQ ID NO. 120 (called R3E9 herein), SEQ ID NO. 121/SEQ ID NO. 122 (called R3E10 herein), SEQ ID NO. 123/SEQ ID

NO. 124 (called R3F7 herein), SEQ ID NO. 125/SEQ ID NO. 126 (called R3F10 herein), SEQ ID NO. 127/SEQ ID NO. 128 (called R4B10 herein), SEQ ID NO. 129/SEQ ID NO. 130 (called R4H1 herein), SEQ ID NO. 131/SEQ ID NO. 132 (called R4A11 herein), SEQ ID NO. 133/SEQ ID NO. 134 (called R3D2 herein), SEQ ID NO. 135/SEQ ID NO. 136 (called R5B8 herein), SEQ ID NO. 137/SEQ ID NO. 138 (called SH1A1Q herein), SEQ ID NO. 139/SEQ ID NO. 140 (called SH1B7B(K) herein), SEQ ID NO. 141/SEQ ID NO. 142 (called SH1C1 herein), SEQ ID NO. 143/SEQ ID NO. 144 (called SH1C8 herein), SEQ ID NO. 145/SEQ ID NO. 146 (called SH1E10 herein), SEQ ID NO. 147/SEQ ID NO. 148 (called SH1E2 herein), SEQ ID NO. 149/SEQ ID NO. 150 (called SH1A9 herein), SEQ ID NO. 151/SEQ ID NO. 152 (called SH1B11 herein), SEQ ID NO. 153/SEQ ID NO. 154 (called SH1E4 herein), SEQ ID NO. 155/SEQ ID NO. 156 (called SH1B3 herein), SEQ ID NO. 157/SEQ ID NO. 158 (called SH1D1 herein), SEQ ID NO. 159/SEQ ID NO. 160 (called SH1D2 herein), SEQ ID NO. 161/SEQ ID NO. 162 (called SH1D12 herein), SEQ ID NO. 163/SEQ ID NO. 164 (called SH1E1 herein), SEQ ID NO. 165/SEQ ID NO. 166 (called SH1G9 herein), SEQ ID NO. 167/SEQ ID NO. 168 (called SH1A11 herein), SEQ ID NO. 169/SEQ ID NO. 170 (called SH1C2 herein), SEQ ID NO. 171/SEQ ID NO. 172 (called SH1G8 herein), SEQ ID NO. 173/SEQ ID NO. 174 (called SH1H2 herein), SEQ ID NO. 175/SEQ ID NO. 176 (called SH1B10 herein), SEQ ID NO. 177/SEQ ID NO. 178 (called SH1B7A(L) herein), SEQ ID NO. 179/SEQ ID NO. 180 (called SH1E6 herein), SEQ ID NO. 181/SEQ ID NO. 182 (called SH1C11 herein), SEQ ID NO. 183/SEQ ID NO. 184 (called SH1A2 herein), SEQ ID NO. 185/SEQ ID NO. 186 (called SH1B1 herein), SEQ ID NO. 187/SEQ ID NO. 188 (called R6B2 herein), SEQ ID NO. 189/SEQ ID NO. 190 (called R6B7 herein), SEQ ID NO. 191/SEQ ID NO. 192 (called R6B11 herein), SEQ ID NO. 193/SEQ ID NO. 194 (called R6D1 herein), SEQ ID NO. 195/SEQ ID NO. 196 (called R6C8 herein), SEQ ID NO. 197/SEQ ID NO. 198 (called R9G8 herein), SEQ ID NO. 199/SEQ ID NO. 200 (called R7D1 herein), SEQ ID NO. 201/SEQ ID NO. 202 (called R7D2 herein), SEQ ID NO. 203/SEQ ID NO. 204 (called R7E7 herein), SEQ ID NO. 205/SEQ ID NO. 206 (called R7F2 herein), SEQ ID NO. 207/SEQ ID NO. 208 (called R7F7 herein), SEQ ID NO. 209/SEQ ID NO. 210 (called R9H2 herein), SEQ ID NO. 211/SEQ ID NO. 212 (called R9H6 herein), SEQ ID NO. 213/SEQ ID NO. 214 (called H6B1L herein), SEQ ID NO. 215/SEQ ID NO. 216 (called H6A1 herein), SEQ ID NO. 217/SEQ ID NO. 218 (called H6B1 herein), SEQ ID NO. 219/SEQ ID NO. 220 (called H6B2 herein), SEQ ID NO. 221/SEQ ID NO. 222 (called H19C herein), SEQ ID NO. 223/SEQ ID NO. 224 (called H110D herein), SEQ ID NO. 225/SEQ ID NO. 226 (called H11F herein), SEQ ID NO. 227/SEQ ID NO. 228 (called H1C1 herein), SEQ ID NO. 229/SEQ ID NO. 230

(called GPG1A2 herein), SEQ ID NO. 231/SEQ ID NO. 232 (called GPGG8 herein), SEQ ID NO. 233/SEQ ID NO. 234 (called GPGG10 herein), SEQ ID NO. 235/SEQ ID NO. 236 (called GPGH7 herein), SEQ ID NO. 237/SEQ ID NO. 238 (called GPGH10 herein), SEQ ID NO. 239/SEQ ID NO. 240 (called GPGH11 herein), SEQ ID NO. 241/SEQ ID NO. 242 (called GPGH10P herein), and combinations thereof.

The present disclosure provides a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2,

SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof. Preferably, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO.

44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO.

224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

The present disclosure provides a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID

NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof. Preferably, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ

ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ

ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

The present disclosure further provides a method for treating a broad spectrum of mammalian cancers or a broad-spectrum of inflammatory diseases and autoimmune diseases, comprising administering an effective amount of an anti-PD-L1 polypeptide, wherein the anti-PD-L1 polypeptide is selected from the group consisting of a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least $10^{-6}$M, a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, and combinations thereof;

wherein the fully human antibody has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID

NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof;

wherein the Fab fully human antibody fragment has the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID

NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116,

SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof; and

wherein the single chain human antibody has the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199,

SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof.

Preferably, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called E6 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called E7 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called E9 herein), SEQ ID NO. 7/SEQ ID

NO. 8 (called E11 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called F1 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called F4 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called F7 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called F8 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called F11 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called G4 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called G9 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called G11 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called G12 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called H1 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called H3 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called H4 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called H5 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called H6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called H10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called H12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called PDL-D2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called PDL-D11 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called PDL-H1 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called RB4 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called RB11 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called RC5 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called RF5 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called RG9 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called RD1 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called RF11 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called RH11 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called RD9 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called RE10 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called RA3 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called RG1 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called RB1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called RG7 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called RA6 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called RA8 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called RA9 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called RB5 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called RB8 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called RC8 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called RC10 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called RD2 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called RE8 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called RE9 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called RG12 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called RSA1 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called R2A7 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called R2B12 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called R2C9 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called R2D5 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called R2D7 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called R2F4 herein), SEQ ID NO. 111/SEQ ID NO. 112 (called R2A10 herein), SEQ ID NO. 113/SEQ ID NO. 114 (called R2E2 herein), SEQ ID NO. 115/SEQ ID NO. 116 (called R3B8 herein), SEQ ID NO. 117/SEQ ID NO. 118 (called R3C3 herein), SEQ ID NO. 119/SEQ ID NO. 120 (called R3E9 herein), SEQ ID NO. 121/SEQ ID NO. 122 (called

R3E10 herein), SEQ ID NO. 123/SEQ ID NO. 124 (called R3F7 herein), SEQ ID NO. 125/SEQ ID NO. 126 (called R3F10 herein), SEQ ID NO. 127/SEQ ID NO. 128 (called R4B10 herein), SEQ ID NO. 129/SEQ ID NO. 130 (called R4H1 herein), SEQ ID NO. 131/SEQ ID NO. 132 (called R4A11 herein), SEQ ID NO. 133/SEQ ID NO. 134 (called R3D2 herein), SEQ ID NO. 135/SEQ ID NO. 136 (called R5B8 herein), SEQ ID NO. 137/SEQ ID NO. 138 (called SH1A1Q herein), SEQ ID NO. 139/SEQ ID NO. 140 (called SH1B7B(K) herein), SEQ ID NO. 141/SEQ ID NO. 142 (called SH1C1 herein), SEQ ID NO. 143/SEQ ID NO. 144 (called SH1C8 herein), SEQ ID NO. 145/SEQ ID NO. 146 (called SH1E10 herein), SEQ ID NO. 147/SEQ ID NO. 148 (called SH1E2 herein), SEQ ID NO. 149/SEQ ID NO. 150 (called SH1A9 herein), SEQ ID NO. 151/SEQ ID NO. 152 (called SH1B11 herein), SEQ ID NO. 153/SEQ ID NO. 154 (called SH1E4 herein), SEQ ID NO. 155/SEQ ID NO. 156 (called SH1B3 herein), SEQ ID NO. 157/SEQ ID NO. 158 (called SH1D1 herein), SEQ ID NO. 159/SEQ ID NO. 160 (called SH1D2 herein), SEQ ID NO. 161/SEQ ID NO. 162 (called SH1D12 herein), SEQ ID NO. 163/SEQ ID NO. 164 (called SH1E1 herein), SEQ ID NO. 165/SEQ ID NO. 166 (called SH1G9 herein), SEQ ID NO. 167/SEQ ID NO. 168 (called SH1A11 herein), SEQ ID NO. 169/SEQ ID NO. 170 (called SH1C2 herein), SEQ ID NO. 171/SEQ ID NO. 172 (called SH1G8 herein), SEQ ID NO. 173/SEQ ID NO. 174 (called SH1H2 herein), SEQ ID NO. 175/SEQ ID NO. 176 (called SH1B10 herein), SEQ ID NO. 177/SEQ ID NO. 178 (called SH1B7A(L) herein), SEQ ID NO. 179/SEQ ID NO. 180 (called SH1E6 herein), SEQ ID NO. 181/SEQ ID NO. 182 (called SH1C11 herein), SEQ ID NO. 183/SEQ ID NO. 184 (called SH1A2 herein), SEQ ID NO. 185/SEQ ID NO. 186 (called SH1B1 herein), SEQ ID NO. 187/SEQ ID NO. 188 (called R6B2 herein), SEQ ID NO. 189/SEQ ID NO. 190 (called R6B7 herein), SEQ ID NO. 191/SEQ ID NO. 192 (called R6B11 herein), SEQ ID NO. 193/SEQ ID NO. 194 (called R6D1 herein), SEQ ID NO. 195/SEQ ID NO. 196 (called R6C8 herein), SEQ ID NO. 197/SEQ ID NO. 198 (called R9G8 herein), SEQ ID NO. 199/SEQ ID NO. 200 (called R7D1 herein), SEQ ID NO. 201/SEQ ID NO. 202 (called R7D2 herein), SEQ ID NO. 203/SEQ ID NO. 204 (called R7E7 herein), SEQ ID NO. 205/SEQ ID NO. 206 (called R7F2 herein), SEQ ID NO. 207/SEQ ID NO. 208 (called R7F7 herein), SEQ ID NO. 209/SEQ ID NO. 210 (called R9H2 herein), SEQ ID NO. 211/SEQ ID NO. 212 (called R9H6 herein), SEQ ID NO. 213/SEQ ID NO. 214 (called H6B1L herein), SEQ ID NO. 215/SEQ ID NO. 216 (called H6A1 herein), SEQ ID NO. 217/SEQ ID NO. 218 (called H6B1 herein), SEQ ID NO. 219/SEQ ID NO. 220 (called H6B2 herein), SEQ ID NO. 221/SEQ ID NO. 222 (called H19C herein), SEQ ID NO. 223/SEQ ID NO. 224 (called H110D herein), SEQ ID NO. 225/SEQ ID NO. 226 (called H11F herein), SEQ ID NO. 227/SEQ ID NO. 228

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91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

Preferably, the broad spectrum of mammalian cancers to be treated is selected from the group consisting of ovarian, colon, breast, lung cancers, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, and combinations

thereof. Preferably, the autoimmune disease or inflammatory disease is selected from the group consisting of intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Cohn's disease, and inflammatory bowel disease.

**Brief Description of the Figures**

Figure 1 shows anti-PD-L1 antibodies H6 and H10 binding to human PD-L1 expressed on human lymphocytes and the $EC_{50}$ determination in the 100 pM range

Figure 2 shows disclosed anti-PD-L1 antibodies binding to human lymphocytes by FACSAria analysis.

Figure 3 shows disclosed anti-PD-L1 antibodies H1, H6 and H10 inhibit lymphocyte proliferation.

Figure 4 shows disclosed anti-PD-L1 antibody H10 inhibit NK cell proliferation.

Figure 5 shows disclosed anti-PD-L1 antibodies H6 and H10 enhance cell activation and that the responsive lymphocyte population is the NK cell.

Figure 6 shows effect of anti-PD-L1 antibodies H6 and H10 on the progression of disease in a murine model of multiple sclerosis (MS)

Figure 7 shows the results of EC50 cell binding flow cytometry experiments, demonstrating that anti-PD-L1 antibody G12 binds the cell surface of CHO cells transfected with full length PD-L1 in a concentration dependent manner.

Figure 8 shows the results of EC50 cell binding flow cytometry experiments, demonstrating that anti-PD-L1 antibody G12 binds in a concentration dependent manner to the cell surface of ES-2 ovarian carcinoma cells induced with IFNγ to increase the level of PD-L1 expression on these cells.

Figure 9 shows IC50 data for the blocking of the interaction between recombinant human PD-1and human PD-L1 expressed on CHO cells by anti-PD-L1 antibody G12.

Figure 10 shows a mixed lymphocyte reaction (MLR) to evaluate the effect of the antibodies on lymphocyte activity in lymphocyte effector cells. IL-2 secretion was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody. The antibodies used were the disclosed G12 antibody as compared to prior disclosed antibodies 10A5 and 12A4 (Bristol-Myers/Medarex) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 the disclosure of which is incorporated by reference herein).

Figure 11 shows a mixed lymphocyte reaction (MLR) was employed to demonstrate the effect of blocking the PD-L1/PD-1 pathway by the listed anti-PD-L1 antibodies on

lymphocyte effector cells. IFN-γ secretion was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody. The antibodies used were the disclosed G12 antibody as compared to prior disclosed antibody 10A5 (Bristol-Myers/Medarex) that was obtained via in-house production from prior-disclosed antibody sequences (see U.S. Patent Application 2009/0055944, the disclosure of which is incorporated by reference herein).

Figure 12 shows a mixed lymphocyte reaction (MLR) was employed to evaluate the effect of the antibodies on lymphocyte activity by the anti-PD-L1 antibodies on lymphocyte effector cells. T cell activation was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody. The antibodies used were the disclosed G12 antibody as compared to prior disclosed antibodies 10A5 and 12A4 (Bristol-Myers/Medarex) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 the disclosure of which is incorporated by reference herein).

Figure 13 shows a mixed lymphocyte reaction (MLR) was employed to evaluate the effect of the antibodies on lymphocyte activity by the anti-PD-L1 antibodies on lymphocyte effector cells. T cell activation was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody. The antibodies used were the disclosed H6B1L, RSA1, RA3, RC5, SH1E2, SH1E4, SH1B11, and SH1C8 as compared to prior disclosed antibodies 10A5 (Bristol-Myers-Squibb/Medarex) and YW243.55S70 (Roche/Genentech) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 and U.S. Patent Application US 2010/0203056; the disclosure of which are incorporated by reference herein).

Figure 14 shows a mixed lymphocyte reaction (MLR) to evaluate the effect of the antibodies on lymphocyte activity in lymphocyte effector cells. IL-2 secretion was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody. The antibodies used were the disclosed H6B1L, RSA1, RA3, RC5, SH1E2, SH1E4, SH1B11, and SH1C8 as compared to prior disclosed antibodies 10A5 (Bristol-Myers-Squibb/Medarex) and YW243.55S70 (Roche/Genentech) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 and U.S. Patent Application US 2010/0203056; the disclosure of which are incorporated by reference herein).

Figure 15 shows a mixed lymphocyte reaction (MLR) was employed to demonstrate the effect of blocking the PD-L1/PD-1 pathway by the listed anti-PD-L1 antibodies on lymphocyte effector cells. IFN-γ secretion was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody. The antibodies used were the disclosed H6B1L, RSA1, RA3, RC5, SH1E2, SH1E4, SH1B11, and SH1C8 as compared to prior disclosed antibodies

10A5 (Bristol-Myers-Squibb/Medarex) and YW243.55S70 (Roche/Genentech) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 and U.S. Patent Application US 2010/0203056; the disclosure of which are incorporated by reference herein).

**Detailed Description**

The present disclosure provides a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of $10^{-6}$M or less, that has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8,

SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof. Preferably, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called E6 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called E7 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called E9 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called E11 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called F1 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called F4 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called F7 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called F8 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called F11 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called G4 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called G9 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called G11 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called G12 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called H1 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called H3 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called H4 herein), SEQ ID

NO. 33/SEQ ID NO. 34 (called H5 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called H6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called H10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called H12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called PDL-D2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called PDL-D11 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called PDL-H1 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called RB4 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called RB11 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called RC5 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called RF5 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called RG9 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called RD1 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called RF11 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called RH11 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called RD9 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called RE10 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called RA3 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called RG1 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called RB1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called RG7 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called RA6 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called RA8 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called RA9 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called RB5 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called RB8 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called RC8 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called RC10 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called RD2 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called RE8 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called RE9 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called RG12 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called RSA1 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called R2A7 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called R2B12 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called R2C9 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called R2D5 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called R2D7 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called R2F4 herein), SEQ ID NO. 111/SEQ ID NO. 112 (called R2A10 herein), SEQ ID NO. 113/SEQ ID NO. 114 (called R2E2 herein), SEQ ID NO. 115/SEQ ID NO. 116 (called R3B8 herein), SEQ ID NO. 117/SEQ ID NO. 118 (called R3C3 herein), SEQ ID NO. 119/SEQ ID NO. 120 (called R3E9 herein), SEQ ID NO. 121/SEQ ID NO. 122 (called R3E10 herein), SEQ ID NO. 123/SEQ ID NO. 124 (called R3F7 herein), SEQ ID NO. 125/SEQ ID NO. 126 (called R3F10 herein), SEQ ID NO. 127/SEQ ID NO. 128 (called R4B10 herein), SEQ ID NO. 129/SEQ ID NO. 130 (called R4H1 herein), SEQ ID NO. 131/SEQ ID NO. 132 (called R4A11 herein), SEQ ID NO. 133/SEQ ID NO. 134 (called R3D2 herein), SEQ ID NO. 135/SEQ ID NO. 136 (called R5B8 herein), SEQ ID NO. 137/SEQ ID NO. 138 (called SH1A1Q herein), SEQ ID NO. 139/SEQ ID NO. 140 (called SH1B7B(K) herein), SEQ ID NO. 141/SEQ ID NO. 142 (called SH1C1 herein), SEQ ID NO. 143/SEQ ID NO. 144 (called SH1C8 herein), SEQ ID NO. 145/SEQ ID

NO. 146 (called SH1E10 herein), SEQ ID NO. 147/SEQ ID NO. 148 (called SH1E2 herein), SEQ ID NO. 149/SEQ ID NO. 150 (called SH1A9 herein), SEQ ID NO. 151/SEQ ID NO. 152 (called SH1B11 herein), SEQ ID NO. 153/SEQ ID NO. 154 (called SH1E4 herein), SEQ ID NO. 155/SEQ ID NO. 156 (called SH1B3 herein), SEQ ID NO. 157/SEQ ID NO. 158 (called SH1D1 herein), SEQ ID NO. 159/SEQ ID NO. 160 (called SH1D2 herein), SEQ ID NO. 161/SEQ ID NO. 162 (called SH1D12 herein), SEQ ID NO. 163/SEQ ID NO. 164 (called SH1E1 herein), SEQ ID NO. 165/SEQ ID NO. 166 (called SH1G9 herein), SEQ ID NO. 167/SEQ ID NO. 168 (called SH1A11 herein), SEQ ID NO. 169/SEQ ID NO. 170 (called SH1C2 herein), SEQ ID NO. 171/SEQ ID NO. 172 (called SH1G8 herein), SEQ ID NO. 173/SEQ ID NO. 174 (called SH1H2 herein), SEQ ID NO. 175/SEQ ID NO. 176 (called SH1B10 herein), SEQ ID NO. 177/SEQ ID NO. 178 (called SH1B7A(L) herein), SEQ ID NO. 179/SEQ ID NO. 180 (called SH1E6 herein), SEQ ID NO. 181/SEQ ID NO. 182 (called SH1C11 herein), SEQ ID NO. 183/SEQ ID NO. 184 (called SH1A2 herein), SEQ ID NO. 185/SEQ ID NO. 186 (called SH1B1 herein), SEQ ID NO. 187/SEQ ID NO. 188 (called R6B2 herein), SEQ ID NO. 189/SEQ ID NO. 190 (called R6B7 herein), SEQ ID NO. 191/SEQ ID NO. 192 (called R6B11 herein), SEQ ID NO. 193/SEQ ID NO. 194 (called R6D1 herein), SEQ ID NO. 195/SEQ ID NO. 196 (called R6C8 herein), SEQ ID NO. 197/SEQ ID NO. 198 (called R9G8 herein), SEQ ID NO. 199/SEQ ID NO. 200 (called R7D1 herein), SEQ ID NO. 201/SEQ ID NO. 202 (called R7D2 herein), SEQ ID NO. 203/SEQ ID NO. 204 (called R7E7 herein), SEQ ID NO. 205/SEQ ID NO. 206 (called R7F2 herein), SEQ ID NO. 207/SEQ ID NO. 208 (called R7F7 herein), SEQ ID NO. 209/SEQ ID NO. 210 (called R9H2 herein), SEQ ID NO. 211/SEQ ID NO. 212 (called R9H6 herein), SEQ ID NO. 213/SEQ ID NO. 214 (called H6B1L herein), SEQ ID NO. 215/SEQ ID NO. 216 (called H6A1 herein), SEQ ID NO. 217/SEQ ID NO. 218 (called H6B1 herein), SEQ ID NO. 219/SEQ ID NO. 220 (called H6B2 herein), SEQ ID NO. 221/SEQ ID NO. 222 (called H19C herein), SEQ ID NO. 223/SEQ ID NO. 224 (called H110D herein), SEQ ID NO. 225/SEQ ID NO. 226 (called H11F herein), SEQ ID NO. 227/SEQ ID NO. 228 (called H1C1 herein), SEQ ID NO. 229/SEQ ID NO. 230 (called GPG1A2 herein), SEQ ID NO. 231/SEQ ID NO. 232 (called GPGG8 herein), SEQ ID NO. 233/SEQ ID NO. 234 (called GPGG10 herein), SEQ ID NO. 235/SEQ ID NO. 236 (called GPGH7 herein), SEQ ID NO. 237/SEQ ID NO. 238 (called GPGH10 herein), SEQ ID NO. 239/SEQ ID NO. 240 (called GPGH11 herein), SEQ ID NO. 241/SEQ ID NO. 242 (called GPGH10P herein), and combinations thereof.

The present disclosure provides a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain,

wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO.

80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof. Preferably, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ

ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

The present disclosure provides a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the

heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82,

SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof. Preferably, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO.

82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

The present disclosure further provides a method for treating a broad spectrum of mammalian cancers or inflammatory diseases or autoimmune diseases, comprising administering an effective amount of an anti-PD-L1 polypeptide, wherein the anti-PD-L1

polypeptide is selected from the group consisting of a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least $10^{-6}$M, a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, and combinations thereof;

wherein the fully human antibody has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12,

SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof;

wherein the Fab fully human antibody fragment has the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97,

SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186,

SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof; and

wherein the single chain human antibody has the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10,

SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof.

Preferably, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ

ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO.

229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof. Preferably, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO.

154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof. Preferably, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO.

76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

Preferably, the broad spectrum of mammalian cancers to be treated is selected from the group consisting of ovarian, colon, breast, lung cancers, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, and combinations thereof. Preferably, the autoimmune disease or inflammatory disease is selected from the group consisting of intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Cohn's disease, and inflammatory bowel disease.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (*e.g.*, an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129; Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold.

An antigen binding protein can have, for example, the structure of a naturally occurring immunoglobulin. An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa or lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed.,

2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

The variable regions of naturally occurring immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in Sequences of Proteins of Immunological Interest, 5$^{th}$ Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. Other numbering systems for the amino acids in immunoglobulin chains include IMGT.RTM. (international ImMunoGeneTics information system; Lefranc et al, *Dev. Comp. Immunol.* 29:185-203; 2005) and AHo (Honegger and Pluckthun, *J. Mol. Biol.* 309(3):657-670; 2001).

Antibodies can be obtained from sources such as serum or plasma that contain immunoglobulins having varied antigenic specificity. If such antibodies are subjected to affinity purification, they can be enriched for a particular antigenic specificity. Such enriched preparations of antibodies usually are made of less than about 10% antibody having specific binding activity for the particular antigen. Subjecting these preparations to several rounds of affinity purification can increase the proportion of antibody having specific binding activity for the antigen. Antibodies prepared in this manner are often referred to as "monospecific." Monospecfic antibody preparations can be made up of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or 99.9% antibody having specific binding activity for the particular antigen.

An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. Antigen binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, *inter alia*, Fab, Fab', $F(ab')_2$, Fv, domain antibodies (dAbs), and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

A Fab fragment is a monovalent fragment having the $V_L$, $V_H$, $C_L$ and $C_{H1}$ domains; a $F(ab')_2$ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the $V_H$ and $C_{H1}$ domains; an Fv fragment has the $V_L$ and

$V_H$ domains of a single arm of an antibody; and a dAb fragment has a $V_H$ domain, a $V_L$ domain, or an antigen-binding fragment of a $V_H$ or VL domain (U.S. Patents 6,846,634; 6,696,245, US App. Pub.20/0202512; 2004/0202995; 2004/0038291; 2004/0009507;20 03/0039958, and Ward et al., *Nature* 341:544-546, 1989).

A single-chain antibody (scFv) is an antibody in which a $V_L$ and a $V_H$ region are joined via a linker (*e.g.*, a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, e.g., Bird et al., 1988, *Science* 242:423-26 and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83). Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises $V_H$ and $V_L$ domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:6444-48, and Poljak et al., 1994, *Structure* 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat et al. *supra*; Lefranc et al., *supra* and/or Honegger and Pluckthun, *supra*. One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding protein may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

An antigen binding protein may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

The term "human antibody" includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully

human antibody). These antibodies may be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes.

A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Patents 6,054,297, 5,886,152 and 5,877,293.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of the CDRs are derived from a human anti-PD-L1 antibody. In another embodiment, all of the CDRs are derived from a human anti-PD-L1 antibody. In another embodiment, the CDRs from more than one human anti-PD-L1 antibodies are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-PAR-2 antibody, a CDR2 and a CDR3 from the light chain of a second human anti-PD-L1 antibody, and the CDRs from the heavy chain from a third anti-PD-L1 antibody. Other combinations are possible.

Further, the framework regions may be derived from one of the same anti-PD-L1 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the

chain(s) is/are identical with, homologous to, or derived from an antibody (-ies) from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (*i.e.*, the ability to specifically bind PD-L1).

A "neutralizing antibody" or an "inhibitory antibody" is an antibody that inhibits the proteolytic activation of PD-L1 when an excess of the anti-PD-L1 antibody reduces the amount of activation by at least about 20% using an assay such as those described herein in the Examples. In various embodiments, the antigen binding protein reduces the amount of amount of proteolytic activation of PD-L1 by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, and 99.9%.

Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification and using techniques known in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, Bowie et al., 1991, *Science* 253:164.

A "CDR grafted antibody" is an antibody comprising one or more CDRs derived from an antibody of a particular species or isotype and the framework of another antibody of the same or different species or isotype.

A "multi-specific antibody" is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a "bi-specific antibody" which recognizes two distinct epitopes on the same or different antigens.

An antigen binding protein "specifically binds" to an antigen (*e.g.*, human PD-L1) if it binds to the antigen with a dissociation constant of 1 nanomolar or less.

An "antigen binding domain," "antigen binding region," or "antigen binding site" is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody that specifically binds to its antigen, this will include at least part of at least one of its CDR domains.

An "epitope" is the portion of a molecule that is bound by an antigen binding protein (*e.g.*, by an antibody). An epitope can comprise non-contiguous portions of the molecule (*e.g.*,

in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

The "percent identity" of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, Calif.)) using its default parameters.

The terms "polynucleotide," "oligonucleotide" and "nucleic acid" are used interchangeably throughout and include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs (*e.g.*, peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutein, or variant thereof.

Two single-stranded polynucleotides are "the complement" of each other if their sequences can be aligned in an anti-parallel orientation such that every nucleotide in one polynucleotide is opposite its complementary nucleotide in the other polynucleotide, without the introduction of gaps, and without unpaired nucleotides at the 5' or the 3' end of either sequence. A polynucleotide is "complementary" to another polynucleotide if the two polynucleotides can hybridize to one another under moderately stringent conditions. Thus, a polynucleotide can be complementary to another polynucleotide without being its complement.

A "vector" is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

A nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (*e.g.*, the level, timing, or location of expression) of the nucleotide sequence. A "regulatory sequence" is a nucleic acid that affects the expression (*e.g.*,

the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (*e.g.*, polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: *Methods in Enzymology* 185, Academic Press, San Diego, Calif. and Baron et al., 1995, *Nucleic Acids Res.* 23:3605-06.

A "host cell" is a cell that can be used to express a nucleic acid, *e.g.*, a nucleic acid of the invention. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a single-celled eukaryote (*e.g.*, a yeast or other fungus), a plant cell (*e.g.*, a tobacco or tomato plant cell), an animal cell (*e.g.*, a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Examples of host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman et al., 1981, *Cell* 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (see Rasmussen et al., 1998, *Cytotechnology* 28:31) or CHO strain DX-B11, which is deficient in DHFR (see Urlaub et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:4216-20), HeLa cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan et al., 1991, *EMBO J.* 10:2821), human embryonic kidney cells such as 293,293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers 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, *e.g.*, mutation or environmental influence, 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.

Preferably, the mammalian cancer to be treated is selected from the group consisting of ovarian, colon, breast or hepatic carcinoma cell lines, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemia's, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, and combinations thereof.

Polypeptides of the present disclosure can be produced using any standard methods known in the art. In one example, the polypeptides are produced by recombinant DNA methods by inserting a nucleic acid sequence (*e.g.*, a cDNA) encoding the polypeptide into a recombinant expression vector and expressing the DNA sequence under conditions promoting expression.

Nucleic acids encoding any of the various polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for E. coli and other bacteria, as well as mammalian cells, plant cells, yeast cells and insect cells. See for example: Mayfield et al., *Proc. Natl. Acad. Sci. USA*. 2003 100(2):438-42; Sinclair et al. *Protein Expr. Purif.* 2002 (1):96-105; Connell N D. *Curr. Opin. Biotechnol.* 2001 12(5):446-9; Makrides et al. *Microbiol. Rev.* 1996 60(3):512-38; and Sharp et al. *Yeast*. 1991 7(7):657-78.

General techniques for nucleic acid manipulation are described for example in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Vols. 1-3, Cold Spring Harbor Laboratory Press, 2 ed., 1989, or F. Ausubel et al., *Current Protocols in Molecular Biology* (Green Publishing and Wiley-Interscience: New York, 1987) and periodic updates, herein incorporated by reference. The DNA encoding the polypeptide is operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants is additionally incorporated.

The recombinant DNA can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in *Cloning Vectors: A Laboratory Manual*, (Elsevier, N.Y., 1985).

The expression construct is introduced into the host cell using a method appropriate to the host cell. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent). Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells.

Suitable bacteria include gram negative or gram positive organisms, for example, *E. coli* or *Bacillus spp*. Yeast, preferably from the *Saccharomyces* species, such as *S. cerevisiae*, may also be used for production of polypeptides. Various mammalian or insect cell culture systems can also be employed to express recombinant proteins. *Baculovirus* systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, (*Bio/Technology*, 6:47, 1988). Examples of suitable mammalian host cell lines include endothelial cells, COS-7 monkey kidney cells, CV-1, L cells, C127, 3T3, Chinese hamster ovary (CHO), human embryonic kidney cells, HeLa, 293, 293T, and BHK cell lines. Purified polypeptides are prepared by culturing suitable host/vector systems to express the recombinant proteins. For many applications, the small size of many of the polypeptides disclosed herein would make expression in *E. coli* as the preferred method for expression. The protein is then purified from culture media or cell extracts.

Proteins disclosed herein can also be produced using cell-translation systems. For such purposes the nucleic acids encoding the polypeptide must be modified to allow in vitro transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized (eukaryotic such as a mammalian or yeast cell-free translation system or prokaryotic such as a bacterial cell-free translation system.

PD-L1-binding polypeptides can also be produced by chemical synthesis (*e.g.*, by the methods described in Solid Phase Peptide Synthesis, 2nd ed., 1984, The Pierce Chemical Co., Rockford, Ill.). Modifications to the protein can also be produced by chemical synthesis.

The polypeptides of the present disclosure can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (*e.g.*, with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography, hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, gel filtration, gel permeation chromatography, affinity chromatography, electrophoresis, countercurrent distribution or any combinations of these. After purification,

polypeptides may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis.

The purified polypeptide is preferably at least 85% pure, more preferably at least 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the polypeptide is sufficiently pure for use as a pharmaceutical product.

Post-Translational Modifications of Polypeptides

In certain embodiments, the binding polypeptides of the invention may further comprise post-translational modifications. Exemplary post-translational protein modifications include phosphorylation, acetylation, methylation, ADP-ribosylation, ubiquitination, glycosylation, carbonylation, sumoylation, biotinylation or addition of a polypeptide side chain or of a hydrophobic group. As a result, the modified soluble polypeptides may contain non-amino acid elements, such as lipids, poly- or mono-saccharide, and phosphates. A preferred form of glycosylation is sialylation, which conjugates one or more sialic acid moieties to the polypeptide. Sialic acid moieties improve solubility and serum half-life while also reducing the possible immunogeneticity of the protein. See Raju et al. *Biochemistry*. 2001 31; 40(30):8868-76. Effects of such non-amino acid elements on the functionality of a polypeptide may be tested for its antagonizing role in PD-L1 or PD-1 function, *e.g.*, its inhibitory effect on angiogenesis or on tumor growth.

In one specific embodiment, modified forms of the subject soluble polypeptides comprise linking the subject soluble polypeptides to nonproteinaceous polymers. In one specific embodiment, the polymer is polyethylene glycol ("PEG"), polypropylene glycol, or polyoxyalkylenes, in the manner as set forth in U.S. Patents 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

PEG is a water soluble polymer that is commercially available or can be prepared by ring-opening polymerization of ethylene glycol according to methods well known in the art (Sandler and Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, pages 138-161). The term "PEG" is used broadly to encompass any polyethylene glycol molecule, without regard to size or to modification at an end of the PEG, and can be represented by the formula: $X\text{--}O(CH_2CH_2O)_n\text{-}1CH_2CH_2OH$ (1), where n is 20 to 2300 and X is H or a terminal modification, *e.g.*, a $C_{1\text{-}4}$ alkyl. In one embodiment, the PEG of the invention terminates on one end with hydroxy or methoxy, *i.e.*, X is H or $CH_3$ ("methoxy PEG"). A PEG can contain further chemical groups which are necessary for binding reactions; which results from the chemical synthesis of the molecule; or which is a spacer for optimal distance of parts of the molecule. In addition, such a PEG can consist of one or more PEG side-chains which are

linked together. PEGs with more than one PEG chain are called multiarmed or branched PEGs. Branched PEGs can be prepared, for example, by the addition of polyethylene oxide to various polyols, including glycerol, pentaerythriol, and sorbitol. For example, a four-armed branched PEG can be prepared from pentaerythriol and ethylene oxide. Branched PEG are described in, for example, EP-A 0 473 084 and U.S. Patent. 5,932,462. One form of PEGs includes two PEG side-chains (PEG2) linked via the primary amino groups of a lysine (Monfardini et al., *Bioconjugate Chem.* 6 (1995) 62-69).

Although PEG is well-known, this is, to our knowledge, the first demonstration that a pegylated $^{10F}$n3 polypeptide can be pegylated and retain ligand binding activity. In a preferred embodiment, the pegylated $^{10F}$n3 polypeptide is produced by site-directed pegylation, particularly by conjugation of PEG to a cysteine moiety at the N- or C-terminus. Accordingly, the present disclosure provides a target-binding $^{10F}$n3 polypeptide with improved pharmacokinetic properties, the polypeptide comprising: a $^{10F}$n3 domain having from about 80 to about 150 amino acids, wherein at least one of the loops of said $^{10F}$n3 domain participate in target binding; and a covalently bound PEG moiety, wherein said $^{10F}$n3 polypeptide binds to the target with a $K_D$ of less than 100 nM and has a clearance rate of less than 30 mL/hr/kg in a mammal. The PEG moiety may be attached to the $^{10F}$n3 polypeptide by site directed pegylation, such as by attachment to a Cys residue, where the Cys residue may be positioned at the N-terminus of the $^{0F}$n3 polypeptide or between the N-terminus and the most N-terminal beta or beta-like strand or at the C-terminus of the $^{10F}$n3 polypeptide or between the C-terminus and the most C-terminal beta or beta-like strand. A Cys residue may be situated at other positions as well, particularly any of the loops that do not participate in target binding. A PEG moiety may also be attached by other chemistry, including by conjugation to amines.

PEG conjugation to peptides or proteins generally involves the activation of PEG and coupling of the activated PEG-intermediates directly to target proteins/peptides or to a linker, which is subsequently activated and coupled to target proteins/peptides (see Abuchowski et al., *J. Biol. Chem.*, 252, 3571 (1977) and *J. Biol. Chem.*, 252, 3582 (1977), Zalipsky, et al., and Harris et. al., in: *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications*; (J. M. Harris ed.) Plenum Press: New York, 1992; Chap.21 and 22). It is noted that a binding polypeptide containing a PEG molecule is also known as a conjugated protein, whereas the protein lacking an attached PEG molecule can be referred to as unconjugated.

A variety of molecular mass forms of PEG can be selected, *e.g.*, from about 1,000 Daltons (Da) to 100,000 Da (n is 20 to 2300), for conjugating to PD-L1-binding polypeptides. The number of repeating units "n" in the PEG is approximated for the molecular mass

described in Daltons. It is preferred that the combined molecular mass of PEG on an activated linker is suitable for pharmaceutical use. Thus, in one embodiment, the molecular mass of the PEG molecules does not exceed 100,000 Da. For example, if three PEG molecules are attached to a linker, where each PEG molecule has the same molecular mass of 12,000 Da (each n is about 270), then the total molecular mass of PEG on the linker is about 36,000 Da (total n is about 820). The molecular masses of the PEG attached to the linker can also be different, *e.g.*, of three molecules on a linker two PEG molecules can be 5,000 Da each (each n is about 110) and one PEG molecule can be 12,000 Da (n is about 270).

In a specific embodiment of the disclosure an PD-L1 binding polypeptide is covalently linked to one poly(ethylene glycol) group of the formula: --CO--$(CH_2)_x$--$(OCH_2CH_2)_m$--OR , with the --CO (*i.e.* carbonyl) of the poly(ethylene glycol) group forming an amide bond with one of the amino groups of the binding polypeptide; R being lower alkyl; x being 2 or 3; m being from about 450 to about 950; and n and m being chosen so that the molecular weight of the conjugate minus the binding polypeptide is from about 10 to 40 kDa. In one embodiment, a binding polypeptide's 6-amino group of a lysine is the available (free) amino group.

The above conjugates may be more specifically presented by formula (II): P--NHCO--$(CH_2)_x$--$(OCH_2CH_2)_m$--OR (II) , wherein P is the group of a binding polypeptide as described herein, (i.e. without the amino group or amino groups which form an amide linkage with the carbonyl shown in formula (II); and wherein R is lower alkyl; x is 2 or 3; m is from about 450 to about 950 and is chosen so that the molecular weight of the conjugate minus the binding polypeptide is from about 10 to about 40 kDa. As used herein, the given ranges of "m" have an orientational meaning. The ranges of "m" are determined in any case, and exactly, by the molecular weight of the PEG group.

One skilled in the art can select a suitable molecular mass for PEG, *e.g.*, based on how the pegylated binding polypeptide will be used therapeutically, the desired dosage, circulation time, resistance to proteolysis, immunogenicity, and other considerations. For a discussion of PEG and its use to enhance the properties of proteins, see Katre, *Advanced Drug Delivery Reviews* 10: 91-114 (1993).

In one embodiment, PEG molecules may be activated to react with amino groups on a binding polypeptide, such as with lysines (Bencham et al., *Anal. Biochem.*, 131, 25 (1983); Veronese et al., *Appl. Biochem.*, 11, 141 (1985).; Zalipsky et al., *Polymeric Drugs and Drug Delivery Systems*, adrs 9-110 ACS Symposium Series 469 (1999); Zalipsky et al., *Europ. Polym. J.*, 19, 1177-1183 (1983); Delgado et al., *Biotechnology and Applied Biochemistry*, 12, 119-128 (1990)).

In one specific embodiment, carbonate esters of PEG are used to form the PEG-binding polypeptide conjugates. N,N'-disuccinimidylcarbonate (DSC) may be used in the reaction with PEG to form active mixed PEG-succinimidyl carbonate that may be subsequently reacted with a nucleophilic group of a linker or an amino group of a binding polypeptide (see U.S. Patents 5,281,698 and 5,932,462). In a similar type of reaction, 1,1'-(dibenzotriazolyl)carbonate and di-(2-pyridyl)carbonate may be reacted with PEG to form PEG-benzotriazolyl and PEG-pyridyl mixed carbonate (U.S. Patent 5,382,657), respectively.

Pegylation of a $^{10F}$n3 polypeptide can be performed according to the methods of the state of the art, for example by reaction of the binding polypeptide with electrophilically active PEGs (supplier: Shearwater Corp., USA, www.shearwatercorp.com). Preferred PEG reagents of the present invention are, e.g., N-hydroxysuccinimidyl propionates (PEG-SPA), butanoates (PEG-SBA), PEG-succinimidyl propionate or branched N-hydroxysuccinimides such as mPEG2-NHS (Monfardini et al., *Bioconjugate Chem.* 6 (1995) 62-69). Such methods may used to pegylated at an f-amino group of a binding polypeptide lysine or the N-terminal amino group of the binding polypeptide.

In another embodiment, PEG molecules may be coupled to sulfhydryl groups on a binding polypeptide (Sartore et al., *Appl. Biochem. Biotechnol.*, 27, 45 (1991); Morpurgo et al., *Biocon. Chem.*, 7, 363-368 (1996); Goodson et al., *Bio/Technology* (1990) 8, 343; U.S. Patent 5,766,897). U.S. Patents 6,610,281 and 5,766,897 describes exemplary reactive PEG species that may be coupled to sulfhydryl groups.

In some embodiments where PEG molecules are conjugated to cysteine residues on a binding polypeptide, the cysteine residues are native to the binding polypeptide, whereas in other embodiments, one or more cysteine residues are engineered into the binding polypeptide. Mutations may be introduced into a binding polypeptide coding sequence to generate cysteine residues. This might be achieved, for example, by mutating one or more amino acid residues to cysteine. Preferred amino acids for mutating to a cysteine residue include serine, threonine, alanine and other hydrophilic residues. Preferably, the residue to be mutated to cysteine is a surface-exposed residue. Algorithms are well-known in the art for predicting surface accessibility of residues based on primary sequence or a protein. Alternatively, surface residues may be predicted by comparing the amino acid sequences of binding polypeptides, given that the crystal structure of the framework based on which binding polypeptides are designed and evolved has been solved (see Himanen et al., *Nature.* (2001) 20-27; 414(6866):933-8) and thus the surface-exposed residues identified. In one embodiment, cysteine residues are introduced into binding polypeptides at or near the N- and/or C-terminus, or within loop regions.

In some embodiments, the pegylated binding polypeptide comprises a PEG molecule covalently attached to the alpha amino group of the N-terminal amino acid. Site specific N-terminal reductive amination is described in Pepinsky et al., (2001) *JPET*, 297, 1059, and U.S. Patent 5,824,784. The use of a PEG-aldehyde for the reductive amination of a protein utilizing other available nucleophilic amino groups is described in U.S. Patent 4,002,531, in Wieder et al., (1979) *J. Biol. Chem.* 254,12579, and in Chamow et al., (1994) *Bioconjugate Chem.* 5, 133.

In another embodiment, pegylated binding polypeptide comprises one or more PEG molecules covalently attached to a linker, which in turn is attached to the alpha amino group of the amino acid residue at the N-terminus of the binding polypeptide. Such an approach is disclosed in U.S. Patent Publication 2002/0044921 and in WO094/01451.

In one embodiment, a binding polypeptide is pegylated at the C-terminus. In a specific embodiment, a protein is pegylated at the C-terminus by the introduction of C-terminal azido-methionine and the subsequent conjugation of a methyl-PEG-triarylphosphine compound via the Staudinger reaction. This C-terminal conjugation method is described in Cazalis et al., *Bioconjug. Chem.* 2004; 15(5):1005-1009.

Monopegylation of a binding polypeptide can also be produced according to the general methods described in WO 94/01451. WO 94/01451 describes a method for preparing a recombinant polypeptide with a modified terminal amino acid alpha-carbon reactive group. The steps of the method involve forming the recombinant polypeptide and protecting it with one or more biologically added protecting groups at the N-terminal alpha-amine and C-terminal alpha-carboxyl. The polypeptide can then be reacted with chemical protecting agents to selectively protect reactive side chain groups and thereby prevent side chain groups from being modified. The polypeptide is then cleaved with a cleavage reagent specific for the biological protecting group to form an unprotected terminal amino acid alpha-carbon reactive group. The unprotected terminal amino acid alpha-carbon reactive group is modified with a chemical modifying agent. The side chain protected terminally modified single copy polypeptide is then deprotected at the side chain groups to form a terminally modified recombinant single copy polypeptide. The number and sequence of steps in the method can be varied to achieve selective modification at the N- and/or C-terminal amino acid of the polypeptide.

The ratio of a binding polypeptide to activated PEG in the conjugation reaction can be from about 1:0.5 to 1:50, between from about 1:1 to 1:30, or from about 1:5 to 1:15. Various aqueous buffers can be used in the present method to catalyze the covalent addition of PEG to the binding polypeptide. In one embodiment, the pH of a buffer used is from about 7.0 to 9.0.

In another embodiment, the pH is in a slightly basic range, *e.g.*, from about 7.5 to 8.5. Buffers having a pKa close to neutral pH range may be used, *e.g.*, phosphate buffer.

Conventional separation and purification techniques known in the art can be used to purify PEGylated binding polypeptide, such as size exclusion (*e.g.* gel filtration) and ion exchange chromatography. Products may also be separated using SDS-PAGE. Products that may be separated include mono-, di-, tri- poly- and un-pegylated binding polypeptide, as well as free PEG. The percentage of mono-PEG conjugates can be controlled by pooling broader fractions around the elution peak to increase the percentage of mono-PEG in the composition. About ninety percent mono-PEG conjugates represents a good balance of yield and activity. Compositions in which, for example, at least ninety-two percent or at least ninety-six percent of the conjugates are mono-PEG species may be desired. In an embodiment of this invention the percentage of mono-PEG conjugates is from ninety percent to ninety-six percent.

In one embodiment, PEGylated binding polypeptide of the invention contain one, two or more PEG moieties. In one embodiment, the PEG moiety(ies) are bound to an amino acid residue which is on the surface of the protein and/or away from the surface that contacts the target ligand. In one embodiment, the combined or total molecular mass of PEG in PEG-binding polypeptide is from about 3,000 Da to 60,000 Da, optionally from about 10,000 Da to 36,000 Da. In a one embodiment, the PEG in pegylated binding polypeptide is a substantially linear, straight-chain PEG.

In one embodiment of the invention, the PEG in pegylated binding polypeptide is not hydrolyzed from the pegylated amino acid residue using a hydroxylamine assay, *e.g.*, 450 mM hydroxylamine (pH 6.5) over 8 to 16 hours at room temperature, and is thus stable. In one embodiment, greater than 80% of the composition is stable mono-PEG-binding polypeptide, more preferably at least 90%, and most preferably at least 95%.

In another embodiment, the pegylated binding polypeptides of the invention will preferably retain at least 25%, 50%, 60%, 70%, 80%, 85%, 90%, 95% or 100% of the biological activity associated with the unmodified protein. In one embodiment, biological activity refers to its ability to bind to PD-L1, as assessed by KD, $k_{on}$ or $k_{off}$. In one specific embodiment, the pegylated binding polypeptide protein shows an increase in binding to PD-L1 relative to unpegylated binding polypeptide.

The serum clearance rate of PEG-modified polypeptide may be decreased by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or even 90%, relative to the clearance rate of the unmodified binding polypeptide. The PEG-modified polypeptide may have a half-life ($t_{1/2}$) which is enhanced relative to the half-life of the unmodified protein. The half-life of PEG-

binding polypeptide may be enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400% or 500%, or even by 1000% relative to the half-life of the unmodified binding polypeptide. In some embodiments, the protein half-life is determined *in vitro*, such as in a buffered saline solution or in serum. In other embodiments, the protein half-life is an *in vivo* half life, such as the half-life of the protein in the serum or other bodily fluid of an animal.

Therapeutic Formulations and Modes of Administration

The present disclosure features methods for treating conditions or preventing pre-conditions which respond to an inhibition of PD-L1 biological activity. Preferred examples are conditions that are characterized by inflammation or cellular hyperproliferation. Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated but can be readily determined by the skilled artisan. In general, regulatory agencies require that a protein reagent to be used as a therapeutic is formulated so as to have acceptably low levels of pyrogens. Accordingly, therapeutic formulations will generally be distinguished from other formulations in that they are substantially pyrogen free, or at least contain no more than acceptable levels of pyrogen as determined by the appropriate regulatory agency (*e.g.*, FDA).

Therapeutic compositions of the present disclosure may be administered with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration may be parenteral (*e.g.*, intravenous, subcutaneous), oral, or topical, as non-limiting examples. In addition, any gene therapy technique, using nucleic acids encoding the polypeptides of the invention, may be employed, such as naked DNA delivery, recombinant genes and vectors, cell-based delivery, including ex vivo manipulation of patients' cells, and the like.

The composition can be in the form of a pill, tablet, capsule, liquid, or sustained release tablet for oral administration; or a liquid for intravenous, subcutaneous or parenteral administration; gel, lotion, ointment, cream, or a polymer or other sustained release vehicle for local administration.

Methods well known in the art for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" (20th ed., ed. A. R. Gennaro A R., 2000, Lippincott Williams & Wilkins, Philadelphia, Pa.). Formulations for parenteral administration may, for example, contain excipients, sterile water, saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds.

Nanoparticulate formulations (*e.g.*, biodegradable nanoparticles, solid lipid nanoparticles, liposomes) may be used to control the biodistribution of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. The concentration of the compound in the formulation varies depending upon a number of factors, including the dosage of the drug to be administered, and the route of administration.

The polypeptide may be optionally administered as a pharmaceutically acceptable salt, such as non-toxic acid addition salts or metal complexes that are commonly used in the pharmaceutical industry. Examples of acid addition salts include organic acids such as acetic, lactic, pamoic, maleic, citric, malic, ascorbic, succinic, benzoic, palmitic, suberic, salicylic, tartaric, methanesulfonic, toluenesulfonic, or trifluoroacetic acids or the like; polymeric acids such as tannic acid, carboxymethyl cellulose, or the like; and inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid phosphoric acid, or the like. Metal complexes include zinc, iron, and the like. In one example, the polypeptide is formulated in the presence of sodium acetate to increase thermal stability.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (*e.g.*, sucrose and sorbitol), lubricating agents, glidants, and anti-adhesives (*e.g.*, magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc).

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium.

A therapeutically effective dose refers to a dose that produces the therapeutic effects for which it is administered. The exact dose will depend on the disorder to be treated, and may be ascertained by one skilled in the art using known techniques. In general, the polypeptide is administered at about 0.01 μg/kg to about 50 mg/kg per day, preferably 0.01 mg/kg to about 30 mg/kg per day, most preferably 0.1 mg/kg to about 20 mg/kg per day. The polypeptide may be given daily (*e.g.*, once, twice, three times, or four times daily) or preferably less frequently (*e.g.*, weekly, every two weeks, every three weeks, monthly, or quarterly). In addition, as is known in the art, adjustments for age as well as the body weight, general health, sex, diet, time of administration, drug interaction, and the severity of the disease may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

Pharmaceutical Formulations of Disclosed Antibodies with Tumor Vaccines

A combined therapeutic product or formulation of a disclosed anti-PD-L1 antibody with a therapeutic vaccine provides synergistic oncologic therapeutic benefit. For example, the present disclosure provides a combination of a disclosed anti-PD-L1 antibody with "Neuvax" which is a E75-derived 9 mer synthetic peptide isolated from HER2/neu combined with GM-CSF as an adjuvant as described in U.S. Patent 8,222,214, the disclosure of which is incorporated by reference herein. In addition, the present disclosure provides a combination of a disclosed anti-PD-L1 antibody with ALVAC-CEA vaccine, which is a canary pox virus combined with carcinoembryonic antigen.

Exemplary Uses

The PD-L1 binding proteins described herein and their related variants are useful in a number of therapeutic and diagnostic applications. These include the inhibition of the biological activity of PD-L1 by competing for or blocking the binding to a PD-L1 as well as the delivery of cytotoxic or imaging moieties to cells, preferably cells expressing PD-L1. The small size and stable structure of these molecules can be particularly valuable with respect to manufacturing of the drug, rapid clearance from the body for certain applications where rapid clearance is desired or formulation into novel delivery systems that are suitable or improved using a molecule with such characteristics.

On the basis of their efficacy as inhibitors of PD-L1 biological activity, the polypeptides of this disclosure are effective against a number of cancer conditions as well as complications arising from cancer, such as pleural effusion and ascites. Preferably, the PD-L1-binding polypeptides of the disclosure can be used for the treatment of prevention of hyperproliferative diseases or cancer and the metastatic spread of cancers. Preferred indications for the disclosed anti-PD-L1antibodies include colorectal cancers, head and neck cancers, small cell lung cancer, non-small cell lung cancer (NSCLC) and pancreatic cancer. Non-limiting examples of cancers include bladder, blood, bone, brain, breast, cartilage, colon kidney, liver, lung, lymph node, nervous tissue, ovary, pancreatic, prostate, skeletal muscle, skin, spinal cord, spleen, stomach, testes, thymus, thyroid, trachea, urogenital tract, ureter, urethra, uterus, or vaginal cancer.

In addition, various inflammatory disorders can be treated with the disclosed anti-PD-L1 binding polypeptides disclosed herein. Such inflammatory disorders include, for example, intestinal mucosa inflammation wasting diseases associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, and Crohn's disease.

A PD-L1 binding polypeptide can be administered alone or in combination with one or more additional therapies such as chemotherapy radiotherapy, immunotherapy, surgical intervention, or any combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above.

In certain embodiments of such methods, one or more polypeptide therapeutic agents can be administered, together (simultaneously) or at different times (sequentially). In addition, polypeptide therapeutic agents can be administered with another type of compounds for treating cancer or for inhibiting angiogenesis.

In certain embodiments, the subject anti-PD-L1antibodies agents of the invention can be used alone. Alternatively, the subject agents may be used in combination with other conventional anti-cancer therapeutic approaches directed to treatment or prevention of proliferative disorders (*e.g.*, tumor). For example, such methods can be used in prophylactic cancer prevention, prevention of cancer recurrence and metastases after surgery, and as an adjuvant of other conventional cancer therapy. The present disclosure recognizes that the effectiveness of conventional cancer therapies (*e.g.*, chemotherapy, radiation therapy, phototherapy, immunotherapy, and surgery) can be enhanced through the use of a subject polypeptide therapeutic agent.

A wide array of conventional compounds have been shown to have anti-neoplastic activities. These compounds have been used as pharmaceutical agents in chemotherapy to shrink solid tumors, prevent metastases and further growth, or decrease the number of malignant cells in leukemic or bone marrow malignancies. Although chemotherapy has been effective in treating various types of malignancies, many anti-neoplastic compounds induce undesirable side effects. It has been shown that when two or more different treatments are combined, the treatments may work synergistically and allow reduction of dosage of each of the treatments, thereby reducing the detrimental side effects exerted by each compound at higher dosages. In other instances, malignancies that are refractory to a treatment may respond to a combination therapy of two or more different treatments.

When a polypeptide therapeutic agent of the present invention is administered in combination with another conventional anti-neoplastic agent, either concomitantly or sequentially, such therapeutic agent may be found to enhance the therapeutic effect of the anti-neoplastic agent or overcome cellular resistance to such anti-neoplastic agent. This allows decrease of dosage of an anti-neoplastic agent, thereby reducing the undesirable side effects, or restores the effectiveness of an anti-neoplastic agent in resistant cells.

Pharmaceutical compounds that may be used for combinatory anti-tumor therapy include, merely to illustrate: aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bicalutamide, bleomycin, buserelin, busulfan, campothecin, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, and vinorelbine.

Certain chemotherapeutic anti-tumor compounds may be categorized by their mechanism of action into, for example, following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine) and purine analogs, folate antagonists and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (etoposide, teniposide), DNA damaging agents (actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, hexamethylmelamineoxaliplatin, iphosphamide, melphalan, merchlorehtamine, mitomycin, mitoxantrone, nitrosourea, plicamycin, procarbazine, taxol, taxotere, teniposide, triethylenethiophosphoramide and etoposide (VP16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil),

ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes--dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (breveldin); immunosuppressives (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); anti-angiogenic compounds (TNP-470, genistein) and growth factor inhibitors (*e.g.*, VEGF inhibitors, fibroblast growth factor (FGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab); cell cycle inhibitors and differentiation inducers (tretinoin); mTOR inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), amsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin and mitoxantrone, topotecan, irinotecan), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylpednisolone, prednisone, and prenisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; and chromatin disruptors.

Depending on the nature of the combinatory therapy, administration of the polypeptide therapeutic agents may be continued while the other therapy is being administered and/or thereafter. Administration of the polypeptide therapeutic agents may be made in a single dose, or in multiple doses. In some instances, administration of the polypeptide therapeutic agents is commenced at least several days prior to the conventional therapy, while in other instances, administration is begun either immediately before or at the time of the administration of the conventional therapy.

In one example of a diagnostic application, a biological sample, such as serum or a tissue biopsy, from a patient suspected of having a condition characterized by inappropriate angiogenesis is contacted with a detectably labeled polypeptide of the disclosure to detect levels of PD-L1. The levels of PD-L1 detected are then compared to levels of PD-L1 detected in a normal sample also contacted with the labeled polypeptide. An increase of at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% in the levels of the PD-L1 may be considered a diagnostic indicator.

In certain embodiments, the PD-L1 binding polypeptides are further attached to a label that is able to be detected (*e.g.*, the label can be a radioisotope, fluorescent compound, enzyme or enzyme co-factor). The active moiety may be a radioactive agent, such as: radioactive heavy metals such as iron chelates, radioactive chelates of gadolinium or manganese, positron emitters of oxygen, nitrogen, iron, carbon, or gallium, $^{43}K$, $^{52}Fe$, $^{57}Co$, $^{67}Cu$, $^{67}Ga$, $^{68}Ga$, $^{123}I$, $^{125}I$, $^{131}I$, $^{132}I$, or $^{99}Tc$. A binding agent affixed to such a moiety may be used as an imaging agent and is administered in an amount effective for diagnostic use in a mammal such as a human and the localization and accumulation of the imaging agent is then detected. The localization and accumulation of the imaging agent may be detected by radioscintigraphy, nuclear magnetic resonance imaging, computed tomography or positron emission tomography. Immunoscintigraphy using PD-L1 binding polypeptides directed at PD-L1 may be used to detect and/or diagnose cancers and vasculature. For example, any of the binding polypeptide against a PD-L1 marker labeled with $^{99}$Technetium, $^{111}$Indium, or $^{125}$Iodine may be effectively used for such imaging. As will be evident to the skilled artisan, the amount of radioisotope to be administered is dependent upon the radioisotope. Those having ordinary skill in the art can readily formulate the amount of the imaging agent to be administered based upon the specific activity and energy of a given radionuclide used as the active moiety. Typically 0.1-100 millicuries per dose of imaging agent, preferably 1-10 millicuries, most often 2-5 millicuries are administered. Thus, compositions according to the present invention useful as imaging agents comprising a targeting moiety conjugated to a radioactive moiety comprise 0.1-100 millicuries, in some embodiments preferably 1-10 millicuries, in some embodiments preferably 2-5 millicuries, in some embodiments more preferably 1-5 millicuries.

The PD-L1 binding polypeptides can also be used to deliver additional therapeutic agents (including but not limited to drug compounds, chemotherapeutic compounds, and radiotherapeutic compounds) to a cell or tissue expressing PD-L1. In one example, the PD-L1 binding polypeptide is fused to a chemotherapeutic agent for targeted delivery of the chemotherapeutic agent to a tumor cell or tissue expressing PD-L1.

The PD-L1 binding polypeptides are useful in a variety of applications, including research, diagnostic and therapeutic applications. For instance, they can be used to isolate and/or purify receptor or portions thereof, and to study receptor structure (*e.g.*, conformation) and function.

In certain aspects, the various binding polypeptides can be used to detect or measure the expression of PD-L1, for example, on endothelial cells (*e.g.*, venous endothelial cells), or on cells transfected with a PD-L1 gene. Thus, they also have utility in applications such as cell

sorting and imaging (*e.g.*, flow cytometry, and fluorescence activated cell sorting), for diagnostic or research purposes.

In certain embodiments, the binding polypeptides of fragments thereof can be labeled or unlabeled for diagnostic purposes. Typically, diagnostic assays entail detecting the formation of a complex resulting from the binding of a binding polypeptide to PD-L1. The binding polypeptides or fragments can be directly labeled, similar to antibodies. A variety of labels can be employed, including, but not limited to, radionuclides, fluorescers, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors and ligands (*e.g.*, biotin, haptens). Numerous appropriate immunoassays are known to the skilled artisan (U.S. Patents. 3,817,827; 3,850,752; 3,901,654; and 4,098,876). When unlabeled, the binding polypeptides can be used in assays, such as agglutination assays. Unlabeled binding polypeptides can also be used in combination with another (one or more) suitable reagent which can be used to detect the binding polypeptide, such as a labeled antibody reactive with the binding polypeptide or other suitable reagent (*e.g.*, labeled protein A).

In one embodiment, the binding polypeptides of the present invention can be utilized in enzyme immunoassays, wherein the subject polypeptides are conjugated to an enzyme. When a biological sample comprising a PD-L1 protein is combined with the subject binding polypeptides, binding occurs between the binding polypeptides and the PD-L1 protein. In one embodiment, a sample containing cells expressing a PD-L1 protein (*e.g.*, endothelial cells) is combined with the subject antibodies, and binding occurs between the binding polypeptides and cells bearing a PD-L1 protein recognized by the binding polypeptide. These bound cells can be separated from unbound reagents and the presence of the binding polypeptide-enzyme conjugate specifically bound to the cells can be determined, for example, by contacting the sample with a substrate of the enzyme which produces a color or other detectable change when acted on by the enzyme. In another embodiment, the subject binding polypeptides can be unlabeled, and a second, labeled polypeptide (*e.g.*, an antibody) can be added which recognizes the subject binding polypeptide.

In certain aspects, kits for use in detecting the presence of a PD-L1 protein in a biological sample can also be prepared. Such kits will include a PD-L1 binding polypeptide which binds to a PD-L1 protein or portion of said receptor, as well as one or more ancillary reagents suitable for detecting the presence of a complex between the binding polypeptide and the receptor protein or portions thereof. The polypeptide compositions of the present invention can be provided in lyophilized form, either alone or in combination with additional antibodies specific for other epitopes. The binding polypeptides and/or antibodies, which can be labeled

or unlabeled, can be included in the kits with adjunct ingredients (*e.g.*, buffers, such as Tris, phosphate and carbonate, stabilizers, excipients, biocides and/or inert proteins, e.g., bovine serum albumin). For example, the binding polypeptides and/or antibodies can be provided as a lyophilized mixture with the adjunct ingredients, or the adjunct ingredients can be separately provided for combination by the user. Generally these adjunct materials will be present in less than about 5% weight based on the amount of active binding polypeptide or antibody, and usually will be present in a total amount of at least about 0.001% weight based on polypeptide or antibody concentration. Where a second antibody capable of binding to the binding polypeptide is employed, such antibody can be provided in the kit, for instance in a separate vial or container. The second antibody, if present, is typically labeled, and can be formulated in an analogous manner with the antibody formulations described above.

Similarly, the present disclosure also provides a method of detecting and/or quantitating expression of PD-L1, wherein a composition comprising a cell or fraction thereof (*e.g.*, membrane fraction) is contacted with a binding polypeptide which binds to a PD-L1 or portion of the receptor under conditions appropriate for binding thereto, and the binding is monitored. Detection of the binding polypeptide, indicative of the formation of a complex between binding polypeptide and PD-L1 or a portion thereof, indicates the presence of the receptor. Binding of a polypeptide to the cell can be determined by standard methods, such as those described in the working examples. The method can be used to detect expression of PD-L1 on cells from an individual. Optionally, a quantitative expression of PD-L1 on the surface of endothelial cells can be evaluated, for instance, by flow cytometry, and the staining intensity can be correlated with disease susceptibility, progression or risk.

The present disclosure also provides a method of detecting the susceptibility of a mammal to certain diseases. To illustrate, the method can be used to detect the susceptibility of a mammal to diseases which progress based on the amount of PD-L1 present on cells and/or the number of PD-L1-positive cells in a mammal.

Polypeptide sequences are indicated using standard one- or three-letter abbreviations. Unless otherwise indicated, each polypeptide sequence has amino termini at the left and a carboxy termini at the right; each single-stranded nucleic acid sequence, and the top strand of each double-stranded nucleic acid sequence, has a 5' termini at the left and a 3' termini at the right. A particular polypeptide sequence also can be described by explaining how it differs from a reference sequence.

The terms "PD-L1 inhibitor" and "PD-L1 antagonist" are used interchangeably. Each is a molecule that detectably inhibits at least one function of PD-L1. Conversely, a "PD-L1

agonist" is a molecule that detectably increases at least one function of PD-L1. The inhibition caused by a PD-L1 inhibitor need not be complete so long as it is detectable using an assay. Any assay of a function of PD-L1 can be used, examples of which are provided herein. Examples of functions of PD-L1 that can be inhibited by a PD-L1 inhibitor, or increased by a PD-L1 agonist, include cancer cell growth or apoptosis (programmed cell death), and so on. Examples of types of PD-L1 inhibitors and PD-L1 agonists include, but are not limited to, PD-L1 binding polypeptides such as antigen binding proteins (*e.g.*, PD-L1 inhibiting antigen binding proteins), antibodies, antibody fragments, and antibody derivatives.

The terms "peptide," "polypeptide" and "protein" each refers to a molecule comprising two or more amino acid residues joined to each other by peptide bonds. These terms encompass, *e.g.*, native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein may be monomeric or polymeric.

A "variant" of a polypeptide (for example, an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Disclosed variants include, for example, fusion proteins.

A "derivative" of a polypeptide is a polypeptide (*e.g.*, an antibody) that has been chemically modified, *e.g.*, via conjugation to another chemical moiety (such as, for example, polyethylene glycol or albumin, *e.g.*, human serum albumin), phosphorylation, and glycosylation. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (*e.g.*, an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003,

*Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129; Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold.

An antigen binding protein can have, for example, the structure of a naturally occurring immunoglobulin. An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa or lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Preferably, the anti-PD-L1 antibodies disclosed herein are characterized by their variable domain region sequences in the heavy $V_H$ and light $V_L$ amino acid sequences. The preferred antibody is A6 which is a kappa IgG antibody. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

A "multi-specific antibody" is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a "bi-specific antibody" which recognizes two distinct epitopes on the same or different antigens.

An antigen binding protein "specifically binds" to an antigen (*e.g.*, human PD-L1) if it binds to the antigen with a dissociation constant of 1 nanomolar or less.

An "antigen binding domain, "antigen binding region," or "antigen binding site" is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody that specifically binds to its antigen, this will include at least part of at least one of its CDR domains.

An "epitope" is the portion of a molecule that is bound by an antigen binding protein (*e.g.*, by an antibody). An epitope can comprise non-contiguous portions of the molecule (*e.g.*, in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary

sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

The "percent homology" of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, Calif.)) using its default parameters.

A "host cell" is a cell that can be used to express a nucleic acid. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a single-celled eukaryote (*e.g.*, a yeast or other fungus), a plant cell (*e.g.*, a tobacco or tomato plant cell), an animal cell (*e.g.*, a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Examples of host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., 1981, *Cell* 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (Rasmussen et al., 1998, *Cytotechnology* 28:31) or CHO strain DX-B11, which is deficient in DHFR (Urlaub et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:4216-20), HeLa cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (McMahan et al., 1991, *EMBO J.* 10:2821), human embryonic kidney cells such as 293,293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers 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, e.g., mutation or environmental influence, 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.

Antigen Binding Proteins

Antigen binding proteins (*e.g.*, antibodies, antibody fragments, antibody derivatives, antibody muteins, and antibody variants) are polypeptides that bind to PD-L1, (preferably,

human PD-L1). Antigen binding proteins include antigen binding proteins that inhibit a biological activity of PD-L1.

Oligomers that contain one or more antigen binding proteins may be employed as PD-L1 antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more antigen binding protein are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

One embodiment is directed to oligomers comprising multiple antigen binding proteins joined via covalent or non-covalent interactions between peptide moieties fused to the antigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of antigen binding proteins attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, *e.g.*, variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have PD-L1 binding activity.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of Fusion Proteins Comprising Certain Heterologous Polypeptides Fused to Various Portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:10535; Byrn et al., 1990, *Nature* 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1-10.19.11.

One embodiment is directed to a dimer comprising two fusion proteins created by fusing a PD-L1 binding fragment of an anti-PD-L1 antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties

(and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, *FEBS Letters* 344:191. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, *Semin. Immunol.* 6:267-78. In one approach, recombinant fusion proteins comprising an anti-PD-L1 antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric anti-PD-L1 antibody fragments or derivatives that form are recovered from the culture supernatant.

Antigen-binding fragments of antigen binding proteins of the invention may be produced by conventional techniques. Examples of such fragments include, but are not limited to, Fab and $F(ab')_2$ fragments.

The present disclosure provides monoclonal antibodies that bind to PD-L1. Monoclonal antibodies may be produced using any technique known in the art, *e.g.*, by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, *e.g.*, by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 48210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

Antigen binding proteins directed against PD-L1 can be used, for example, in assays to detect the presence of PD-L1 polypeptides, either *in vitro* or *in vivo*. The antigen binding

proteins also may be employed in purifying PD-L1 proteins by immunoaffinity chromatography. Blocking antigen binding proteins can be used in the methods disclosed herein. Such antigen binding proteins that function as PD-L1 antagonists may be employed in treating any PD-L1-induced condition, including but not limited to various cancers.

Antigen binding proteins may be employed in an *in vitro* procedure, or administered *in vivo* to inhibit PD-L1-induced biological activity. Disorders caused or exacerbated (directly or indirectly) by the proteolytic activation of PD-L1, examples of which are provided herein, thus may be treated. In one embodiment, the present invention provides a therapeutic method comprising *in vivo* administration of a PD-L1 blocking antigen binding protein to a mammal in need thereof in an amount effective for reducing an PD-L1-induced biological activity.

Antigen binding proteins include fully human monoclonal antibodies that inhibit a biological activity of PD-L1.

Antigen binding proteins may be prepared by any of a number of conventional techniques. For example, they may be purified from cells that naturally express them (*e.g.*, an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression systems, using any technique known in the art. See, for example, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.), Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1988).

Any expression system known in the art can be used to make the recombinant polypeptides of the invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired polypeptide. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *bacilli*. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., 1981, *Cell* 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) as described by McMahan et al., 1991, *EMBO J.* 10: 2821. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., 1985).

The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures.

One such purification procedure includes the use of affinity chromatography, *e.g.*, over a matrix having all or a portion (*e.g.*, the extracellular domain) of PD-L1 bound thereto. Polypeptides contemplated for use herein include substantially homogeneous recombinant mammalian anti-PD-L1 antibody polypeptides substantially free of contaminating endogenous materials.

Antigen binding proteins may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating a nucleic acid encoding a polypeptide chain (or portion thereof) of an antigen binding protein of interest (*e.g.*, an anti-PD-L1 antibody), and manipulating the nucleic acid through recombinant DNA technology. The nucleic acid may be fused to another nucleic acid of interest, or altered (*e.g.*, by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides ($V_L$ and $V_H$). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (*e.g.*, dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, *Prot. Eng.* 10:423; Kortt et al., 2001, *Biomol. Eng.* 18:95-108). By combining different $V_L$ and $V_H$-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., 2001, *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Patent 4,946,778; Bird, 1988, *Science* 242:423; Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879; Ward et al., 1989, *Nature* 334:544, de Graaf et al., 2002, *Methods Mol. Biol.* 178:379-87.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, *i.e.*, subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, *e.g.*, DNA encoding the constant domain of an antibody of the desired isotype (Lantto et al., 2002, *Methods Mol. Biol.* 178:303-16). Moreover, if an IgG4 is desired, it may also be desired

to introduce a point mutation (CPSCP->CPPCP) in the hinge region (Bloom et al., 1997, *Protein Science* 6:407) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

In particular embodiments, antigen binding proteins of the present invention have a binding affinity ($K_a$) for PD-L1 of at least $10^6$. In other embodiments, the antigen binding proteins exhibit a $K_a$ of at least $10^7$, at least $10^8$, at least $10^9$, or at least $10^{10}$. In another embodiment, the antigen binding protein exhibits a $K_a$ substantially the same as that of an antibody described herein in the Examples.

In another embodiment, the present disclosure provides an antigen binding protein that has a low dissociation rate from PD-L1. In one embodiment, the antigen binding protein has a $K_{off}$ of $1 \times 10^{-4}$ to $^{-1}$ or lower. In another embodiment, the $K_{off}$ is $5 \times 10^{-5}$ to $^{-1}$ or lower. In another embodiment, the $K_{off}$ is substantially the same as an antibody described herein. In another embodiment, the antigen binding protein binds to PD-L1 with substantially the same $K_{off}$ as an antibody described herein.

In another aspect, the present disclosure provides an antigen binding protein that inhibits an activity of PD-L1. In one embodiment, the antigen binding protein has an $IC_{50}$ of 1000 nM or lower. In another embodiment, the $IC_{50}$ is 100 nM or lower; in another embodiment, the $IC_{50}$ is 10 nM or lower. In another embodiment, the $IC_{50}$ is substantially the same as that of an antibody described herein in the Examples. In another embodiment, the antigen binding protein inhibits an activity of PD-L1 with substantially the same $IC_{50}$ as an antibody described herein.

In another aspect, the present disclosure provides an antigen binding protein that binds to human PD-L1 expressed on the surface of a cell and, when so bound, inhibits PD-L1 signaling activity in the cell without causing a significant reduction in the amount of PD-L1 on the surface of the cell. Any method for determining or estimating the amount of PD-L1 on the surface and/or in the interior of the cell can be used. In other embodiments, binding of the antigen binding protein to the PD-L1-expressing cell causes less than about 75%, 50%, 40%, 30%, 20%, 15%, 10%, 5%, 1%, or 0.1% of the cell-surface PD-L1 to be internalized.

In another aspect, the present disclosure provides an antigen binding protein having a half-life of at least one day *in vitro* or *in vivo* (*e.g.*, when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antigen binding protein has a half-life of four days or longer. In another embodiment, the antigen binding protein has a half-life of eight days or longer. In another embodiment, the antigen binding protein is derivatized or modified such that it has a longer

half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, the antigen binding protein contains one or more point mutations to increase serum half life, such as described in WO00/09560, incorporated by reference herein.

The present disclosure further provides multi-specific antigen binding proteins, for example, bispecific antigen binding protein, *e.g.*, antigen binding protein that bind to two different epitopes of PD-L1, or to an epitope of PD-L1 and an epitope of another molecule, via two different antigen binding sites or regions. Moreover, bispecific antigen binding protein as disclosed herein can comprise a PD-L1 binding site from one of the herein-described antibodies and a second PD-L1 binding region from another of the herein-described antibodies, including those described herein by reference to other publications. Alternatively, a bispecific antigen binding protein may comprise an antigen binding site from one of the herein described antibodies and a second antigen binding site from another PD-L1 antibody that is known in the art, or from an antibody that is prepared by known methods or the methods described herein.

Numerous methods of preparing bispecific antibodies are known in the art. Such methods include the use of hybrid-hybridomas as described by Milstein et al., 1983, *Nature* 305:537, and chemical coupling of antibody fragments (Brennan et al., 1985, *Science* 229:81; Glennie et al., 1987, *J. Immunol.* 139:2367; U.S. Patent 6,010,902). Moreover, bispecific antibodies can be produced via recombinant means, for example by using leucine zipper moieties (*i.e.*, from the *Fos* and *Jun* proteins, which preferentially form heterodimers; Kostelny et al., 1992, *J. Immunol.* 148:1547) or other lock and key interactive domain structures as described in U.S. Patent 5,582,996. Additional useful techniques include those described in U.S. Patents 5,959,083; and 5,807,706.

In another aspect, the antigen binding protein comprises a derivative of an antibody. The derivatized antibody can comprise any molecule or substance that imparts a desired property to the antibody, such as increased half-life in a particular use. The derivatized antibody can comprise, for example, a detectable (or labeling) moiety (*e.g.*, a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (*e.g.*, gold bead), or a molecule that binds to another molecule (*e.g.*, biotin or streptavidin), a therapeutic or diagnostic moiety (*e.g.*, a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody for a particular use (*e.g.*, administration to a subject, such as a human subject, or other *in vivo* or *in vitro* uses). Examples of molecules that can be used to derivatize an antibody include albumin (*e.g.*, human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one

embodiment, the antibody is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyurrolidone), polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

Indications

In one aspect, the present disclosure provides methods of treating a subject. The method can, for example, have a generally salubrious effect on the subject, *e.g.*, it can increase the subject's expected longevity. Alternatively, the method can, for example, treat, prevent, cure, relieve, or ameliorate ("treat") a disease, disorder, condition, or illness ("a condition"). Among the conditions to be treated are conditions characterized by inappropriate expression or activity of PD-L1. In some such conditions, the expression or activity level is too high, and the treatment comprises administering a PD-L1 antagonist as described herein. The disorders or conditions are cancer-related. In particular, those cancers include, but are not limited to, lung, ovarian and colon carcinoma and various myelomas.

Specific medical conditions and diseases that are treatable or preventable with the antigen binding proteins of this disclosure include various cancers.

Therapeutic Methods and Administration of Antigen Binding Proteins

Certain methods provided herein comprise administering a PD-L1 binding antigen binding protein to a subject, thereby reducing a PD-L1-induced biological response that plays a role in a particular condition. In particular embodiments, methods of the invention involve contacting endogenous PD-L1 with a PD-L1 binding antigen binding protein, *e.g.*, via administration to a subject or in an *ex vivo* procedure.

The term "treatment" encompasses alleviation or prevention of at least one symptom or other aspect of a disorder, or reduction of disease severity, and the like. An antigen binding protein need not effect a complete cure, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject,

is sufficient. One embodiment of the invention is directed to a method comprising administering to a patient a PD-L1 antagonist in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

As is understood in the pertinent field, pharmaceutical compositions comprising the antibodies and fragments thereof of the disclosure are administered to a subject in a manner appropriate to the indication. Pharmaceutical compositions may be administered by any suitable technique, including but not limited to, parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Localized administration, *e.g.* at a site of disease or injury is contemplated, as are transdermal delivery and sustained release from implants. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

Use of antigen binding proteins in *ex vivo* procedures also is contemplated. For example, a patient's blood or other bodily fluid may be contacted with an antigen binding protein that binds PD-L1 *ex vivo*. The antigen binding protein may be bound to a suitable insoluble matrix or solid support material.

Advantageously, antigen binding proteins are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents, for example, a second inflammation- or immune-inhibiting substance, an anti-angiogenic substance, an analgesic substance, etc., non-exclusive examples of which are provided herein. In various particular embodiments, the composition comprises one, two, three, four, five, or six physiologically active agents in addition to a PD-L1 binding antigen binding protein

Combination Therapy

In another aspect, the present disclosure provides a method of treating a subject with a PD-L1 inhibiting antigen binding protein and one or more other treatments. In one embodiment, such a combination therapy achieves synergy or an additive effect by, for example, attacking multiple sites or molecular targets in a tumor. Types of combination therapies that can be used in connection with the present invention include inhibiting or

activating (as appropriate) multiple nodes in a single disease-related pathway, multiple pathways in a target cell, and multiple cell types within a target tissue.

In another embodiment, a combination therapy method comprises administering to the subject two, three, four, five, six, or more of the PD-L1 agonists or antagonists described herein. In another embodiment, the method comprises administering to the subject two or more treatments that together inhibit or activate (directly or indirectly) PD-L1-mediated signal transduction. Examples of such methods include using combinations of two or more PD-L1 inhibiting antigen binding proteins, of a PD-L1 inhibiting antigen binding protein and one or more other therapeutic moiety having anti-cancer properties (for example, cytotoxic agents, and/or immunomodulators), or of a PD-L1 inhibiting antigen binding protein and one or more other treatments (*e.g.*, surgery, or radiation). Furthermore, one or more anti-PD-L1 antibodies or antibody derivatives can be used in combination with one or more molecules or other treatments, wherein the other molecule(s) and/or treatment(s) do not directly bind to or affect PD-L1, but which combination is effective for treating or preventing the condition being treated. In one embodiment, one or more of the molecule(s) and/or treatment(s) treats or prevents a condition that is caused by one or more of the other molecule(s) or treatment(s) in the course of therapy, *e.g.*, nausea, fatigue, alopecia, cachexia, insomnia, etc. In every case where a combination of molecules and/or other treatments is used, the individual molecule(s) and/or treatment(s) can be administered in any order, over any length of time, which is effective, *e.g.*, simultaneously, consecutively, or alternately. In one embodiment, the method of treatment comprises completing a first course of treatment with one molecule or other treatment before beginning a second course of treatment. The length of time between the end of the first course of treatment and beginning of the second course of treatment can be any length of time that allows the total course of therapy to be effective, *e.g.*, seconds, minutes, hours, days, weeks, months, or even years.

In another embodiment, the method comprises administering one or more of the PD-L1 antagonists described herein and one or more other treatments (*e.g.*, a therapeutic or palliative treatment). Where a method comprises administering more than one treatment to a subject, it is to be understood that the order, timing, number, concentration, and volume of the administrations is limited only by the medical requirements and limitations of the treatment, *i.e.*, two treatments can be administered to the subject, *e.g.*, simultaneously, consecutively, alternately, or according to any other regimen.

**Example 1**

This example provides a characterization of the disclosed anti-PD-L1 antibodies binding to human PD-L1 expressed on human lymphocytes. Human peripheral blood mononuclear cells were activated by culture with anti-CD3 for three days to promote expression of PD-L1. Binding was assessed by adding serial dilutions of the antibody to the activated lymphocytes. After washing, binding was detected by staining with a phycoerythrin labeled anti-human Ig reagent followed by analysis using a FACS Aria (Becton Dickinson, San Jose, CA). Since the anti-human Ig reagent reacts with immunoglobulin on B lymphocytes the cells were co-staining with an anti-human CD19 APC-Cy5 reagent. Data were obtained by gating on the CD19 negative lymphocytes and the results are shown in Figure 1. Both H6 and H10 antibodies show potent binding activity with an $EC_{50}$ in the 100 pM range.

**Example 2**

This example provides the results from binding the disclosed anti-PD-L1 antibodies to human lymphocytes. Anti-PD-L1 antibodies were assayed for binding to non-activated lymphocytes. Peripheral blood mononuclear cells were incubated with anti-PD-L1 antibodies (1 μg/ml) followed by washing. Binding of the anti-PD-L1 antibody was detected by staining with a phycoerythrin conjugated and human Ig reagent. To identify the stained populations the cells were co-stained with an anti-CD3 FITC or an anti-CD56 APC reagent. Since the anti-human Ig reagent reacts with immunoglobulin on B lymphocytes the cells were also stained with an anti-human CD19 APC-Cy5 reagent. The data in Figure 2 were derived from the CD19 negative lymphocytes following analysis using a FACSAria (Becton Dickinson, San Jose, CA). The results show that CD56 positive NK cells, but not CD3+ T cells, react with the anti-PD-L1 antibodies.

**Example 3**

This example provides a showing of the effect of disclosed anti-PD-L1 antibodies on lymphocyte proliferation. Anti-PD-L1 antibodies were assayed for their ability to modulate the response of lymphocytes to stimulation. The anti-PD-L1 antibodies H1, H6 and H10 were added at 10 μg/ml to cultures of peripheral blood mononuclear cells labeled with the fluorescent dye carboxyfluorescein (CFSE) and stimulated with anti-CD3 (1 ng/ml). After three days of culture, the cells were assayed for proliferative activity by flow cytometry using a FACS Aria (Becton Dickinson, San Jose, CA). The results, shown in Figure 3, show that the anti-PD-L1 antibodies inhibited lymphocyte proliferation.

**Example 4**

This example provides a showing of the effect of NK cells on the disclosed anti-PD-L1 antibodies on mediated inhibition of proliferation. With the anti-PD-L1 antibodies showing a

preferential binding to NK cells, the significance of this in the inhibition of proliferation was tested. By cell sorting using a FACS Aria (Becton Dickinson, Dan Jose, CA) purified population of CD4+, CD8+, CD56+ (NK) and monocytes were obtained. As a base culture, 1.5 x $10^5$ CD4+ cells and 3 x $10^4$ monocytes were stimulated with anti-CD3 (1 ng/ml) with or without H10 anti-PD-L1 antibody (10 μg/ml). In separate cultures, either CD8+ cells or NK cells (both at 3 x $10^4$) were added to this base culture. After three days of culture, cells were stained for expression of CD25 as a measure of lymphocyte activation as measured by flow cytometry. The results shown in Figure 4 were compared to those obtained using whole, unfractionated PBMC (1.5 x $10^5$). The anti-PD-L1 antibody inhibited the activation of lymphocytes in the cultures containing whole PBMC and those where NK cells were added, but not in the absence of NK cells.

**Example 5**

This example provides a showing of an effect of anti-PD-L1 on NK cell activation. Disclosed anti-PD-L1 antibodies were assayed for their ability to promote the activation of lymphocytes. Peripheral blood mononuclear cells or purified populations of lymphocyte subsets isolated by cell sorting were cultured with IL-2 (100 U/ml) in the presence or absence of added anti-PD-L1 antibodies (10 μg/ml). After five days of culture, cells were stained for expression of CD25 as a measure of cell activation and analyzed by flow cytometry. The results shown in Figure 5 reveal that H6 and H10 enhance cell activation and that the responsive lymphocyte population is the NK cell.

**Example 6**

This example provides a showing of an effect of disclosed anti-PD-L1 antibodies on the progression of disease in a murine model of multiple sclerosis (MS). Anti-PD-L1 antibodies were assayed for their ability to modulate the course of disease in mice induced to develop experimental autoimmune encephalitis (EAE) as a model of MS. Disease was induced in C57Bl/6 mice following injection of myelin oligodendrocyte glycoprotein (MOG) peptide and pertussis toxin. Once symptoms of disease developed, the mice were treated every second day with an intraperitoneal injection of anti-PD-L1 antibody (0.1 mg). The results shown in Figure 6 provide that both anti-PD-L1 antibodies H6 and H10 impacted the course of disease development with H6 greatly reducing disease severity.

**Example 7**

This example provides a characterization of the disclosed G12 anti-PD-L1 antibody. rhPD-L1 was immobilized on CM5 sensor chip using standard NHS/EDC coupling methodology. All measurements were conducted in HBS-EP buffer with a flow rate of 30

μL/min. Antibody was diluted so as to obtain a series of concentrations. A 1:1 (Langmuir) binding model was used to fit the data.

Table 1 provides the binding data for G12.

| | | G12 |
|---|---|---|
| **Biacore** | $k_{on}$ ($M^{-1}$ $s^{-1}$) | 1.31E+07 |
| | $k_{off}$ ($s^{-1}$) | 4.90E-04 |
| | Kd (M) | 3.74E-11 |

**Example 8**

This example provides the results from an experiment showing that G12 blocks the interaction between rhPD-1 and rhPD-L1. A 96-well ELISA plate was coated with 1 ng/μL PD1/His at 4 °C overnight, then blocked with casein in PBS. Pre-mixed 20 μl serial 2-fold diluted IgGs (started from 20 μg/ml) and 20 μl 0.25 μl/ml PD-L1/Fc and incubated the mixtures 30 min. washed the plate with PBS-Tween (PBST) 3 times. Transferred 25 μl the mixtures to the ELISA plate and incubated 30 min with shaking. Washed 3 times with PBST. Added HRP conjugated Goat anti-human Fc (1:500 in casein), used TMB as substrate and developed 30 min. 2M $H_2SO_4$ was added to stop the reaction. Read the OD at 450nm.

Table 2

| | | G12 |
|---|---|---|
| **Blocking PD-1/PD-L1 interaction (M)** | $IC_{50}$ | 7.288E-11 |

**Example 9**

This example illustrates *in vitro* $EC_{50}$ data for the binding of G12 to human PD-L1 expressed on the surface of CHO cells. This example shows the binding characteristic for this antibody in terms of the maximal cell binding and the concentration at which 50% binding saturation ($EC_{50}$) is reached. In this example, the experimental procedure is as follows: 50,000 CHO-PD-L1 cells were aliquoted into the wells of a 96-well, v-bottom plate in 100 μl FACS Buffer (PBS + 2% FBS). A dilution curve of the antibody was made in FACS Buffer encompassing the concentrations shown in Figure 7. Cells were spun down, washed 1x with FACS Buffer, and then resuspended in 25 μl of antibody solution in triplicate. After 0.5 hr incubation, cells were washed 1x with FACS Buffer and resuspended in 50 μl PE-conjugated, goat anti-human IgG (γ-chain specific) secondary antibody (Southern Biotech Cat #2040-09). Cells were further incubated for 0.5 hr and then washed 1x with FACS Buffer. Cells were resuspended in 25 μl FACS Buffer and the median fluorescence intensity in the FL2-H channel was determined using the Intellicyt HTFC flow cytometer.

Results: As shown in Figure 7 and Table 3, the cell binding $EC_{50}$ for the G12 anti-PD-L1 antibody on CHO-PD-L1 cells was 1.71E-09 M. Data was collected on the Intellicyt HTFC

flow cytometer, processed using FlowJo software, and analyzed and plotted in Graph Pad Prizm using non-linear regression fit. Data points are shown as the median fluorescence intensity (MFI) of positively labeled cells +/- Std Error.

Table 3

| | | G12 5 |
|---|---|---|
| **Cell Binding EC50 (M)** | CHO-PD-L1 | 1.71E-09 |

**Example 10**

This example provides in vitro $IC_{50}$ data for the blocking of the interaction between recombinant human PD-1 (PD-1-Fc Chimera; Sino Biologics) and human PD-L1 expressed CHO cells by anti-PD-L1 antibody G12. Here, CHO cells expressing PD-L1 were pre-incubated with G12 prior to the addition of rhPD-1-Fc chimeric protein. After incubation and washing, PD-1 binding to cell surface expressed PD-L1 was detected using an Alexa-Fluor 647 tagged anti-PD-1 antibody by flow cytometry (Intellicyt HTFC; FL-4H). This example shows that anti-PD-L1 monoclonal antibody G12 was able to inhibit efficiently the binding of PD-1 to PD-L1 expressed on the surface of CHO cells.

Results: As shown in Figure 8 and Table 4, the $IC_{50}$ for blocking of the PD-1/PD-L1 cellular interaction by G12 is 1.76E-09 M. Data was collected on the Intellicyt HTFC flow cytometer, processed using FlowJo software, and analyzed and plotted in Graph Pad Prizm using non-linear regression fit. Data points are shown as the median fluorescence detected in the FL-4H channel +/- Std Error.

Table 4

| | | G12 |
|---|---|---|
| **Inhibition of PD-1/PD-L1 Interaction IC50 (M)** | CHO-PD-L1/ rhPD-1-Fc | 1.76E-09 |

**Example 11**

This example illustrates *in vitro* $EC_{50}$ data for the binding of G12 to PD-L1 expressed on the surface of ES-2 human ovarian carcinoma cells. This example shows the binding characteristic for this antibody in terms of the maximal cell binding and the concentration at which 50% binding saturation ($EC_{50}$) is reached. In this example, the experimental procedure is as follows: ES-2 cells were treated with 500IU/ml IFNγ for 18 hours to increase PD-L1 levels above basal expression. After induction, 50,000 ES-2 cells were aliquoted into the wells of a 96-well, v-bottom plate in 100 µl FACS Buffer (PBS + 2% FBS). A dilution curve of the antibody was made in FACS Buffer encompassing the concentrations shown in Figure 9. Cells were spun down, washed 1x with FACS Buffer, and then resuspended in 25 µl of antibody solution in triplicate. After 0.5 hr incubation, cells were washed 1x with FACS Buffer and resuspended in

50 µl PE-conjugated, goat anti-human IgG (γ-chain specific) secondary antibody (Southern Biotech Cat #2040-09). Cells were further incubated for 0.5 hr and then washed 1x with FACS Buffer. Cells were resuspended in 25 µl FACS Buffer and the median fluorescence intensity in the FL2-H channel was determined using the Intellicyt HTFC flow cytometer.

Results: As shown in Figure 9 and Table 5, the cell binding $EC_{50}$ for the G12 anti-PD-L1 antibody on ES-2 ovarian carcinoma cells was 4.58E-11 M. Data was collected on the Intellicyt HTFC flow cytometer, processed using FlowJo software, and analyzed and plotted in Graph Pad Prizm using non-linear regression fit. Data points are shown as the median fluorescence detected in the FL-2H channel +/- Std Error. Cell binding $EC_{50}$ for anti-PD-L1 mAb G12 against human PD-L1 expressed on ES-2 ovarian cancer cells after treatment with 500 IU/ml recombinant hIFNγ for 18hr is shown in Table 5.

**Table 5**

| | | G12 [15] |
|---|---|---|
| **Cell Binding EC50 (M)** | ES-2 | 4.58E-11 |

**Example 12**

This example provides a mixed lymphocyte reaction (MLR) to evaluate the effect of the antibodies on lymphocyte activity in lymphocyte effector cells. IL-2 secretion was measured in the presence or absence of an anti-PD-L1 human monoclonal antibody (Figure 10). The functional activity of the antibodies was assessed in an allogeneic mixed lymphocyte reaction (MLR) consisting of purified CD4+ T lymphocytes and allogeneic dendritic cells. The antibodies used were the disclosed G12 antibody as compared to prior disclosed antibodies 10A5 and 12A4 (Bristol-Myers/Medarex) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 the disclosure of which is incorporated by reference herein). To prepare the dendritic cells, monocytes, purified using a discontinuous Percoll gradient, were cultured with GM-CSF (1,000 U/ml) plus IL-4 (500 U/ml) for seven days. The CD4+ cells were prepared by negative selection using biotinylated antibodies reactive with CD8, CD16, CD19 and CD20. Removal of the reactive cells was achieved using biotin binding magnetic beads. The antibodies were added at the indicated concentrations to wells containing $10^5$ CD4+ cells labeled with carboxyfluorecein (CFSE) and $10^4$ dendritic cells. After five days of culture, supernatants were harvested for cytokine determination.

**Example 13**

This example provides a mixed lymphocyte reaction (MLR) was employed to demonstrate the effect of blocking the PD-L1/PD-1 pathway by the anti-PD-L1 antibodies on lymphocyte effector cells. T cell activation was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody (Figure 12). The functional activity of the antibodies was assessed in an allogeneic mixed lymphocyte reaction (MLR) consisting of purified CD4+ T lymphocytes and allogeneic dendritic cells. The antibodies used were the disclosed H6B1L, RSA1, RA3, RC5, SH1E2, SH1E4, SH1B11, and SH1C8 as compared to prior disclosed antibodies 10A5 (Bristol-Myers-Squibb/Medarex) and YW243.55S70 (Roche/Genentech) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 and U.S. Patent Application US 2010/0203056; the disclosure of which are incorporated by reference herein). To prepare the dendritic cells, monocytes, purified using a discontinuous Percoll gradient, were cultured with GM-CSF (1,000 U/ml) plus IL-4 (500 U/ml) for seven days. The CD4+ cells were prepared by negative selection using biotinylated antibodies reactive with CD8, CD16, CD19 and CD20. Removal of the reactive cells was achieved using biotin binding magnetic beads. The antibodies were added at the indicated concentrations to wells containing $10^5$ CD4+ cells labeled with carboxyfluorecein (CFSE) and $10^4$ dendritic cells. After five days of culture, the cells were collected and stained for CD25 expression as a measure of cell activation. Cell activation was measured by flow cytometry.

The results for cell activation are shown in Figure 13. With all anti-PD-L1 antibodies there was an increase in cell activation. In Figure 13, the data are expressed as a percentage of test value with of the respect to that obtained in the absence of any added antibody. In this way, the percent increase in cell activation was realized.

**Example 14**

The ability of anti-PD-L1 antibodies to modulate immune responsiveness was assessed using a mixed lymphocyte reaction (MLR). With this assay, the effects anti-PD-L1 antibodies on cell activation and the production of IL-2 were measured. The MLR was performed by culturing $10^5$ purified human CD4+ cells from one donor with $10^4$ monocyte derived dendritic cells prepared from another donor. To prepare the dendritic cells, purified monocytes were cultured with GM-CSF (1,000 U/ml) and IL-4 (500 U/ml) for seven days. Anti-PD-L1 or control antibodies were added to the allogeneic MLR cultures at 10 μg/ml unless stated otherwise. Parallel plates were set up to allow collection of supernatants at day 3 and at day 5 to measure IL-2 using a commercial ELISA kit (Biolegend). The antibodies used were the

disclosed H6B1L, RSA1, RA3, RC5, SH1E2, SH1E4, SH1B11, and SH1C8 as compared to prior disclosed antibodies 10A5 (Bristol-Myers-Squibb/Medarex) and YW243.55S70 (Roche/Genentech) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 and U.S. Patent Application US 2010/0203056; the disclosure of which are incorporated by reference herein).

Production of IL-2 was enhanced by the addition of the anti-PD-L1 antibodies.

**Example 15**

This example provides a mixed lymphocyte reaction (MLR) was employed to demonstrate the effect of blocking the PD-L1/PD-1 pathway by the anti-PD-L1 antibodies on lymphocyte effector cells. IFN-γ secretion was measured in the presence or absence of the anti-PD-L1 human monoclonal antibody (Figure 11). The functional activity of the antibodies was assessed in an allogeneic mixed lymphocyte reaction (MLR) consisting of purified CD4+ T lymphocytes and allogeneic dendritic cells. The antibodies used were the disclosed H6B1L, RSA1, RA3, RC5, SH1E2, SH1E4, SH1B11, and SH1C8 as compared to prior disclosed antibodies 10A5 (Bristol-Myers-Squibb/Medarex) and YW243.55S70 (Roche/Genentech) that were obtained via in-house production from prior-disclosed antibody sequences (U.S. Patent Application 2009/0055944 and U.S. Patent Application US 2010/0203056; the disclosure of which are incorporated by reference herein).

To prepare the dendritic cells, monocytes, purified using a discontinuous Percoll gradient, were cultured with GM-CSF (1,000 U/ml) plus IL-4 (500 U/ml) for seven days. The CD4+ cells were prepared by negative selection using biotinylated antibodies reactive with CD8, CD16, CD19 and CD20. Removal of the reactive cells was achieved using biotin binding magnetic beads. The antibodies were added at the indicated concentrations to wells containing $10^5$ CD4+ cells labeled with carboxyfluorecein (CFSE) and $10^4$ dendritic cells. After five days of culture, supernatants were harvested for cytokine determination.

Production of IFN-γ was enhanced by the addition of the anti-PD-L1 antibodies.

**Sequence Listing**

| | Heavy chain variable domain region | Light chain variable domain region |
|---|---|---|
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFNTYAIS | DIVMTQTPYSVSASVGDRVTITCRASQEVSR |
| | WVRQAPGQGLEWMGGIIPLFGKADYAQKFQDRVT | WVAWYQQKPGQAPKSLIYASSRLQSGVPS |
| | ITADESTSTAYMELSSLRSEDTAVYYCARDKGREELG | RFTASGSGTDFTLVISSLQPEDFATYYCQQYS |
| E6 | GNYYYAVDVWGPGTTVTVSS SEQ ID NO. 1 | RFPLTFGGGTKVEIK SEQ ID NO. 2 |

| | | |
|---|---|---|
| | QVQLQQLGPGLVKPSQTLSLTCAISGDSVSSNSAA | QPVLTQPASVSGSPGQSITISCTGTSSDVGG |
| | WNWIRQSPSRGLEWLGRTYYRSKWYTNYAVSMRS | YNYVSWYQQHPGKAPKLMVYDVSKRPSGV |
| | RITINPDTSKNQFSLQLNSVTPEDTAVYFCAGGNSSS | SNRFSGSKSGNTASLTISGLQTEDEADYYCSS |
| E7 | HDDYWGQGTLVTVSS SEQ ID NO. 3 | YTSSNTRVFGTGTKLTVL SEQ ID NO. 4 |
| | EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW | DIVMTQSPSTLSASVGDRVTITCRASQSFTT |
| | VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVT | YLAWYQQKPGKAPKLLIYQTSNLESGVPSRF |
| | MTTDTSTSTAYMELRSLRSDDTAVYYCARDLFPTIF | SGSGSGTEFTLTISSLQPDDFATYYCQQYSRY |
| E9 | WEGGAFDIWGQGTMVTVSS SEQ ID NO. 5 | WWSFGQGTRLEIK SEQ ID NO. 6 |
| | EVQLVQSGAEVKKPGASLKVSCKASGYTFNSYDINW | AIQMTQSPSSLSASVGDRVTITCRASQSISSY |
| | VRQAPGQGLEWMGWINPNSGGTNYAQKFQGRV | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | TMTRDTSTSTVYMELSSLTSEDTAVYYCARDLFPHIY | GSGSGTDFTLTISSLQPEDFATYYCQQSSSTP |
| E11 | GNYYGMDIWGQGTTVTVSS SEQ ID NO. 7 | LTFGQGTKVEIK SEQ ID NO. 8 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | QAVLTQPRSVSGSPGQSVTISCTGTSSDVG |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | GYNYVSWYQQHPGKAPKLMIYDVRTRPSG |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | VSDRFSGSKSGNTASLSISGLQAEDEADYYC |
| F1 | DYWGQGTLVTVSS SEQ ID NO. 9 | SSHSSSTTVIFGGGTKLTVL SEQ ID NO. 10 |
| | EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGWINPNSDNTGSAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| F4 | FDFWGQGTLVTVSS SEQ ID NO. 11 | ITFGQGTRLEIK SEQ ID NO. 12 |
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYWMS | QAVLTQPPSVSAAPGQRVTISCSGSNSNIAD |
| | WVRQAPGKGLEWVANIKQDGSEKYYVDSVKGRFTI | TYVSWYQQLPGTAPRLLIYDNDQRPSGIPD |
| | SRDNAKNSLYLQMNSLRAEDTAVYYCAREGEHDAF | RFSGSKSGTSATLGITGLQTGDEADYYCGT |
| F7 | DIWGQGTMVTVSS SEQ ID NO. 13 | WDSSLSGVFGTGTKVTVL SEQ ID NO. 14 |
| | QVQLVQSGGGVVQPGRSPRLSCAASGFTFNTYGM | QSVLTQPASVSGSPGQSVTISCTGTSSDVGG |
| | HWVRQAPGKGLEWVAVISDGGNNKKYADSVKGRF | FNSVSWYQQHPGKAPKLMIYDVSKRPSEIS |
| | TISRDNAKNSLYLQMNSLRAEDTALYYCAKDIGESYY | DRFSGSKSGNTASLTISGLQPEDEADYYCSSY |
| F8 | YYMDVWGKGTTVTVSS SEQ ID NO. 15 | TSSSTLVFGGGTKLTVL SEQ ID NO. 16 |
| | QVQLQQSGPGLVKPSQSLSLTCAISGDSLSSNSAAW | SYVLTQPPSVSVSPGQTASISCSGYKLENKYV |
| | NWIRQSPSGGLEWLGRTYYRSKWYNEYVESLKSRIT | SWYQQRAGQSPVLVIYQDNKRPSGIPERFS |
| | INSDISRNQFSLHLNSVTPEDTAVYYCASGTGARGM | GSNSGNTASLTITGLQPEDEADYYCSAWDS |
| F11 | DVWGQGTTVTVSS SEQ ID NO. 17 | SLRAWVFGGGTQLTVL SEQ ID NO. 18 |
| | QVQLQQSGPGLVKPSETLSLTCAISGDSVSENSAAW | QPVLTQPPSVSVSPGQTASITCSGDELGNKY |
| | NWIRQSPSGGLEWLGRTYYRSKWYNEYVESLKSRIT | VYWYQQKPGRSPVLVIYQDSKRPSGFPARF |
| | INSDISRNQFSLHLNSVTPEDTAVYYCASGTGARGM | SGANSGNTATLTISGTQAMDEADYFCQAW |
| G4 | DVWGQGTTVTVSS SEQ ID NO. 19 | DSSTAWVFGGGTKLTVL SEQ ID NO. 20 |
| | EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGWINPNSDNTGSAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| G9 | FDFWGQGTLVTVSS SEQ ID NO. 21 | ITFGQGTRLEIK SEQ ID NO. 22 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSRYGVH | LPVLTQPASVSGSPGQSVTISCTGTSSDVGG |
| | WVRQAPGQGLEWMGRLIPIVSMTNYAQKFQDRV | HNYVSWYQQHPGKAPKLMIYEVNKRPSGV |
| | SITTDKSTGTAYMELRSLTSEDTALYYCASVGQQLP | PDRFSGSKSDYTASLTISGLQPDDEADYFCSS |
| G11 | WVFFAWGQGTLVTVSS SEQ ID NO. 23 | YTATTTGVVFGTGTKVTVL SEQ ID NO. 24 |

| | | |
|---|---|---|
| | EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGWINPNSDNTGSAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| G12 | FDFWGQGTLVTVSS SEQ ID NO. 25 | ITFGQGTRLEIK SEQ ID NO. 26 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGNTFTNYYMH | DIVMTQSPPSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGIMNPSGGSTSYAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VTMTRDKSTSTVYMELSSLTSEDTAVYYCARDLFPHI | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| H1 | YGNYYGMDIWGQGTTVTVSS SEQ ID NO. 27 | YTFGQGTKVEIK SEQ ID NO. 28 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW | QSVVTQPPSVSAAPGQKVTISCSGSTSNIEN |
| | VRQAPGQGLEWMGGIIPIFGTASYAQKFQGRVTIT | YSVSWYQQLPGTAPKLLIYDNNKRPSGIPDR |
| | ADESTTTAYMELSSLRSEDTAVYYCAREGPEYCSGG | FSGSKSGTSATLGITGLQTGDEADYYCGTW |
| H3 | TCYSADAFDIWGQGTMVTVSS SEQ ID NO. 29 | DNRLSSVVFGGGTKVTVL SEQ ID NO. 30 |
| | | QPVLTQPPSVSAAPGQKVTISCSGSSSNIGN |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW | SHVSWFQQLPGTAPKLVIYDNDKRPSGIAD |
| | VRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITA | RFSGSKSGTSATLGITGLQTGDEADYYCGT |
| | DKSTSTAYMELSSLRSEDTAVYYCARSESGSYSHDY | WDSSLSAGVFGGGTKLTVL SEQ ID NO. |
| H4 | WGQGTTVTVSS SEQ ID NO. 31 | 32 |
| | | QAVVTQPPSASGTPGQRVTISCSGSSSNVG |
| | QVQLVESGAEVKKPGASVKVSCKASGYTFTSYYIHW | VNHVFWYQHLPGMAPKLLIHRTNQWPSG |
| | VRQAPGQGLEWMGIINPSGGSTTYAQKFQGRVSM | VPDRFSGSKSGTSATLGITGLQTGDEADYYC |
| | TRDTSTRTVYMELSGLISDDTAIYYCARDDDFYSGYP | GTWDSSLSAVFGGGTKLTVL SEQ ID NO. |
| H5 | GDYWGQGTLVTVSS SEQ ID NO. 33 | 34 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS | SYELMQPPSVSVAPGKTATIACGGENIGRKT |
| | WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVT | VHWYQQKPGQAPVLVIYYDSDRPSGIPERF |
| | ITADESTSTAYMELSSLRSEDTAVYYCARGNIVATITP | SGSNSGNTATLTISRVEAGDEADYYCQVWD |
| H6 | LDYWGQGTLVTVSS SEQ ID NO. 35 | SSSDHRIFGGGTKLTVL SEQ ID NO. 36 |
| | EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMN | EIVLTQSPSSLSASIGDRVTLTCRASQSIRRFL |
| | WVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISR | NWYQQKPGKAPELLIYTASSLQSGVPSRFSG |
| | DNAKNSLYLQMNSLRDEDTAVYYCARGDYYYGMD | SGSGTDFTLTINSLQPEDFATYYCQQSYAVS |
| H10 | VWGQGTTVTVSS SEQ ID NO. 37 | PYTFGQGTKVEIR SEQ ID NO. 38 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGN |
| | WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVT | NYVSWYQQLPGTAPKLLIYDNNKRPSGIPD |
| | ITADESTSTAYMELSSLRSEDTAVYYCARGDFWSGY | RFSGSKSGTSATLGITGLQTGDEADYYCGT |
| H12 | RTYYYYYGMDVWGQGTMVTVSS SEQ ID NO. 39 | WDSSLSAVVFGGGTKLTVL SEQ ID NO. 40 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGYTFTSNAIG | ALTQPASVSGSLGQSITISCTGSSSDVGGYKY |
| | WVRQAPGQGLEWMGWISAYNGNTNYAQNLQGR | VSWYQQHPGKAPKLMIYDVINRPSGVSSRF |
| | VTMTTDTSTSTAYMELRSLRSDDTAVFYCARKGTGL | SGSKSANTASLTISGLQAEDEADYYCFSYSSR |
| PDL-D2 | HFDYWGQGTLVTVSS SEQ ID NO. 41 | STRIFGSGTKVTVL SEQ ID NO. 42 |
| | | QTVVTQPPSVSKDLGQTATLTCTGNNNNV |
| | QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAA | GNHGAAWLQQHQGHPPKLLSYRNNNRPS |
| | WNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKS | GISERLSASRSGNTASLTITGLQPEDEADYYC |
| | RITINPDTSKNQFSLQLNSVTPEDTAVYYCARGAAG | SAWDRSLSAWVFGGGTKLTVL SEQ ID |
| PDL-D11 | RAFDIWGQGTMVTVSS SEQ ID NO. 43 | NO. 44 |
| | EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMN | EIVLTQSPSSLSASIGDRVTLTCRASQSIRRFL |
| | WVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISR | NWYQQKPGKAPELLIYTASSLQSGVPSRFSG |
| | DNAKNSLYLQMNSLRDEDTAVYYCARGDYYYGMD | SGSGTDFTLTINSLQPEDFATYYCQQSYAVS |
| PDL-H1 | VWGQGTTVTVSS SEQ ID NO. 45 | PYTFGQGTKVEIK SEQ ID NO. 46 |

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|---|---|---|
| | EVQLVESGGGLVQPGGSLRLSCAASGFYLGSYWMA WVRQAPGKGLEWVAAIRQDGSETIYVDSVKGRFIIS RDNGGNSVTLQMTTLRAGDTAVYYCARAHYFGFD | QSVLTQPASVSGSPGQSISVSCTGTSSDVGR YNFVSWYQQHPGKAPKLMVFDVSNRPSGI SNRFSGSKSGNTASLTISGLQAEDEADYYCS |
| RB4 | NWGQGTLVTVSS SEQ ID NO. 47 | SYTTNSTYVFGSGTKVTVL SEQ ID NO. 48 |
| | QMQLVQSGAEVKKPGASVKISCKASGYPFRNYYIH WVRQAPGQGLEWVGIINPDGGTITYAGKFQGRVS MTRDTSTSTVYMELSSLTSEDTAVYYCARDLFPHIYG | QPVLTQPPSVSAAPGQKVTISCSGSSSNIAN NYVSWYQQLPGTAPKLLIFANNKRPSGIPD RFSGSKSGTSAALDITGLQTGDEADYYCGT WDSDLRAGVFGGGTKLTVL SEQ ID NO. |
| RB11 | NYYGMDIWGQGTTVTVSS SEQ ID NO. 49 | 50 |
| | EVQLLESGGGVVQPGGSLRLSCAASGFTFSSYWMS WVRQAPGKGLEWVANIKQDGSEKYYVDSVKGRFTI SRDNSKNTVSLQMNSLRAEDTAVYYCAKDRYYNFP | AIRMTQSPSSLSASVGDRVTITCRASQSISSY LNWYQQKPGKAPKLLIYTTSSLKSGVPSRFS GSGSGTDFTLTISRLQPEDFATYYCQQSYSST |
| RC5 | LGMDVWGQGTTVTVSS SEQ ID NO. 51 | WTFGRGTKVEIK SEQ ID NO. 52 |
| | EVQLLESGAEVKKPGSSVKVSCKSSGDTFTNFAINWI RQAPGQGLEWMGRIIPLFGTTNYAQKFQGRVTITA DESTSTAFMDLNSLTSEDTAVYYCARTLGGDYYDSR | QSVLTQPASVSGSPGQSITISCTGTSSDVGSY NLVSWYQQYPGKAPKLMIYEVSERPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY |
| RF5 | GYYNWGQGTLVTVSS SEQ ID NO. 53 | TDSNNFRVFGGGTKLTVL SEQ ID NO. 54 |
| | QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSVV WNWFRQSPSRGLEWLGRAYYRSKWYNDYAVSVKS RITINPDTSKNQLSLQLNSVTPEDTAVYYCAKGLDV | EIVMTQSPSSLYASVGDRVTITCRASQSISSY LNWYQQKPGKVPKLLIYAASSLQSGVPSRFS GSGSGTDFTLTISGLQPEDFATYYCQQSYTP |
| RG9 | WGQGTTVTVSS SEQ ID NO. 55 | AWTFGQGTKLEIK SEQ ID NO. 56 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT ADESTSTAYMELSSLRSEDTAVYYCARDGIVADFQH | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGN NYVSWYQQVPGTAPKLLIYDNDKRPSGIPD RFSGSKSGTSATLAITGLQTGDEADYYCGT WDSSLNAWVFGGGTKLTVL SEQ ID NO. |
| RD1 | WGQGTLVTVSS SEQ ID NO. 57 | 58 |
| | QVQLVQSGAEVKKPGASVRVSCKASGGTFSSYAIS WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVT ITADESTSTAYMELSSLRSEDTAVYYCARDGIVADFQ | QSVLTQPPSVSAAPGQKVTISCSGSSSNIEN NYVSWYQHLPGTAPKLLIYDDFKRPSGIPDR FSGSKSGTSATLGITGLQTGDEADYYCGTW |
| RF11 | HWGQGTLVTVSS SEQ ID NO. 59 | DSSLSAVVFGGGTKLTVL SEQ ID NO. 60 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFNSYPIS WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVT ITADESTSTAYMELSSLRSEDTAMYYCAKNHPTATL | QSVLTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGV PDRFSGSKSGNTASLTVSGLQAEDEADYYCS SYAGSNNLGVFGGGTKLTVL SEQ ID NO. |
| RH11 | DYWGQGTLVTVSS SEQ ID NO. 61 | 62 |
| | QVQLVQSGGNLVKPGGSLRLSCAASGFSFSSYDMN WVRQAPGRGLEWVSSISGTGRYEYYSPSVKGRFTIS RDNANTSLYLQMNSLTADDTAVYFCTRGDILTGASA | DIQLTQSPSSLSASVGDRVTITCRASQGISS WLAWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQAN |
| RD9 | MDVWGQGTTVTVSS SEQ ID NO. 63 | SFPLTFGGGTKVEIK SEQ ID NO. 64 |
| | EVQLLESGGNLVKPGGSLRLSCAASGFSFSSYDMN WVRQAPGRGLEWVSSISGTGRYEYYSPSVKGRFTIS RDNANTSLYLQMNSLTADDTAVYFCTRGDILTGASA | DVVMTQSPSTLSASVGDRVTITCRASQSIGT WLAWYQQKPGKAPNLLIYKASSLESGVPSR FSGSGSGTEFTLTISSLQPDDFATYYCQQAN |
| RE10 | MDVWGQGTTVTVSS SEQ ID NO. 65 | SFPLTFGGGTKVEIK SEQ ID NO. 66 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSRYGVH WVRQAPGQGLEWMGRLIPIVSMTNYAQKFQDRV SITTDKSTGTAYMELRSLTSEDTALYYCASVGQQLP | DIQMTQSPSSLSASVGDRVTITCQASQDISN YLNWYQQKPGKAPKLLIYDASTLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQSYS |
| RA3 | WVFFAWGQGTLVTVSS SEQ ID NO. 67 | SHWTFGQGTKVEIK SEQ ID NO. 68 |
| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSRYGVH WVRQAPGQGLEWMGRLIPIVSMTNYAQKFQDRV SITTDKSTGTAYMELRSLTSEDTALYYCASVGQQLP | QSVVTQPPSVSGAPGQRVTISCTGSSSNIGA GYGVHWYQHLPGSAPKLLIYGNSNRPSGVT DRISGSKSGTSASLAITGLQAEDEAVYYCQSY |
| RG1 | WVFFAWGQGTLVTVSS SEQ ID NO. 69 | DSSLSTSVVFGGGTKLTVL SEQ ID NO. 70 |

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|---|---|---|
| | QMQLVQSGGGLIQPGGSLRLSCAASGFTFSSYAMH | QAGLTQPASVSGSPGQSITISCTGTSSDVGG |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | YNYVSWYQQHPGKAPKLMIYDVTKRPSGV |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | SNRFSGSKSGNTASLTISGLQAEDEANYYCS |
| RB1 | DYWGQGTLVTVSS SEQ ID NO. 71 | SYTSRSTSVLFGGGTKLTVL SEQ ID NO. 72 |
| | EVQLVESGGGVVLPGRSLRLSCAASGFTFSSYAMH | QPVLTQPPSVSEAPRQRVTISCSGSSSNIGH |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | NAVTWYQQVPGKAPKLLIYYDDLLPSGVSD |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | RFSGSKSGTSASLAISGLQSEDEADYYCAAW |
| RG7 | DYWGQGTLVTVSS SEQ ID NO. 73 | DDSLNGWVFGGGTKLTVL SEQ ID NO. 74 |
| | | QAGLTQPASVSGSPGQSITISCTGTSSDVGG |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | YNYVSWYQQHPGKAPKLMIYDVSNRPSGV |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | PDRFSGSKSGNTASLTISGLQAEDDADYYCA |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | SYTSTSTLGVVFGGGTKLTVL SEQ ID NO. |
| RA6 | DYWGQGTLVTVSS SEQ ID NO. 75 | 76 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | QPVLTQPASVSGSPGQSITISCTGTSSDVGG |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | YNYVSWYQHHPGKAPKLMIFDVNKRPSGV |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | SNRFSGSKSGNTASLTISGLQAEDEADYYCN |
| RA8 | DYWGQGTLVTVSS SEQ ID NO. 77 | SYTTSSTYVVFGGGTKLTVL SEQ ID NO. 78 |
| | | QSVLTQPPSASGTPGQRVTISCSGSSSNIGS |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | NTVHWYQQLPGTAPKVLIYTNNQRPSGVP |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | DRFSGSKSGTSASLAISGLQSEDEADYYCAA |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | WDGRLQGWVFGGGTKLTVL SEQ ID NO. |
| RA9 | DYWGQGTLVTVSS SEQ ID NO. 79 | 80 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | QSVVTQPPSVSAAPGQKVTISCSGSNSNIAN |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | NYVSWYQQLPGTAPKLLIYDSNKRPSGIPDR |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | FSGSKSGTSATLGITGLQTGDEADYYCGSW |
| RB5 | DYWGQGTLVTVSS SEQ ID NO. 81 | DSSLSVWMFGGGTKLTVL SEQ ID NO. 82 |
| | | LPVLTQPRSVSGSPGQSVTISCTGTSSDVGG |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | YNYVSWYQQHPGKAPKLMIYDVTKRPSGV |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | PDRFSGSKSGNTASLTISGLQAEDEADYYCS |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | SYTGSSTLGPVFGGGTKLTVL SEQ ID NO. |
| RB8 | DYWGQGTLVTVSS SEQ ID NO. 83 | 84 |
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | QSVLTQPPSVSAAPGQKVTISCSGNSSNIGN |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | NYVSWYQQLPGTAPKLLIYDNDKRPSGIPD |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | RFSGSKSGTSASLAISELRFEDEADYYCAAW |
| RC8 | DYWGQGTLVTVSS SEQ ID NO. 85 | DDTLSGHVFGPGTKLTVL SEQ ID NO. 86 |
| | | SYELMQPPSVSVPPGETARITCGGNNIGNK |
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | NVHWYQQKPGQAPVLVVREDSARPAGIPE |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | RFSGSNSGNSATLTISRVEAGDEADYYCQV |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | WDNTSDHVVFGGGTKLTVL SEQ ID NO. |
| RC10 | DYWGQGTLVTVSS SEQ ID NO. 87 | 88 |
| | | SYELMQPPSVSEVPGQRVTISCSGSSSNIGN |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | NAVNWFQQLPGKAPKLLVYYDDWVPSGIS |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | GRFSASKSGTSASLAISGLQSGDEGDYYCAV |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | WDDRLSGVVFGGGTKLTVL SEQ ID NO. |
| RD2 | DYWGQGTLVTVSS SEQ ID NO. 89 | 90 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGN |
| | WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI | NYVSWYQQLPGTAPTLLIYDSNKRPSVIPDR |
| | SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | FSGSKSGTSATLGITGLQTGDEADYYCGTW |
| RE8 | DYWGQGTLVTVSS SEQ ID NO. 91 | DDSLNGWVFGGGTKLTVL SEQ ID NO. 92 |

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|---|---|---|
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCS |
| RE9 | DYWGQGTMVTVSS SEQ ID NO. 93 | SYRSSTLGPVFGGGTKLTVL SEQ ID NO. 94 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | QAGLTQPPSASGSPGQSVTISCTGTSSDVG GYNYVSWYQQHPGKAPKLMIYDVSNRPSG VPDRFSGSKSGNTASLTISGLQAEDEADYYC SSYTSSSTLVVFGGGTKLTVL SEQ ID NO. |
| RG12 | DYWGQGTLVTVSS SEQ ID NO. 95 | 96 |
| | EVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYSMN WVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISR DNAKNSLYLQMNSLRDEDTAVYYCARGDYYYGMD | NIQMTQSPSSVSASVGDRVTITCRASQDISR WLAWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFALTISSLQPEDFATYYCQQAD |
| RSA1 | VWGQGTTVTVSS SEQ ID NO. 97 | SFFSITFGQGTRLEIK SEQ ID NO. 98 |
| | QVQLVQSGSEVKKPGASVKVSCRASGYLFTNYGIS WVRQAPGQGLEWMGWVSAHGEFTKYAPSLQDR VTMTSDISTTTAYMELRSLRSDDAGVYYCARDRGA | AIQLTQSPATLSLSPGERATLSCRASQSVGVY LAWYQQKPGQSPRLLIYDTSKRATGIPDRFS ASGSGTDFTLTISRLEPEDFAVYYCHQRHSW |
| R2A7 | DHFDTWGQGTLVTVSS SEQ ID NO. 99 | PTTFGQGTRLEIK SEQ ID NO. 100 |
| | EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMH WVRQAPGQGLEWMGMINPSSATTTYTQKFQGRV SMTRDTSTSTVYMELSSLTSEDTAVYYCARDLFPHIY | NIQMTQSPSSLSASVGDRVTITCRASQSISSY LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQSYSTL |
| R2B12 | GNYYGMDIWGQGTTVTVSS SEQ ID NO. 101 | TFGGGTKVEIK SEQ ID NO. 102 |
| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSHVISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT ADESTSTAYMELSSMRSEDTAVYYCATSGVVAATHF | QSVLTQPASVSGSPGQSITISCTGTSSDVGD YNLVSWYQQHPGKAPKLIIYEVNKRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSS YAGYNNLYVFGTGTKVTVL SEQ ID NO. |
| R2C9 | GYWGQGTLVTVSS SEQ ID NO. 103 | 104 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT ADESTSTAYMELSSLRSEDTAVYYCARGASGSYFITT | QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLIIYDVNMRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCS SYAGLYFPLFGGGTQLTVL SEQ ID NO. |
| R2D5 | YVDYWGQGTLVTVSS SEQ ID NO. 105 | 106 |
| | EVQLVESGGGLVQPGGPLRLSCAASGFTLSSYWMS WVRQAPGKGLEWVANIKYDGSETYYADSVKGRFTI SRDNAKNSLYLQMNRLRLEDTAVYYCAREVSSAATS | DIVMTQSPSSLSASVGDRVTITCRASQSISSY LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQSHSS |
| R2D7 | PLDRWGRGTLVTVSS SEQ ID NO. 107 | RYTFGQGTKLEIK SEQ ID NO. 108 |
| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSRYGVH WVRQAPGQGLEWMGRLIPIVSMTNYAQKFQDRV SITTDKSTGTAYMELRSLTSEDTALYYCASVGQQLP | QSVVTQPPSVSGAPGQRVTISCTGSSSNIGA GYGVHWYQHLPGSAPKLLIYGNSNRPSGVT DRISGSKSGTSASLAITGLQAEDEAVYYCQSY |
| R2F4 | WVFFAWGQGTLVTVSS SEQ ID NO. 109 | DSSLSTSVVFGGGTKLTVL SEQ ID NO. 110 |
| | EVQLVESGGGVVQPGGSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVHWYQQLPGTAPKVLIYTNNQRPSGVP DRFSGSKSGTSASLAISGLQSEDEADYYCAA WDGRLQGWVFGGGTQLTVL SEQ ID NO. |
| R2A10 | DYWGQGTLVTVSS SEQ ID NO. 111 | 112 |
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | QAGLTQPPSASGTPGQRVTISCFGSSSDIGS NTVNWYQQVSGRAPKLLLYTNGQRPSGVP DRFSGSKSGSSASLAISGLQSEDEADYYCAS WDDSLKGYVFGTGTKVTVL SEQ ID NO. |
| R2E2 | DYWGQGTLVTVSS SEQ ID NO. 113 | 114 |

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|---|---|---|
| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW | QSVLTQPPSVSAAPGQKVTISCSGSSSNIGN |
| | VRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITA | SYVSWYQHLPGTAPKLLIYDNNKRPSGIPDR |
| | DKSTSTAYMELSSLRSEDTAVYYCARVGGGAQTPFD | FSGSKSATSATLGITGLQTADEADYYCGTW |
| R3B8 | YWGQGTLVTVSS SEQ ID NO. 115 | DSSLGVVFGGGTKLTVL SEQ ID NO. 116 |
| | QVQLVQSGSEVKRPGASVRVSCKASGYIFSQYTIHW | QSALTQPASVSGSPGQSITISCTGTSSDVGG |
| | VRQAPGERLEWLGWINAVTGNTKYAQKFQGRVTIT | YNYVSWYQQHPGKAPKLMIYNVSKRPSGV |
| | MDSSASTAFMEMSSLRSEDAGVYFCARDMVPFGG | SNRFSGSKSGNTASLTISGLQAEDEADYYCS |
| R3C3 | EIKYGFDFWGQGTMITVSS SEQ ID NO. 117 | SYTSSSTFVFGTGTKVTVL SEQ ID NO. 118 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMH | SYELMQPPSVSVAPGETARITCGGNNIGSKS |
| | WVRQAPGKGLEWVALISYDGSNKYYADSMKGRFTI | VHWYQQKPGQAPILVIYYDSGRPSGIPERFS |
| | SRDNSKNTLFLQMNSLRAEDTAVYYCAKTLMPASI | GSNSGNTATLTISRAEAGDEADYYCHVWDS |
| R3E9 | MGYFTHWGQGTLVTVSS SEQ ID NO. 119 | YTDHVVFGGGTKLTVL SEQ ID NO. 120 |
| | QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMH | QPVLTQPPSLSVAPGKTASIACGGNNIGSKR |
| | WVRQAPGQGLEWMGIINPSDGSTSYAQKFQGRVT | VHWYQQKPGQAPVLVIYYESDRPSGIPERF |
| | MTRDTSTSTVYMELSSLRSEDTAVYYCARGYYGSGI | SGTISQNTATLSISRVEAGDEADYYCQVWD |
| R3E10 | AMDVWGQGTTVTVSS SEQ ID NO. 121 | RSSAHVVFGGGTKVTVL SEQ ID NO. 122 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW | AIQMTQSPSSLSASVGDRVTITCRASQSISTY |
| | VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT | LNWYQQKPGKAPKLLIYAASSLQNGVPSRF |
| | ADESTSTAYMELSSLRPEDTAVYYCARDNGDLGFDY | SGSGSGTDFTLTISSLQPEDFATYYCQQSYST |
| R3F7 | WGQGTLVTVSS SEQ ID NO. 123 | PRTFGPGTKVDIK SEQ ID NO. 124 |
| | EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMS | DIQMTQSPSSLSASVGDRVTITCQASQDISN |
| | WVRQAPGKGLEWVSVIYSGGTIYYADSVKGRFTISR | YLNWYQQKPGKAPKLLIFAGSNLQSGVPSR |
| | DSSKNTLYLHMNSLRAEDTGVYYCAKGVGSWSIFD | FSGSGSGTDFTLTITSLQPEDFATYYCQQSYT |
| R3F10 | YWGQGTLVTVSS SEQ ID NO. 125 | TPTFGQGTKVEIK SEQ ID NO. 126 |
| | EVQLVESGAELKKPGSSMKVSCKASGGTFSSYAISW | QSVVTQPASVSGSPGQSITISCTGTSSDVGS |
| | VRQAPGQGLEYIGRIIPIFGVTYYAQKFQGRVTISAD | YNLVSWYQQHPGKAPKLMIYEGSKRPSGVS |
| | KSTSTVYLDLRSLRSEDTAVYYCARDLGGGDGDWG | TRFSGSKSGNTASLTISGLQAEDESDYYCSSY |
| R4B10 | QGTLVTVSS SEQ ID NO. 127 | TGSAWVFGGGTKLTVL SEQ ID NO. 128 |
| | EVQLVQSGAEVKKPGSSVKVSCKASGYTFTGYYMH | QSVVTQPPSVSATPGQKVTISCSGSDSNIGN |
| | WVRQAPGQGLEWMGRIIPIFGTANYAQKFQGRVT | NYVSWFLQLPGTAPKLLIHNNDQRPSGVPD |
| | ITADESTSTAYMELSSLRSEDTAVYFCVTSAWSDWG | RFSGSKSGTSASLAITGLQAEDEADYYCQSF |
| R4H1 | QGTLVTVSS SEQ ID NO. 129 | DDSLRGYLFGTGTKVTVL SEQ ID NO. 130 |
| | | QAVLTQPPSVSAAPGQKVTISCSGGSSNIAN |
| | EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMS | NYVSWYQHLPGTAPKLLIYDDNKRPSGIPD |
| | WVRQAPGKGLEWVANIKQDGSEKYYVDSVKGRFTI | RFSGSKSGTSATLGITGLQTGDGADYYCGT |
| | SRDNSKNTLYLQMNSLGAEDTAVYYCAKGFYYPDH | WDNSLNSDWVFGGGTKL SEQ ID NO. |
| R4A11 | WGQGTLVTVSS SEQ ID NO. 131 | 132 |
| | EVQLVESGGGVVQPGGSLRLSCEVSGFIFSDYGMH | QSVLTQPPSVSVAPGKTARITCGGNNIGSKS |
| | WVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISR | VHWYQQKPGQAPVLVIYYDSDRPSGIPERF |
| | DNAKNSLYLQMNSLRAEDTAMYYCARSWNYGRFF | SGSNSGNTATLTISRVEAGDEADYYCQVWD |
| R3D2 | DYWDQGTLVTVSS SEQ ID NO. 133 | SSSDHYVFGTGTKLTVL SEQ ID NO. 134 |
| | EVQLVESGGGLVQPGGSLRLSCAASGFTSSRNWM | VIWMTQSPSSLSASVGDRVTITCRASQTISS |
| | HWVRLAPGKGLVWVSLIAPDGSLTTYADSVKGRFTI | YLNWYQQKPGKAPKLLIYAASSLQSGVPSRF |
| | SRDTAKNSVQLLLNSLRAEDTGLYFCAREAGVSGGL | SGSGSGTDFTLTISSLQPEDFATYYCQQANS |
| R5B8 | DVWGQGTLVTVSS SEQ ID NO. 135 | FPLTFGGGTKVEIK SEQ ID NO. 136 |
| | | QSVLTQPPSVSAAPGQKVTISCSGNNSNIA |
| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW | NNYVSWYQQLPGTAPKLLIYDNNYRPSGIP |
| | VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT | DRFSGSKSGTSATLDITGLQTGDEADYYCGV |
| | ADKSTSTAYMELSSLRSEDTAVYYCAREGTIYDSSGY | WDGSLTTGVFGGGTKLTVL SEQ ID NO. |
| SH1A1Q | SFDYWGQGTLVTVSS SEQ ID NO. 137 | 138 |

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| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVSM TRDTSTSTVYMELSSLTSEDTAVYYCARDLFPHIYGN | AIQMTQSPSSLSASVGDRVTITCRASQGISN YLAWYQQKPGKVPKLLIYAASTLESGVPSRF SGSGSGTDFTLTISSLQPEDLATYYCQQLHTF |
| SH1B7B(K) | YYGMDIWGQGTTVTVSS SEQ ID NO. 139 | PLTFGGGTKVEIK SEQ ID NO. 140 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT ADKSTSTAYMELSSLRSEDTAVYYCARLAVPGAFDI | QPVLTQPPSASGSPGQSVTISCTGTSSDVGA YNFVSWYRQHPGKAPKLMIYEVNKRPSGV PDRFSGSKSGNTASLTVSGLQAEDEADYYCS SYAGTNSLGIFGTGTKLTVL SEQ ID NO. |
| SH1C1 | WGQGTMVTVSS SEQ ID NO. 141 | 142 |
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCARGQWLVTE | QSVVTQPPSVSAAPGQKVTISCSGSSSDIGN HYVSWYQQLPGTAPKLLIYDNNQRPSGIPD RFSGSKSGTSATLAITGLQTGDEADYYCGT WDNSLSPHLLFGGGTKLTVL SEQ ID NO. |
| SH1C8 | LDYWGQGTLVTVSS SEQ ID NO. 143 | 144 |
| | EVQLVESGSEVEKPGSSVKVSCKASGGTFSDSGISW VRQAPGQGLEWMGGIIPMFATPYYAQKFQDRVTI TADESTSTVYMELSGLRSDDTAVFYCARDRGRGHLP | QSVLTQPPSVSAAPGQKVTISCSGSSSNMG NNYVSWYKQVPGTAPKLLIYENDKRPSGIP DRFSGSKSGTSATLGITGLQTGDEADYYCGT WDNSLSGFVFASGTKVTVL SEQ ID NO. |
| SH1E10 | WYFDLWGRGTLVTVSS SEQ ID NO. 145 | 146 |
| | EVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT ADESTSTAYMELSSLRSEDTAVYYCARAPYYYYYMD | QSALTQPASVSGSLGQSVTISCTGSSSDVGS YNLVSWYQQHPGKAPNLMIYDVSKRSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSS |
| SH1E2 | VWGQGTTVTVSS SEQ ID NO. 147 | YTGISTVVFGGGTKLTVL SEQ ID NO. 148 |
| | EVQLLESGAEVKKPGSSVKVSCKASGGTLSRYALSW VRQAPGQGPEWVGAIIPIFGTPHYSKKFQDRVIITV DTSTNTAFMELSSLRFEDTALYFCARGHDEYDISGYH | QSVLTQPASVSGSPGQSITISCTGTSSDVGSY NLVSWYQQHPGKAPKLMIYEVSKRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSS |
| SH1A9 | RLDYWGQGTLVTVSS SEQ ID NO. 149 | YGGFNNLLFGGGTKLTVL SEQ ID NO. 150 |
| | QVQLVQSGSELKKPGSSVKVSCKASGYSFSGYYIHW VRQAPGQGLEWMGWIDPNSGVTNYVRRFQGRVT MTRDTSLSTAYMELSGLTADDTAVYYCARDENLWQ | DIVMTQSPSSLSASIGDRVTITCRASQRISAY VNWYQQKPGKAPKVLIYAASSLRSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQTYSS |
| SH1B11 | FGYLDYWGQGTLVTVSS SEQ ID NO. 151 | PWTFGQGTKVEIK SEQ ID NO. 152 |
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSRYGVH WVRQAPGQGLEWMGRLIPIVSMTNYAQKFQDRV SITTDKSTGTAYMELRSLTSEDTALYYCASVGQQLP | QSVLTQPPSASGSPGQSVTISCTGTSSDIGG YDSVSWYQQHPGKAPKLMIYDVSKRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSIFFYVFGTGTKVTVL SEQ ID NO. |
| SH1E4 | WVFFAWGQGTLVTVSS SEQ ID NO. 153 | 154 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | LPVLTQPASVSGSPGQSITISCTGTTSDIGGY DYVSWYQQHPGKAPKLMIYDVSKRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSS |
| SH1B3 | DYWGQGTLVTVSS SEQ ID NO. 155 | YTSSSTHVFGTGTKLTVL SEQ ID NO. 156 |
| | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCS SYRSSTLGPVFGGGTKLTVL SEQ ID NO. |
| SH1D1 | DYWGQGTLVTVSS SEQ ID NO. 157 | 158 |
| | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI | QAGLTQPPSVSEAPRQRVTISCSGSSSNIGN NAVNWYQQLPGKAPKLLIYYDDLLPSGVSD RFSGSKSGTSASLAISGLQSEDEADYYCAAW |
| SH1D2 | DYWGQGTLVTVSS SEQ ID NO. 159 | DDSLNGYVFGTGTKLTVL SEQ ID NO. 160 |

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| SH1D12 | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI DYWGQGTLVTVSS SEQ ID NO. 161 | QSALTQPRSVSGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSTTHVFGTGTKVTVL SEQ ID NO. 162 |
| SH1E1 | EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI DYWGQGTLVTVSS SEQ ID NO. 163 | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGN NYVSWYQQLPGTAPKLLIYDNNKRPSGIPD RFSGSKSGTSATLGITGLQTGDEADYYCGT WDSSLSVWVFGGGTQLTVL SEQ ID NO. 164 |
| SH1G9 | QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMH WVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTI SRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDI DYWGQGTLVTVSS SEQ ID NO. 165 | QSVLTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGRAPRLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEGDYYCS SYTSGGTLGPVFGGGTKLTVL SEQ ID NO. 166 |
| SH1A11 | EVQLVQSGGGLVQPGGSLRLSCAASGFTFSDYGMH WVRQPPGKGLEWLAVISYDGSYKIHADSVQGRFTIS RDNAKNSVFLQMNSLKTEDTAVYYCTTDRKWLAW HGMDVWGQGTTVTVSS SEQ ID NO. 167 | QAGLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYSNNQRPSGVP DRFSGSKSGTSASLAISGLQSEDEADYYCAA WDDSLNGWVFGGGTKLTVL SEQ ID NO. 168 |
| SH1C2 | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISW VRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTIT ADESTSTAYMELSSLRSEDTAVYYCARDGIVADFQH WGQGTLVTVSS SEQ ID NO. 169 | AIRMTQSPSSLSASVGDRVTITCRASQSISNY LNWYQQRPGKAPNLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQTYST PYTFGQGTKLEIK SEQ ID NO. 170 |
| SH1G8 | EVQLVESGAEVKKPGASVKVSCKASGDTFSRYGITW VRQAPGRGLEWMGNIVPFFGATNYAQKFQGRLTIT ADKSSYTSYMDLSSLRSDDTAVYYCARDHFYGSGGY FDYWGQGTLVTVSS SEQ ID NO. 171 | QSVLTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYRQHPGKAPKLMIYDVSYRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSS YTDSSTRYVFGTGTKLTVL SEQ ID NO. 172 |
| SH1H2 | EVQLLESGAEVKKPGASVKVSCKASGYTFNSYDINW VRQAPGQGLEWMGGIIPVFGTANYAESFQGRVTM TADHSTSTAYMELNNLRSEDTAVYYCARDRWHYES RPMDVWGQGTTVTVSS SEQ ID NO. 173 | QPVLTQPPSASGTPGQRVAISCSGSRSNIEI NSVNWYQQLPGTAPKLLIYDNNKRPSGIPD RFSGSKSGTSATLGITGLQTGDEADYYCGS WDSSLSADVFGTGTKLTVL SEQ ID NO. 174 |
| SH1B10 | EVQLVESGGGLVRPGGSLRLACAASGFSFSDYYMT WIRQAPGRGLEWIAYISDSGQTVHYADSVKGRFTIS RDNTKNSLFLQVNTLRAEDTAVYYCAREDLLGYYLQ SWGQGTLVTVSS SEQ ID NO. 175 | QSVLTQPPSVSAAPGKKVTISCSGSSSNIGN NYVSWYQQLPGTAPKLLIYRNNQRPSGVPD RFSGSKSGTSASLAISGLQSEDEADYYCATW DDSLNGWVFGGGTKLTVL SEQ ID NO. 176 |
| SH1B7A(L) | QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAA WNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKS RITINPDTSKNQFSLQLNSVTPEDTAVYYCARDEPRA VAGSQAYYYYGMDVWGQGTTVTVSS SEQ ID NO. 177 | QSVVTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNNNRHSGV PDRFSGSKSGTSASLAITGLQAEDEAEFFCG TWDSRLTTYVFGSGTKLTVL SEQ ID NO. 178 |
| SH1E6 | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSRYGVH WVRQAPGQGLEWMGRLIPIVSMTNYAQKFQDRV SITTDKSTGTAYMELRSLTSEDTALYYCASVGQQLP WVFFAWGQGTLVTVSS SEQ ID NO. 179 | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGN NYVSWYQQLPGTAPKLLIYDNNKRPSGIPD RFSGSKSGTSATLGITGLQTGDEADYYCGT WDSSLSAVVFGGGTKLTVL SEQ ID NO. 180 |
| SH1C11 | EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMH WVRQAPGQGLEWMGIINPSDGSTSYAQKFQGRVT MTRDTSTSTVHMELSSLRSEDTAVYYCARDLFPHIY GNYYGMDIWGQGTTVTVSS SEQ ID NO. 181 | VIWMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYEASTLESGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQSYST PYTFGQGTKLEIK SEQ ID NO. 182 |

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| SH1A2 | QMQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTISRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDIDYWGQGTLVTVSS SEQ ID NO. 183 | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQVPGTAPKLLIYDNNKRPSGIPDRFSGSNSDTSATLGITGLQTGDEADYYCGTWDSSLSAWVFGGGTKLTVL SEQ ID NO. 184 |
| SH1B1 | QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISFDGSNKYYADSVRGRFTISRDNSKNTLYLQMNSLRTEDTAVYYCARGWLDRDIDYWGQGTLVTVSS SEQ ID NO. 185 | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAGSVVFGGGTKLTVL SEQ ID NO. 186 |
| R6B2 | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDGIVADFQHWGQGTLVTVSS SEQ ID NO. 187 | QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNFVSWYQQNPGKAPKLMIYDVSKRPSGVPDRFSGSKSGNTASLTVSGLRAEDEADYYCASYAGGRTFVFGGGTKVTVL SEQ ID NO. 188 |
| R6B7 | QMQLVQSGAEVKKPGSSVKVSCKASGGTFNSYPISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAMYYCAKNHPTATLDYWGQGTLVTVSS SEQ ID NO. 189 | QSVLTQSPSSFSASTGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISCLQSEDFATYYCQQYYSYPLTFGGGTKVTVL SEQ ID NO. 190 |
| R6B11 | QVQLVQSGGGVVQPGRSLRLSCAASGFPFRSYDMHWVRQAPGEGLEWVALISSDGSNKYYLDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLLPYSSSWDYYYYYGMDVWGQGTTVTVSS SEQ ID NO. 191 | LPVLTQPASVSASAGQSIAISCTGISSDIGDYNSVSWYQRHPGKAPKLIIYDVSSRPSGVADRFSGSKSGSTASLSISGLQAEDEADYYCASYTASDNPVFGGGTKLTVL SEQ ID NO. 192 |
| R6D1 | EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS SEQ ID NO. 193 | SYELMQPPSVSVAPGKTATIACGGENIGRKTVHWYQQKPGQAPVLVIYYDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHRIFGGGTKLTVL SEQ ID NO. 194 |
| R6C8 | EVQLVESGGGLVKPGGSRKLSCAASGFTFSNYGMHWVRQAPEKGLEWVAYISSGSSTIYYADTVKGRFTISRDNAKNTLFLQMTSLRSEDTAMYYCARRGLLLDYWGQGTTLTVSS SEQ ID NO. 195 | QSVLTQPPSVSAAPGQEVTISCSGSNSNIGNNYVSWYQQLPGTAPKLLIYDNNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAGVFGGGTKLTVL SEQ ID NO. 196 |
| R9G8 | EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDLFPTIFWEGGAFDIWGQGTMVTVSS SEQ ID NO. 197 | QSVLTQPPSVSAAPGQEVTISCSGSNSNIGNNYVSWYQQLPGTAPKLLIYDNNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAGVFGGGTKLTVL SEQ ID NO. 198 |
| R7D1 | QVQLVQSGSEVEKPGSSVKVSCKASGGTFSDSGISWVRQAPGQGLEWMGGIIPMFATPYYAQKFQDRVTITADESTSTVYMELSGLRSDDTAVFYCARDRGRGHLPWYFDLWGRGTLVTVSS SEQ ID NO. 199 | QSVLTQPPSVSAAPGQEVTISCSGSNSNIGNNYVSWYQQLPGTAPKLLIYDNNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAGVFGGGTKLTVL SEQ ID NO. 200 |
| R7D2 | QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDGIVADFQHWGQGTLVTVSS SEQ ID NO. 201 | AIRMTQSPSSLSASVGDRVTITCRASQSISNYLNWYQQRPGKAPNLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYSTPYTFGQGTKLEIK SEQ ID NO. 202 |
| R7E7 | EVQLLESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGIADYAQKFQGRVTITADKFTSTAYMELSSLRSEDTAVYYCATVEGWGAVTTFDYWGQGTLVTVSS SEQ ID NO. 203 | QSVLTQPPSVSAAPGQEVTISCSGSNSNIGNNYVSWYQQLPGTAPKLLIYDNNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAGVFGGGTKLTVL SEQ ID NO. 204 |

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|---|---|---|
| | QVQLVQSGAEVKKPGSSVKVSCKASGGTLSSYAISW | QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA |
| | VRQVPGHGLEWMGRIISMLGVSNYAQNFQGRVTI | GYDVYWYQHLLGKAPKLLIYGNSNRPSGVS |
| | TADKSTSTAYMELRSLTSDDTAVYYCATVTIFDGDYY | DRFSASKSGTSVSLAITGLQAEDEADYYCQS |
| R7F2 | AMDVWGQGTTVTVSS SEQ ID NO. 205 | YDSSLSGYVFGTGTKLTVL SEQ ID NO. 206 |
| | EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSHVISW | QPVLTQPASVSGSPGQSITISCTGTSSDVGS |
| | VRQAPGQGLEWMGIILPSFGKTNYAQKFQGRVTM | YNLVSWYQQHPGKAPKLMIYEVSKRPSGVS |
| | TGDTSTSTVYMELSSLTSEDTAVYYCVREFSGGYFDY | NRFSGSKSGNTASLTISGLQAEDEADYYCNT |
| R7F7 | WGQGTLVTVSS SEQ ID NO. 207 | YTSSGTYVIGTGTKVTVL SEQ ID NO. 208 |
| | QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVIH | QPVLTQPASVSGSPGQSITISCTGTSSDIGRY |
| | WVRQAPGQRLEWMGWIHAGNGHTKYAQNFQGR | NYVSWYQQHPGKAPKVMIYDVSNRPSGVS |
| | VTITRDTSATTAYVEVSSLGSEDTALYYCAREGSDIGL | NRFSGSKSGNTASLTISGLQAEDEADYYCSS |
| R9H2 | DLHYWGQGTLVTVSS SEQ ID NO. 209 | YTSSSTWVFGGGTKLTVL SEQ ID NO. 210 |
| | EVQLVQSGGGVVQPGRSLRLSCEASGFTFRNFAMH | QSVVTQPPSVSAAPGQKVTISCSGSSSNIGN |
| | WVRQAPGKGLEWAAVISVDGSREHYADSVKGRFTI | NYVSWYQQLPGTAPKILIYDNDKRPSGIPDR |
| | SRDNSQNTVYLQMNGLRPEDTAEYYCAREGEGST | FSGSKSGTSATLGITGLQTGDEADYYCGTW |
| R9H6 | WSSFDYWGQGTLVTVSS SEQ ID NO. 211 | DRSLSGYVFGTGTKVTVL SEQ ID NO. 212 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAYS | SYELMQPPSVSVAPGKTATIACGGENIGRKT |
| | WVRQAPGQGLEWMGGIIPSFGTANYAQKFQGRV | VHWYQQKPGQAPVLVIYYDSDRPSGIPERF |
| | TITADESTSTAYMELSSLRSEDTAVYYCARGPIVATIT | SGSNSGNTATLTISRVEAGDEADYYCLVWD |
| H6B1L | PLDYWGQGTLVTVSS SEQ ID NO. 213 | SSSDHRIFGGGTKLTVL SEQ ID NO. 214 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAYS | SYELMQPPSVSVAPGKTATIACGGENIGRKT |
| | WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVT | VHWYQQKPGQAPVLVIYYDSDRPSGIPERF |
| | ITADESTSTAYMELSSLRSEDTAVYYCARGPIVATITP | SGSNSGNTATLTISRVEAGDEADYYCQVWD |
| H6A1 | LDYWGQGTLVTVSS SEQ ID NO. 215 | SSSDHRIFGGGTKLTVL SEQ ID NO. 216 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAYS | SYELMQPPSVSVAPGKTATIACGGENIGRKT |
| | WVRQAPGQGLEWMGGIIPSFGTANYAQKFQGRV | VHWYQQKPGQAPVLVIYYDSDRPSGIPERF |
| | TITADESTSTAYMELSSLRSEDTAVYYCARGPIVATIT | SGSNSGNTATLTISRVEAGDEADYYCQVWD |
| H6B1 | PLDYWGQGTLVTVSS SEQ ID NO. 217 | SSSDHRIFGGGTKLTVL SEQ ID NO. 218 |
| | QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS | SYELMQPPSVSVAPGKTATIACGGENIGRKT |
| | WVRQAPGQGLEWMGGIIPAFGTANYAQKFQGRV | VHWYQQKPGQAPVLVIYYDSDRPSGIPERF |
| | TITADESTSTAYMELSSLRSEDTAVYYCARGPIVATIT | SGSNSGNTATLTISRVEAGDEADYYCQVWD |
| H6B2 | PLDYWGQGTLVTVSS SEQ ID NO. 219 | SSSDHRIFGGGTKLTVL SEQ ID NO. 220 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGNTFTNYALH | DIVMTQSPPSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGGMKPSGGSTSIAQKFQGR | LNWYQQKPGKAPKLLIYATSSLQYGVPSRFS |
| | VTMTRDKSTSTVYMELSSLTSEDTAVYYCARDLFPHI | GSGSGTDFTLTISSLQPEDFATYYCQGSYSTP |
| H19C | FGNYYGMDIWGQGTTVTVSS SEQ ID NO. 221 | YTFGQGTKVEIK SEQ ID NO. 222 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGNTFTNYYMH | DIVMTQSPPSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGSMQPSGGSTSLAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VTMTRDKSTSTVYMELSSLTSEDTAVYYCARDLFPHI | GSGSGTDFTLTISSLQPEDFATYYCQGSYSTP |
| H110D | LGNYYGMDIWGQGTTVTVSS SEQ ID NO. 223 | YTFGQGTKVEIK SEQ ID NO. 224 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGNTFTNYPM | DIVMTQSPPSLSASVGDRVTITCRASQSISSY |
| | HWVRQAPGQGLEWMGSMKPSGGSTSLAPKFQGR | LNWYQQKPGKAPKLLIYAASSLQYGVPSRFS |
| | VTMTRDKSTSTVYMELSSLTSEDTAVYYCARDLFPHI | GSGSGTDFTLTISSLQPEDFATYYCQGSYSTP |
| H11F | IGNYYGMDIWGQGTTVTVSS SEQ ID NO. 225 | YTFGQGTKVEIK SEQ ID NO. 226 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGNTFTNYSMH | DIVMTQSPPSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGIMNPSGGSTSYAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VTMTRDKSTSTVYMELSSLTSEDTAVYYCARDLFPHI | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| H1C1 | YGNYYGMDIWGQGTTVTVSS SEQ ID NO. 227 | YTFGQGTKVEIK SEQ ID NO. 228 |
| | EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSF |
| | WVRQAPGQGLEWMGWINPNSDNTGSAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| GPG1A2 | FDFWGQGTLVTVSS SEQ ID NO. 229 | ITFGQGTKVEIK SEQ ID NO. 230 |

| | | |
|---|---|---|
| | QVQLVQSGAEVKKLGASVKVSCKASGYPFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRATPSTSSY |
| | WVRQAPGQGLEWMGWINPNGDNTGLAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| GPGG8 | FDFWGQGTLVTVSS SEQ ID NO. 231 | ITFGQGTKLEIK SEQ ID NO. 232 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGYPFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSY |
| | WVRQAPGQGLEWMGWINPLSDTTGSAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| GPGG10 | FDFWGQGTLVTVSS SEQ ID NO. 233 | ITFGQGTKLEIK SEQ ID NO. 234 |
| | QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSF |
| | WVRQAPGQGLEWMGWINPLSDNTGSAQKFQGR | LNWYQQKPGKAPKLLIYLASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| GPGH7 | FDFWGQGTLVTVSS SEQ ID NO. 235 | ITFGQGTKVEIK SEQ ID NO. 236 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSF |
| | WVRQAPGQGLEWMGWINPNSDNTGYAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQAYST |
| GPGH10 | FDFWGQGTLVTVSS SEQ ID NO. 237 | PITFGQGTKVEIK SEQ ID NO. 238 |
| | QVQLVQSGAEVKKPGASVKVSCKASGYPFTGYYMH | |
| | WVRQAPGQGLEWMGWINPLSDSTGSAQKFQGRV | DIVMTQSPSSLSASVGDRVTITCRASQSISSY |
| | FMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGYF | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | DFWGQGTLVTVSS SEQ ID NO. 2 SEQ ID NO. | GSGSGTDFTLTISSLQPEDFATYYCQQSYSTP |
| GPGH11 | 239 | ITFGQGTKLEIK SEQ ID NO. 240 |
| | QVQLVQSGAEVKKPGASVKVSCKTSGYTFTGYYMH | DIVMTQSPSSLSASVGDRVTITCRASQSISSF |
| | WVRQAPGQGLEWMGWINPNSDNTGYAQKFQGR | LNWYQQKPGKAPKLLIYAASSLQSGVPSRFS |
| | VFMTKTTSLNTAYMELSGLRSEDTAIYYCARERSSGY | GSGSGTDFTLTISSLQPEDFATYYCQQPYSTP |
| GPGH10P | FDFWGQGTLVTVSS SEQ ID NO. 241 | ITFGQGTKVEIK SEQ ID NO. 242 |

We claim:

1. A fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least $10^{-6}$M, that has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56,

SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof.

2. The fully human antibody of claim 1, wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called E6 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called E7 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called E9 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called E11 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called F1 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called F4 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called F7 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called F8 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called F11 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called G4 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called G9 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called G11 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called G12 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called H1 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called H3 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called H4 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called H5 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called H6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called H10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called H12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called PDL-D2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called PDL-D11 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called PDL-H1 herein),

SEQ ID NO. 47/SEQ ID NO. 48 (called RB4 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called RB11 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called RC5 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called RF5 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called RG9 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called RD1 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called RF11 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called RH11 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called RD9 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called RE10 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called RA3 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called RG1 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called RB1 herein), SEQ ID NO. 73/SEQ ID NO. 74 (called RG7 herein), SEQ ID NO. 75/SEQ ID NO. 76 (called RA6 herein), SEQ ID NO. 77/SEQ ID NO. 78 (called RA8 herein), SEQ ID NO. 79/SEQ ID NO. 80 (called RA9 herein), SEQ ID NO. 81/SEQ ID NO. 82 (called RB5 herein), SEQ ID NO. 83/SEQ ID NO. 84 (called RB8 herein), SEQ ID NO. 85/SEQ ID NO. 86 (called RC8 herein), SEQ ID NO. 87/SEQ ID NO. 88 (called RC10 herein), SEQ ID NO. 89/SEQ ID NO. 90 (called RD2 herein), SEQ ID NO. 91/SEQ ID NO. 92 (called RE8 herein), SEQ ID NO. 93/SEQ ID NO. 94 (called RE9 herein), SEQ ID NO. 95/SEQ ID NO. 96 (called RG12 herein), SEQ ID NO. 97/SEQ ID NO. 98 (called RSA1 herein), SEQ ID NO. 99/SEQ ID NO. 100 (called R2A7 herein), SEQ ID NO. 101/SEQ ID NO. 102 (called R2B12 herein), SEQ ID NO. 103/SEQ ID NO. 104 (called R2C9 herein), SEQ ID NO. 105/SEQ ID NO. 106 (called R2D5 herein), SEQ ID NO. 107/SEQ ID NO. 108 (called R2D7 herein), SEQ ID NO. 109/SEQ ID NO. 110 (called R2F4 herein), SEQ ID NO. 111/SEQ ID NO. 112 (called R2A10 herein), SEQ ID NO. 113/SEQ ID NO. 114 (called R2E2 herein), SEQ ID NO. 115/SEQ ID NO. 116 (called R3B8 herein), SEQ ID NO. 117/SEQ ID NO. 118 (called R3C3 herein), SEQ ID NO. 119/SEQ ID NO. 120 (called R3E9 herein), SEQ ID NO. 121/SEQ ID NO. 122 (called R3E10 herein), SEQ ID NO. 123/SEQ ID NO. 124 (called R3F7 herein), SEQ ID NO. 125/SEQ ID NO. 126 (called R3F10 herein), SEQ ID NO. 127/SEQ ID NO. 128 (called R4B10 herein), SEQ ID NO. 129/SEQ ID NO. 130 (called R4H1 herein), SEQ ID NO. 131/SEQ ID NO. 132 (called R4A11 herein), SEQ ID NO. 133/SEQ ID NO. 134 (called R3D2 herein), SEQ ID NO. 135/SEQ ID NO. 136 (called R5B8 herein), SEQ ID NO. 137/SEQ ID NO. 138 (called SH1A1Q herein), SEQ ID NO. 139/SEQ ID NO. 140 (called SH1B7B(K) herein), SEQ ID NO. 141/SEQ ID NO. 142 (called SH1C1 herein), SEQ ID NO. 143/SEQ ID NO. 144 (called SH1C8 herein), SEQ ID NO. 145/SEQ ID NO. 146 (called SH1E10 herein), SEQ ID NO. 147/SEQ ID NO. 148 (called SH1E2 herein), SEQ ID NO. 149/SEQ ID NO. 150 (called SH1A9 herein), SEQ ID NO. 151/SEQ ID NO. 152 (called SH1B11 herein), SEQ ID NO. 153/SEQ ID NO. 154 (called SH1E4 herein), SEQ ID NO. 155/SEQ ID NO. 156 (called SH1B3 herein), SEQ ID NO. 157/SEQ ID NO. 158 (called

SH1D1 herein), SEQ ID NO. 159/SEQ ID NO. 160 (called SH1D2 herein), SEQ ID NO. 161/SEQ ID NO. 162 (called SH1D12 herein), SEQ ID NO. 163/SEQ ID NO. 164 (called SH1E1 herein), SEQ ID NO. 165/SEQ ID NO. 166 (called SH1G9 herein), SEQ ID NO. 167/SEQ ID NO. 168 (called SH1A11 herein), SEQ ID NO. 169/SEQ ID NO. 170 (called SH1C2 herein), SEQ ID NO. 171/SEQ ID NO. 172 (called SH1G8 herein), SEQ ID NO. 173/SEQ ID NO. 174 (called SH1H2 herein), SEQ ID NO. 175/SEQ ID NO. 176 (called SH1B10 herein), SEQ ID NO. 177/SEQ ID NO. 178 (called SH1B7A(L) herein), SEQ ID NO. 179/SEQ ID NO. 180 (called SH1E6 herein), SEQ ID NO. 181/SEQ ID NO. 182 (called SH1C11 herein), SEQ ID NO. 183/SEQ ID NO. 184 (called SH1A2 herein), SEQ ID NO. 185/SEQ ID NO. 186 (called SH1B1 herein), SEQ ID NO. 187/SEQ ID NO. 188 (called R6B2 herein), SEQ ID NO. 189/SEQ ID NO. 190 (called R6B7 herein), SEQ ID NO. 191/SEQ ID NO. 192 (called R6B11 herein), SEQ ID NO. 193/SEQ ID NO. 194 (called R6D1 herein), SEQ ID NO. 195/SEQ ID NO. 196 (called R6C8 herein), SEQ ID NO. 197/SEQ ID NO. 198 (called R9G8 herein), SEQ ID NO. 199/SEQ ID NO. 200 (called R7D1 herein), SEQ ID NO. 201/SEQ ID NO. 202 (called R7D2 herein), SEQ ID NO. 203/SEQ ID NO. 204 (called R7E7 herein), SEQ ID NO. 205/SEQ ID NO. 206 (called R7F2 herein), SEQ ID NO. 207/SEQ ID NO. 208 (called R7F7 herein), SEQ ID NO. 209/SEQ ID NO. 210 (called R9H2 herein), SEQ ID NO. 211/SEQ ID NO. 212 (called R9H6 herein), SEQ ID NO. 213/SEQ ID NO. 214 (called H6B1L herein), SEQ ID NO. 215/SEQ ID NO. 216 (called H6A1 herein), SEQ ID NO. 217/SEQ ID NO. 218 (called H6B1 herein), SEQ ID NO. 219/SEQ ID NO. 220 (called H6B2 herein), SEQ ID NO. 221/SEQ ID NO. 222 (called H19C herein), SEQ ID NO. 223/SEQ ID NO. 224 (called H110D herein), SEQ ID NO. 225/SEQ ID NO. 226 (called H11F herein), SEQ ID NO. 227/SEQ ID NO. 228 (called H1C1 herein), SEQ ID NO. 229/SEQ ID NO. 230 (called GPG1A2 herein), SEQ ID NO. 231/SEQ ID NO. 232 (called GPGG8 herein), SEQ ID NO. 233/SEQ ID NO. 234 (called GPGG10 herein), SEQ ID NO. 235/SEQ ID NO. 236 (called GPGH7 herein), SEQ ID NO. 237/SEQ ID NO. 238 (called GPGH10 herein), SEQ ID NO. 239/SEQ ID NO. 240 (called GPGH11 herein), SEQ ID NO. 241/SEQ ID NO. 242 (called GPGH10P herein), and combinations thereof.

3. A Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID

NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126,

SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof.

4. The fully human antibody Fab fragment of claim 3, wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110,

SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

5. A single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID

NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136,

SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof.

6. The fully human single chain antibody of claim 5, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114,

SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

7. The fully human single chain antibody of claim 5, wherein the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO.

30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO. 178, SEQ ID NO. 179/SEQ ID NO. 180, SEQ ID NO. 181/SEQ ID NO. 182, SEQ ID NO. 183/SEQ ID NO. 184, SEQ ID NO. 185/SEQ ID NO. 186, SEQ ID NO. 187/SEQ ID NO. 188, SEQ ID NO. 189/SEQ ID NO. 190, SEQ ID NO. 191/SEQ ID NO. 192, SEQ ID NO. 193/SEQ ID NO. 194, SEQ ID NO. 195/SEQ ID NO. 196, SEQ ID NO. 197/SEQ ID NO. 198, SEQ ID NO. 199/SEQ ID NO. 200, SEQ ID NO. 201/SEQ ID NO. 202, SEQ ID NO. 203/SEQ ID NO. 204, SEQ ID NO. 205/SEQ ID NO. 206, SEQ ID NO. 207/SEQ ID NO. 208, SEQ ID NO. 209/SEQ ID NO. 210, SEQ ID

NO. 211/SEQ ID NO. 212, SEQ ID NO. 213/SEQ ID NO. 214, SEQ ID NO. 215/SEQ ID NO. 216, SEQ ID NO. 217/SEQ ID NO. 218, SEQ ID NO. 219/SEQ ID NO. 220, SEQ ID NO. 221/SEQ ID NO. 222, SEQ ID NO. 223/SEQ ID NO. 224, SEQ ID NO. 225/SEQ ID NO. 226, SEQ ID NO. 227/SEQ ID NO. 228, SEQ ID NO. 229/SEQ ID NO. 230, SEQ ID NO. 231/SEQ ID NO. 232, SEQ ID NO. 233/SEQ ID NO. 234, SEQ ID NO. 235/SEQ ID NO. 236, SEQ ID NO. 237/SEQ ID NO. 238, SEQ ID NO. 239/SEQ ID NO. 240, SEQ ID NO. 241/SEQ ID NO. 242, and combinations thereof.

8. A method for treating a broad spectrum of mammalian cancers or treating inflammatory diseases or autoimmune diseases, comprising administering an effective amount of an anti-PD-L1 polypeptide, wherein the anti-PD-L1 polypeptide is selected from the group consisting of a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least $10^{-6}$ M, a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, and combinations thereof;

wherein the fully human antibody has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID

NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof;

wherein the Fab fully human antibody fragment has the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169, SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90,

SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof; and

wherein the single chain human antibody has the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 73, SEQ ID NO. 75, SEQ ID NO. 77, SEQ ID NO. 79, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, SEQ ID NO. 95, SEQ ID NO. 97, SEQ ID NO. 99, SEQ ID NO. 101, SEQ ID NO. 103, SEQ ID NO. 105, SEQ ID NO. 107, SEQ ID NO. 109, SEQ ID NO. 111, SEQ ID NO. 113, SEQ ID NO. 115, SEQ ID NO. 117, SEQ ID NO. 119, SEQ ID NO. 121, SEQ ID NO. 123, SEQ ID NO. 125, SEQ ID NO. 127, SEQ ID NO. 129, SEQ ID NO. 131, SEQ ID NO. 133, SEQ ID NO. 135, SEQ ID NO. 137, SEQ ID NO. 139, SEQ ID NO. 141, SEQ ID NO. 143, SEQ ID NO. 145, SEQ ID NO. 147, SEQ ID NO. 149, SEQ ID NO. 151, SEQ ID NO. 153, SEQ ID NO. 155, SEQ ID NO. 157, SEQ ID NO. 159, SEQ ID NO. 161, SEQ ID NO. 163, SEQ ID NO. 165, SEQ ID NO. 167, SEQ ID NO. 169,

SEQ ID NO. 171, SEQ ID NO. 173, SEQ ID NO. 175, SEQ ID NO. 177, SEQ ID NO. 179, SEQ ID NO. 181, SEQ ID NO. 183, SEQ ID NO. 185, SEQ ID NO. 187, SEQ ID NO. 189, SEQ ID NO. 191, SEQ ID NO. 193, SEQ ID NO. 195, SEQ ID NO. 197, SEQ ID NO. 199, SEQ ID NO. 201, SEQ ID NO. 203, SEQ ID NO. 205, SEQ ID NO. 207, SEQ ID NO. 209, SEQ ID NO. 211, SEQ ID NO. 213, SEQ ID NO. 215, SEQ ID NO. 217, SEQ ID NO. 219, SEQ ID NO. 221, SEQ ID NO. 223, SEQ ID NO. 225, SEQ ID NO. 227, SEQ ID NO. 229, SEQ ID NO. 231, SEQ ID NO. 233, SEQ ID NO. 235, SEQ ID NO. 237, SEQ ID NO. 239, SEQ ID NO. 241, and combinations thereof, and that has the light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 74, SEQ ID NO. 76, SEQ ID NO. 78, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, SEQ ID NO. 94, SEQ ID NO. 96, SEQ ID NO. 98, SEQ ID NO. 100, SEQ ID NO. 102, SEQ ID NO. 104, SEQ ID NO. 106, SEQ ID NO. 108, SEQ ID NO. 110, SEQ ID NO. 112, SEQ ID NO. 114, SEQ ID NO. 116, SEQ ID NO. 118, SEQ ID NO. 120, SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 126, SEQ ID NO. 128, SEQ ID NO. 130, SEQ ID NO. 132, SEQ ID NO. 134, SEQ ID NO. 136, SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 152, SEQ ID NO. 154, SEQ ID NO. 156, SEQ ID NO. 158, SEQ ID NO. 160, SEQ ID NO. 162, SEQ ID NO. 164, SEQ ID NO. 166, SEQ ID NO. 168, SEQ ID NO. 170, SEQ ID NO. 172, SEQ ID NO. 174, SEQ ID NO. 176, SEQ ID NO. 178, SEQ ID NO. 180, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202, SEQ ID NO. 204, SEQ ID NO. 206, SEQ ID NO. 208, SEQ ID NO. 210, SEQ ID NO. 212, SEQ ID NO. 214, SEQ ID NO. 216, SEQ ID NO. 218, SEQ ID NO. 220, SEQ ID NO. 222, SEQ ID NO. 224, SEQ ID NO. 226, SEQ ID NO. 228, SEQ ID NO. 230, SEQ ID NO. 232, SEQ ID NO. 234, SEQ ID NO. 236, SEQ ID NO. 238, SEQ ID NO. 240, SEQ ID NO. 242, and combinations thereof.

9. The method for treating a broad spectrum of mammalian cancers of claim 8, wherein the fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170,

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10. The method for treating a broad spectrum of mammalian cancers of claim 8, wherein the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO.

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11. The method for treating a broad spectrum of mammalian cancers of claim 8, wherein the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a

heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 73/SEQ ID NO. 74, SEQ ID NO. 75/SEQ ID NO. 76, SEQ ID NO. 77/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 80, SEQ ID NO. 81/SEQ ID NO. 82, SEQ ID NO. 83/SEQ ID NO. 84, SEQ ID NO. 85/SEQ ID NO. 86, SEQ ID NO. 87/SEQ ID NO. 88, SEQ ID NO. 89/SEQ ID NO. 90, SEQ ID NO. 91/SEQ ID NO. 92, SEQ ID NO. 93/SEQ ID NO. 94, SEQ ID NO. 95/SEQ ID NO. 96, SEQ ID NO. 97/SEQ ID NO. 98, SEQ ID NO. 99/SEQ ID NO. 100, SEQ ID NO. 101/SEQ ID NO. 102, SEQ ID NO. 103/SEQ ID NO. 104, SEQ ID NO. 105/SEQ ID NO. 106, SEQ ID NO. 107/SEQ ID NO. 108, SEQ ID NO. 109/SEQ ID NO. 110, SEQ ID NO. 111/SEQ ID NO. 112, SEQ ID NO. 113/SEQ ID NO. 114, SEQ ID NO. 115/SEQ ID NO. 116, SEQ ID NO. 117/SEQ ID NO. 118, SEQ ID NO. 119/SEQ ID NO. 120, SEQ ID NO. 121/SEQ ID NO. 122, SEQ ID NO. 123/SEQ ID NO. 124, SEQ ID NO. 125/SEQ ID NO. 126, SEQ ID NO. 127/SEQ ID NO. 128, SEQ ID NO. 129/SEQ ID NO. 130, SEQ ID NO. 131/SEQ ID NO. 132, SEQ ID NO. 133/SEQ ID NO. 134, SEQ ID NO. 135/SEQ ID NO. 136, SEQ ID NO. 137/SEQ ID NO. 138, SEQ ID NO. 139/SEQ ID NO. 140, SEQ ID NO. 141/SEQ ID NO. 142, SEQ ID NO. 143/SEQ ID NO. 144, SEQ ID NO. 145/SEQ ID NO. 146, SEQ ID NO. 147/SEQ ID NO. 148, SEQ ID NO. 149/SEQ ID NO. 150, SEQ ID NO. 151/SEQ ID NO. 152, SEQ ID NO. 153/SEQ ID NO. 154, SEQ ID NO. 155/SEQ ID NO. 156, SEQ ID NO. 157/SEQ ID NO. 158, SEQ ID NO. 159/SEQ ID NO. 160, SEQ ID NO. 161/SEQ ID NO. 162, SEQ ID NO. 163/SEQ ID NO. 164, SEQ ID NO. 165/SEQ ID NO. 166, SEQ ID NO. 167/SEQ ID NO. 168, SEQ ID NO. 169/SEQ ID NO. 170, SEQ ID NO. 171/SEQ ID NO. 172, SEQ ID NO. 173/SEQ ID NO. 174, SEQ ID NO. 175/SEQ ID NO. 176, SEQ ID NO. 177/SEQ ID NO.

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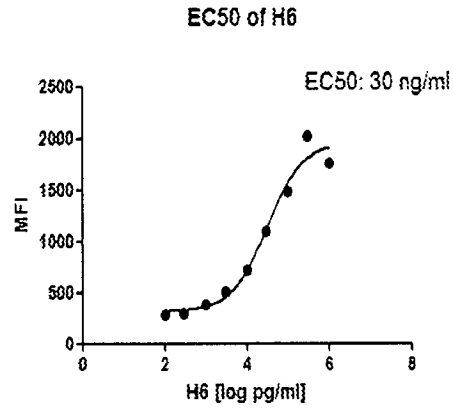
12. The method for treating a broad spectrum of mammalian cancers or inflammatory diseases or autoimmune diseases of claim 8, wherein the broad spectrum of mammalian cancers to be treated is selected from the group consisting of ovarian, colon, breast, lung cancers, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, and combinations thereof.

13. The method for treating a broad spectrum of mammalian cancers or inflammatory diseases or autoimmune diseases of claim 8, wherein the broad the autoimmune disease or inflammatory disease is selected from the group consisting of intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Cohn's disease, and inflammatory bowel disease.

Figure 1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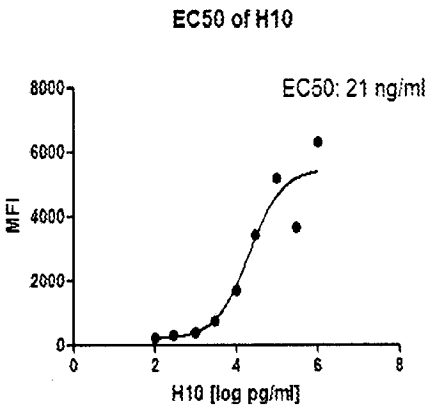
H6 [log pg/ml]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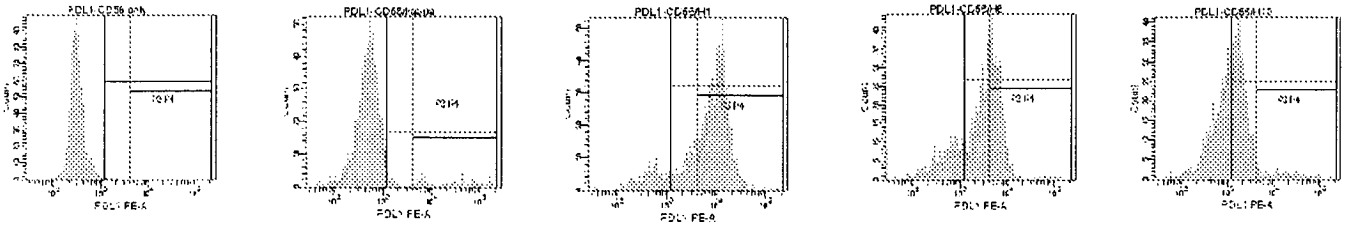
0
2
4
6
8
H10 [log pg/ml]

Figure 2

**Gated on CD56+**



**Gated on CD3+**

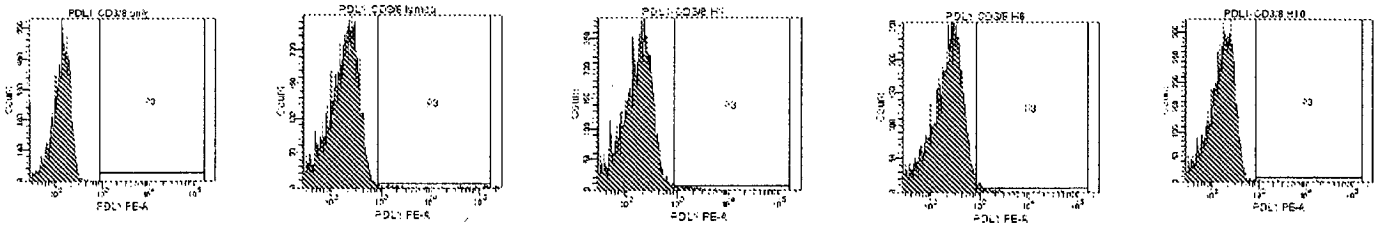
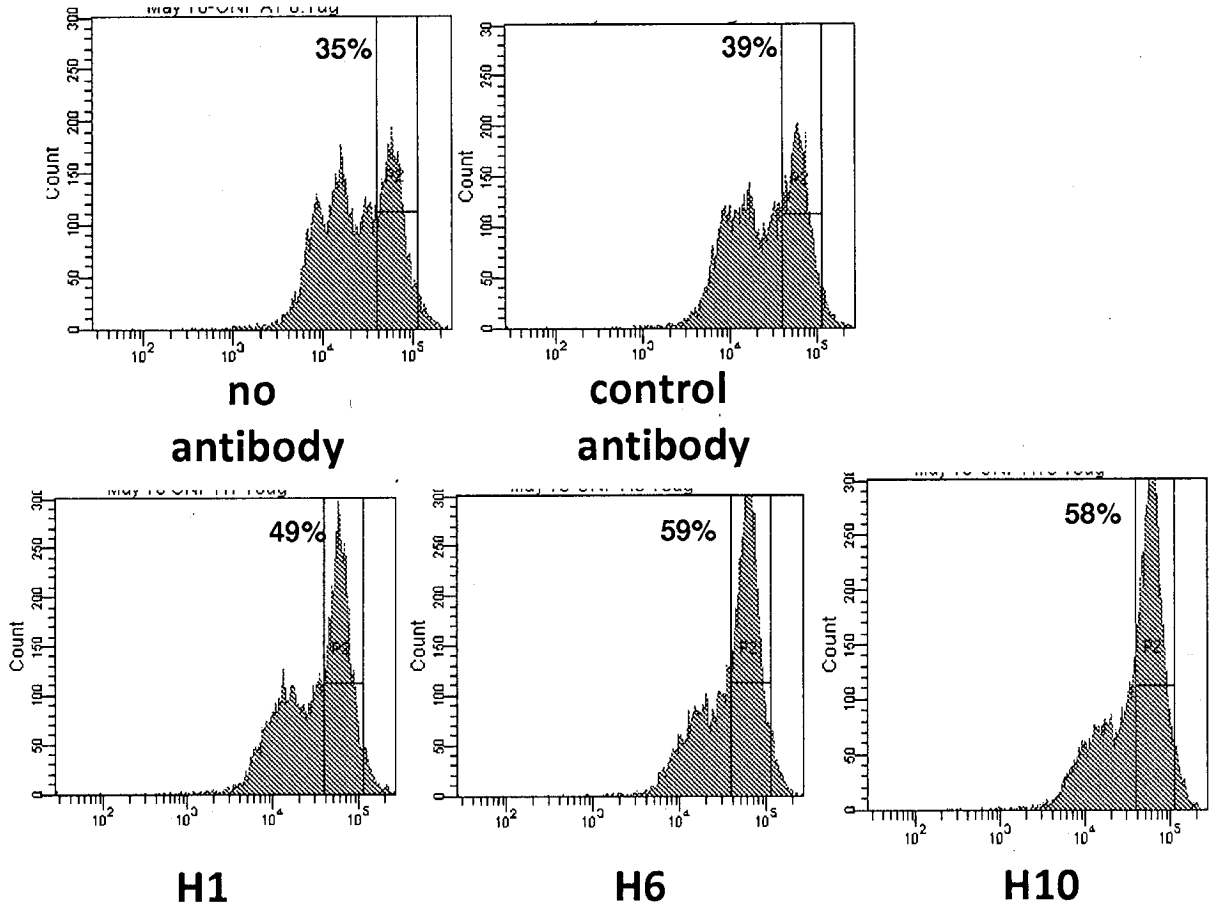


Figure 3



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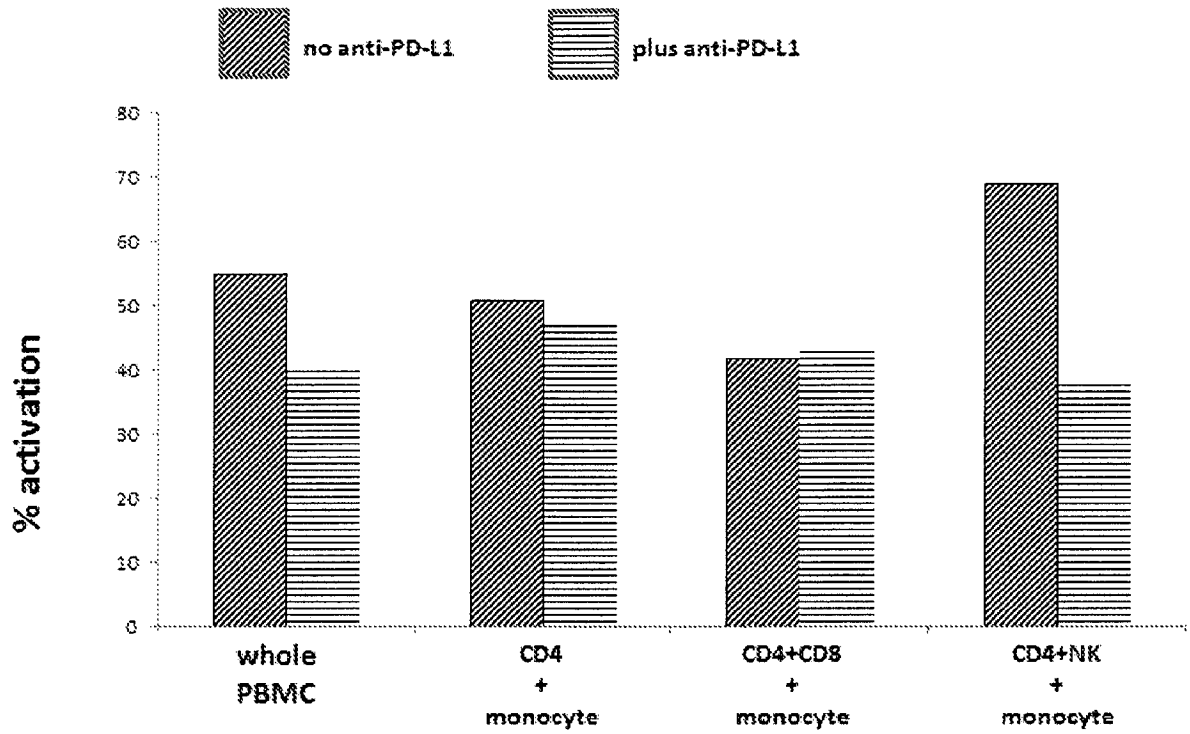
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plus anti-PD-L1
% activation
80
70
60
50
40
30
20
10
0
whole PBMC
CD4 + monocyte
CD4+CD8 + monocyte
CD4+NK + monocyte

Figure 5

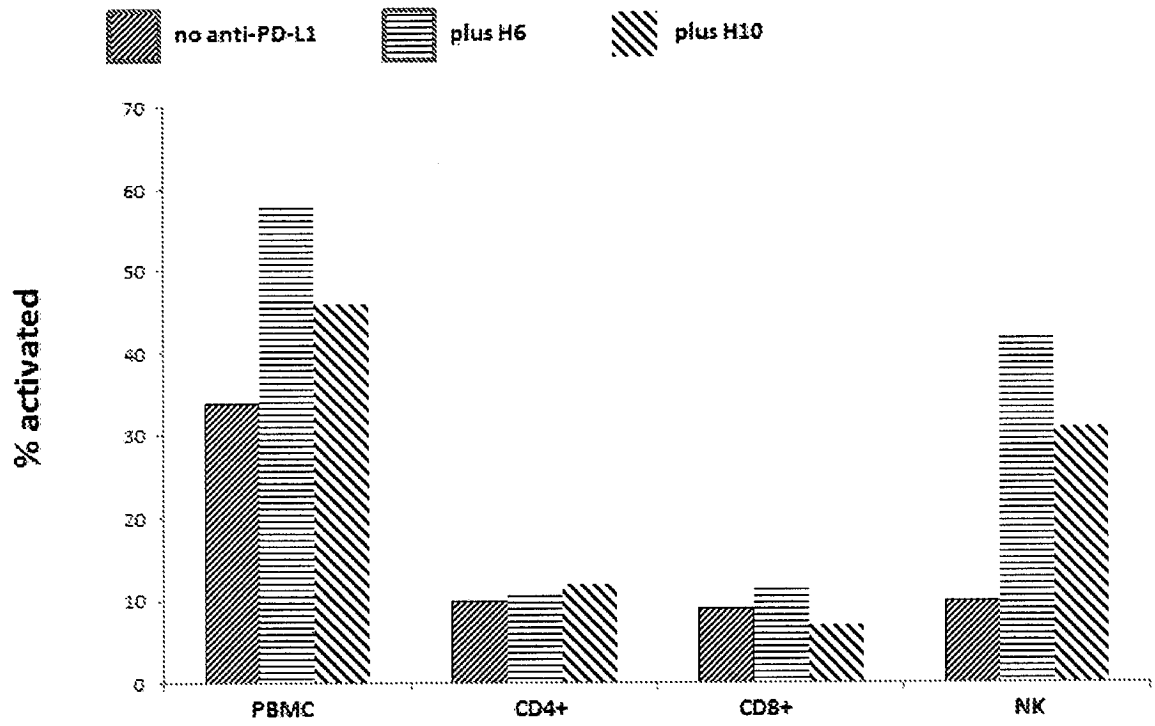
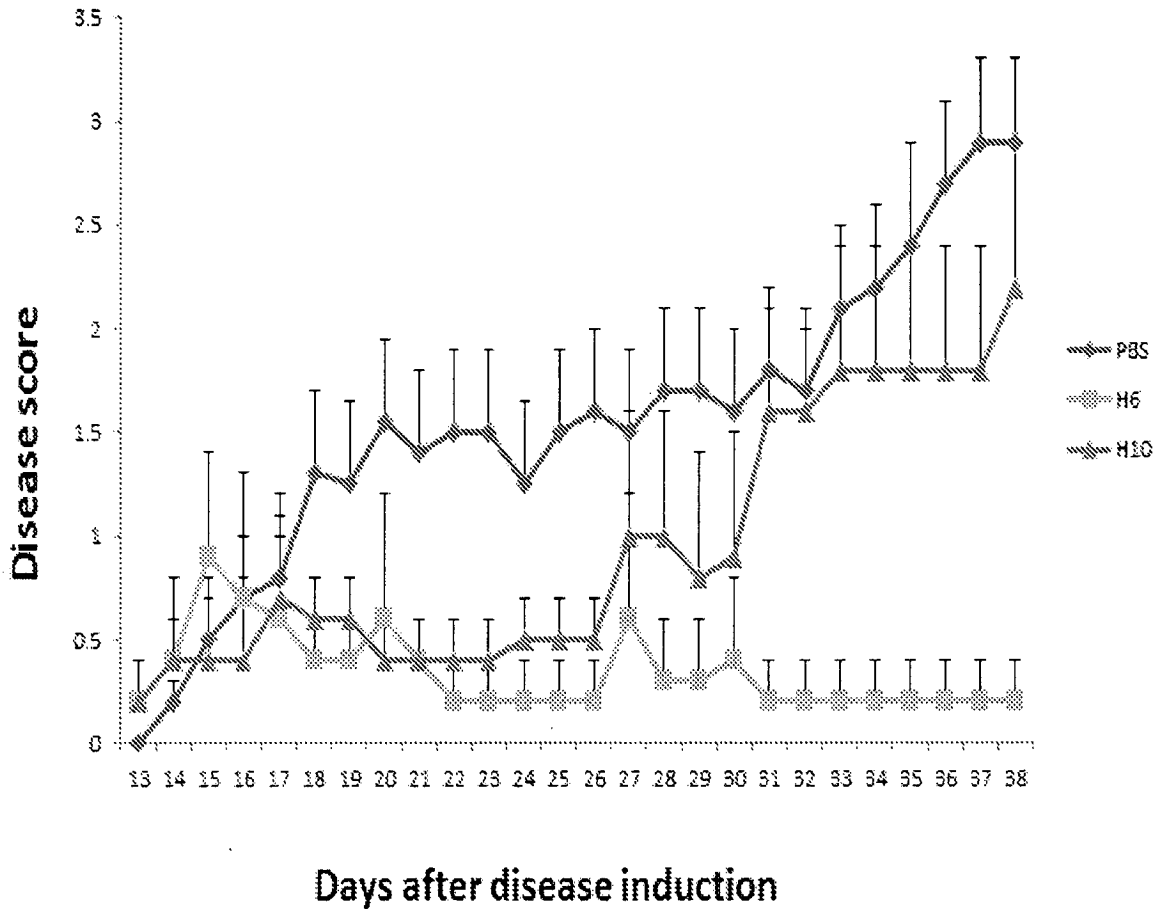

no anti-PD-L1
plus H6
plus H10
% activated
70
60
50
40
30
20
10
0
PBMC
CD4+
CD8+
NK

Figure 6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3
2.5
2
1.5
1
0.5
0
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PBS
H6
H10
Days after disease induction

Figure 7

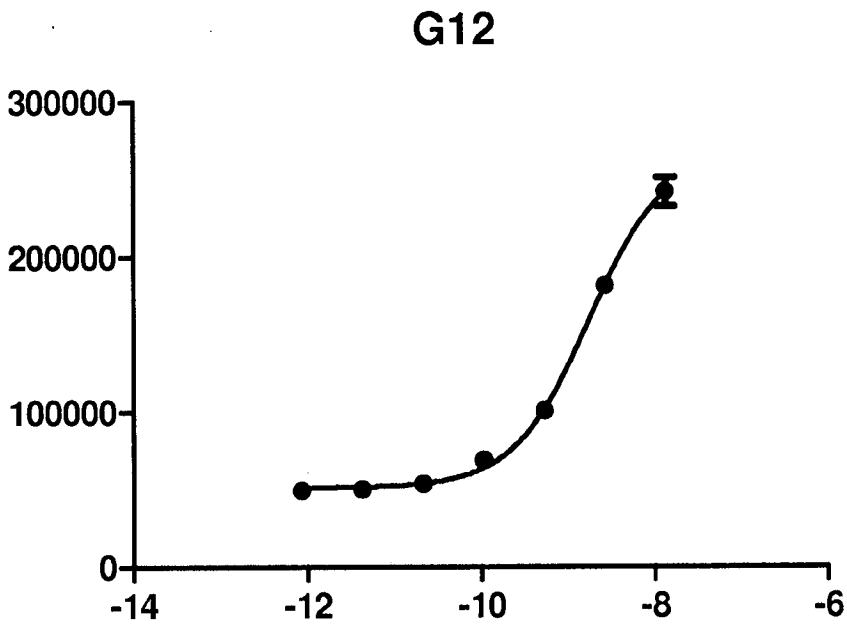
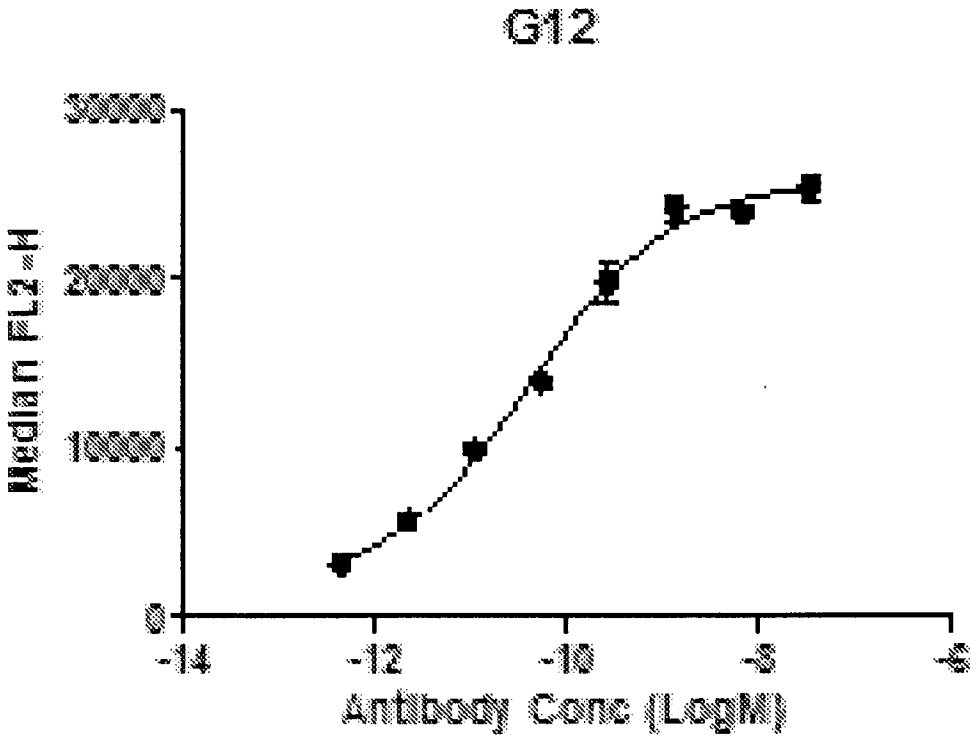


Figure 8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20000
10000
0
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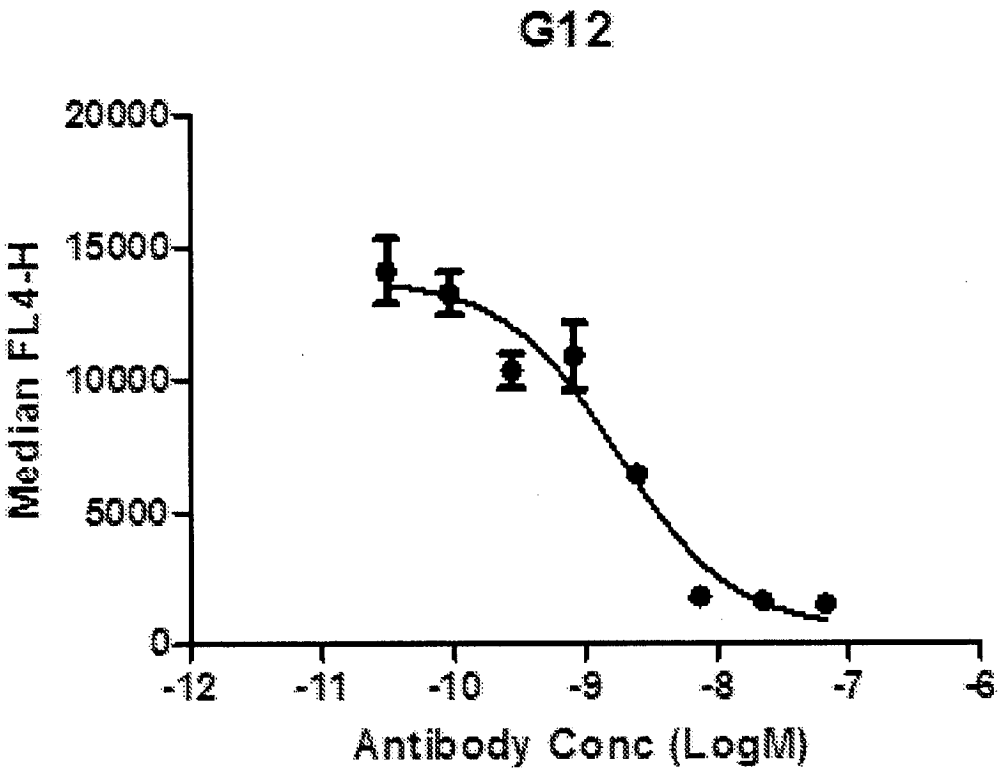
-12
-10
-8
-6
Antibody Conc (LogM)

Figure 9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10000
5000
0
Median FL4-H
-12
-11
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-9
-8
-7
-6
Antibody Conc (LogM)

Figure 10

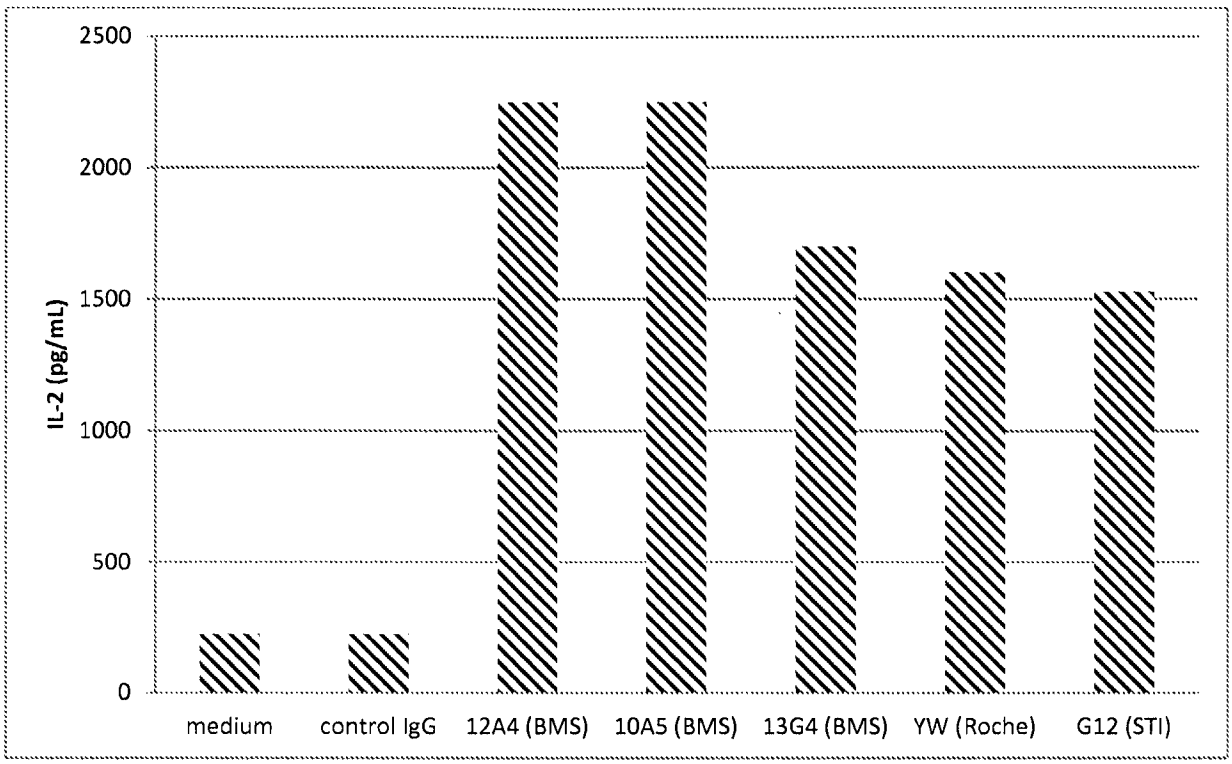

2500
2000
1500
1000
500
0
IL-2 (pg/mL)
medium
control IgG
12A4 (BMS)
10A5 (BMS)
13G4 (BMS)
YW (Roche)
G12 (STI)

Figure 11

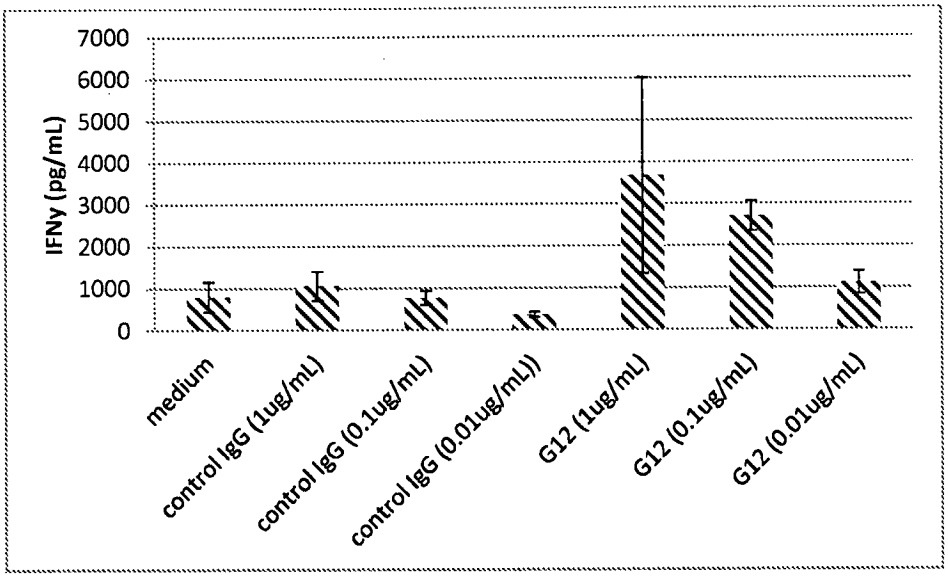

7000
6000
5000
4000
3000
2000
1000
0
IFNγ (pg/mL)
medium
control IgG (1ug/mL)
control IgG (0.1ug/mL)
control IgG (0.01ug/mL))
G12 (1ug/mL)
G12 (0.1ug/mL)
G12 (0.01ug/mL)

Figure 12

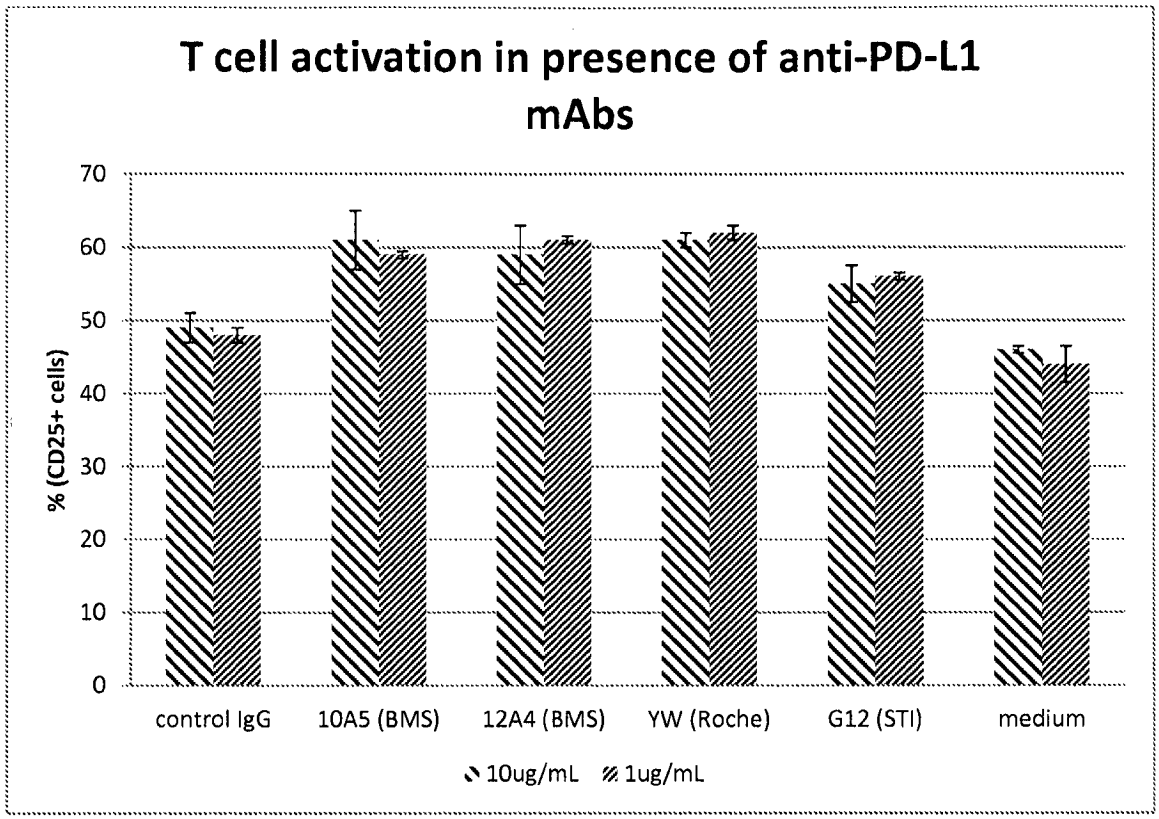
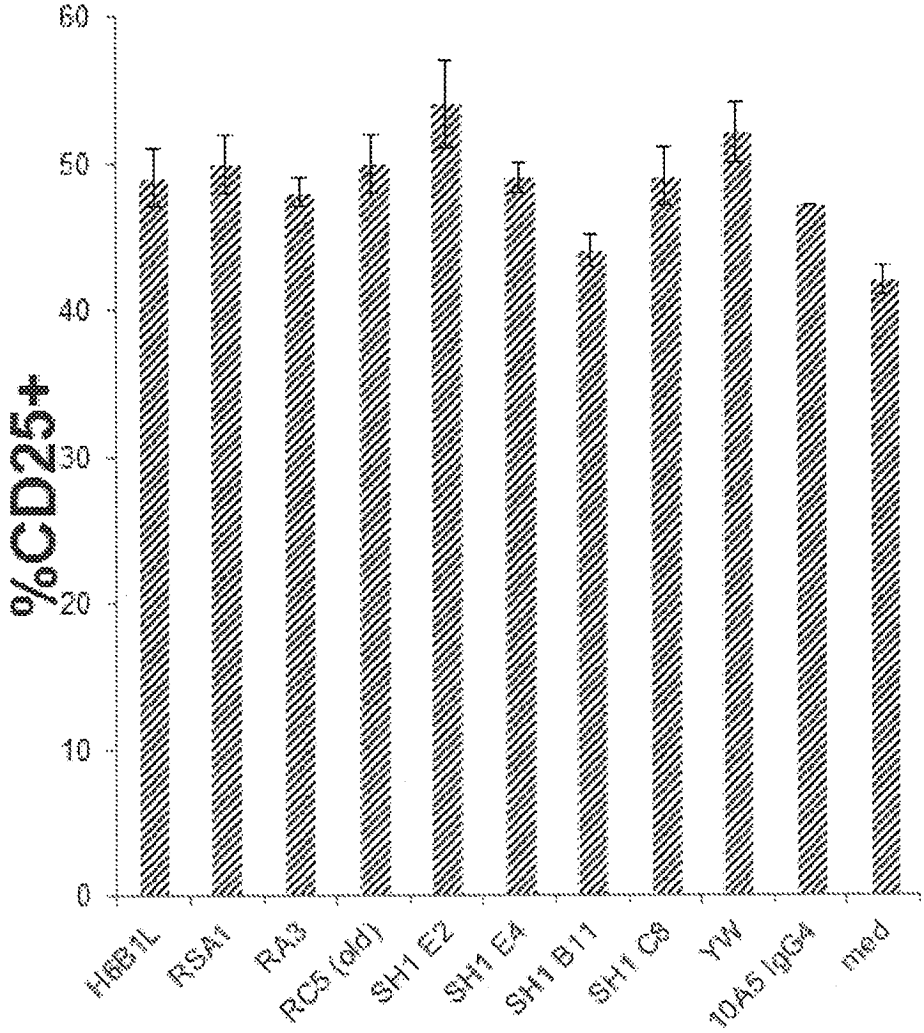
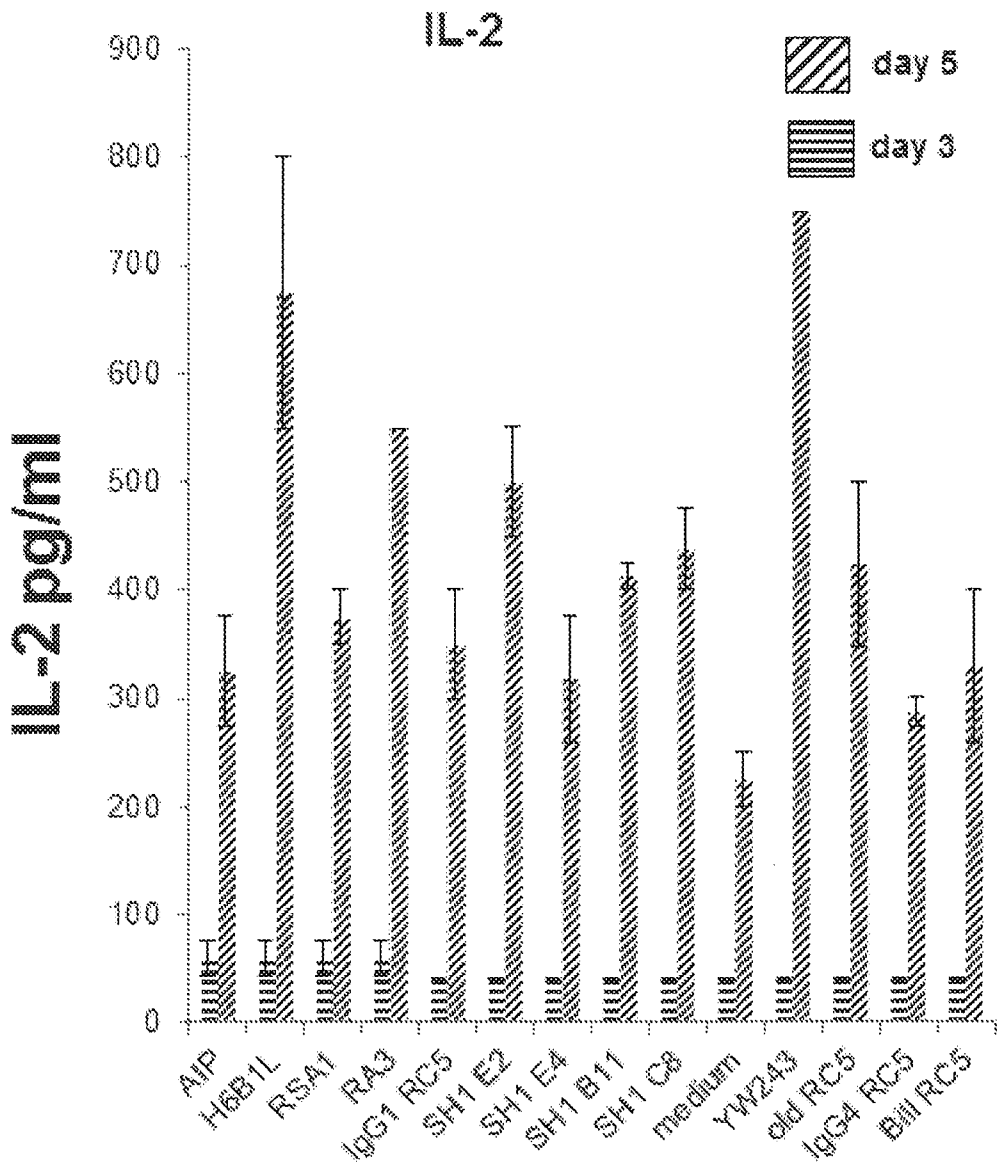

T cell activation in presence of anti-PD-L1 mAbs
% (CD25+ cells)
70
60
50
40
30
20
10
0
control IgG
10A5 (BMS)
12A4 (BMS)
YW (Roche)
G12 (STI)
medium
10ug/mL
1ug/mL

Figure 13



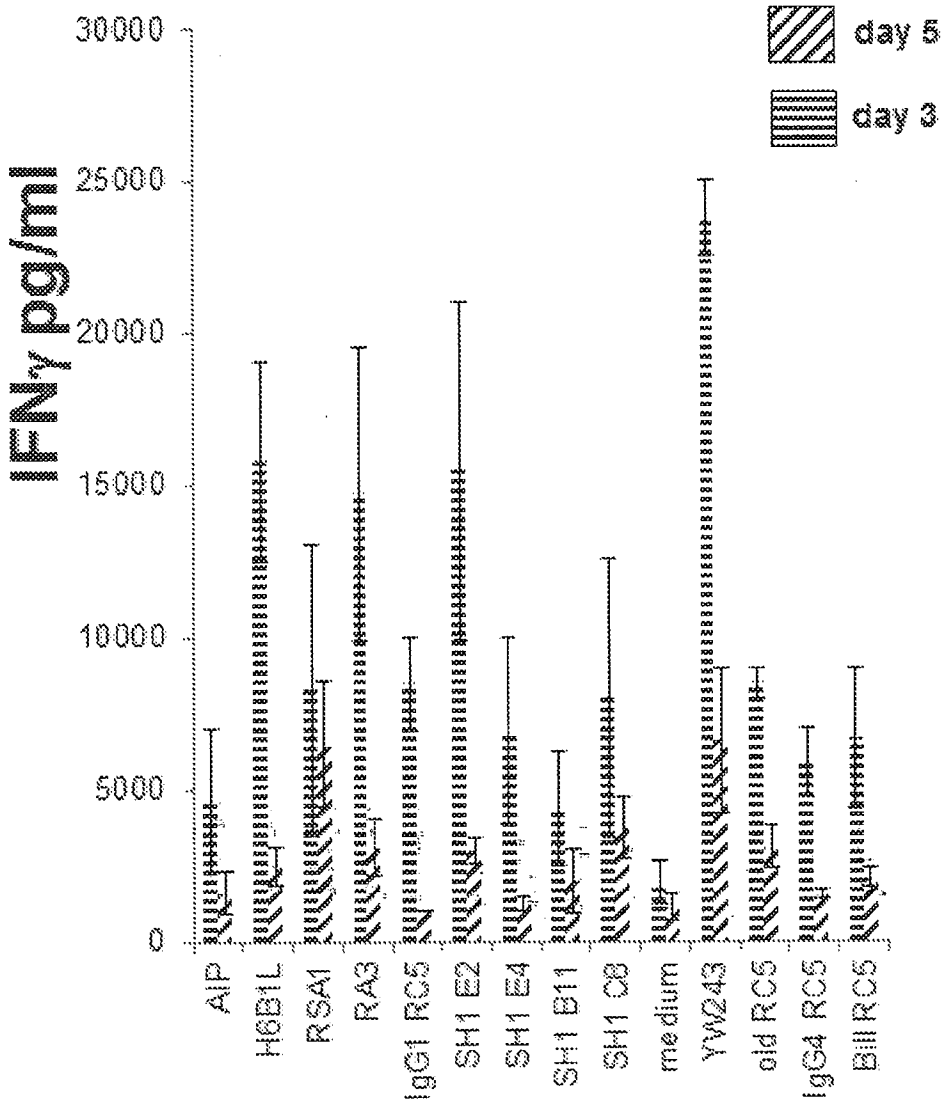

Values on ordinate are %CD25+

Figure 14




Ordinate is IL-2 pg/ml

Figure 15




Ordinate is IFNγ pg/ml

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(54) Title: ANTIGEN BINDING PROTEINS THAT BIND PD-L1

(57) Abstract: There is disclosed compositions and methods relating to or derived from anti-PD-L1 antibodies. More specifically, there is disclosed fully human antibodies that bind PD-L1, PD- L1 -binding fragments and derivatives of such antibodies, and PD-L1 -binding polypeptides comprising such fragments. Further still, there is disclosed nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having PD-L1 related disorders or conditions, including various inflammatory disorders and various cancers.

WO 2013/181634 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/43775

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; A61K 39/395 (2013.01)
USPC - 424/142.1, 424/135.1; 424/158.1, 424/174.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/00; A61K 39/395; G01N 33/53 (2013.01)
USPC - 424/142.1, 424/135.1; 424/158.1, 424/174.1; 424/130.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/00; A61K 39/395; G01N 33/53 (2013.01) - see keyword below
USPC - 424/142.1, 424/135.1; 424/158.1, 424/174.1; 424/130.1; 435/7.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: PD-L1, B7-H1, CD274, anti-PD-L1, Programmed death ligand, MDX-1105, MED14736, antibody, scFv, Fab, affinity, KD, cancer, lymphoma, tumor, ovarian, colon, breast, lung, myeloma, neuroblastic, leukemia, mast cell, T cell, B-cell, Fab, single chain, CDR, heavy chain, light chain, variable, VH, V

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2007/005874 A2 (KORMAN et al.) 11 January 2007 (11.01.2007), Abstract; pg 1, ln 29 to pg 2, ln 7; pg 4, ln 15-32; pg 7, ln 7-10; pg 11, ln 29-30; pg 21, ln 2-5; pg 22, ln 13-14 and 16-22; pg 72, ln 16-18; pg 76, ln 30-31; and pg 80, ln 23 to pg 81, ln 6 | 1-13 |
| A | US 2009/0117095 A1 (MESSMER et al.) 07 May 2009 (07.05.2009), Abstract, and Sequence Listing: SEQ ID NO: 173 | 1-13 |
| A | US 2011/0200615 A1 (MARKS et al.) 18 August 2011 (18.08.2011), Abstract, para [0017], and SEQ ID NO: 45 | 1-13 |
| A | US 2011/0020325 A1 (KWON et al.) 27 January 2011 (27.01.2011), para [0014]-[0015], [0017]-[0018], and [0051] | 1-13 |
| A | US 2009/0055944 A1 (KORMAN et al.) 26 February 2009 (26.02.2009), Entire documentation, especially Abstract | 1-13 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 December 2013 (19.12.2013) | 09 JAN 2014 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)

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PCT/US 13/43775

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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USPC - 424/142.1, 424/135.1; 424/158.1, 424/174.1; 424/130.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/00; A61K 39/395; G01N 33/53 (2013.01) - see keyword below
USPC - 424/142.1, 424/135.1; 424/158.1, 424/174.1; 424/130.1; 435/7.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: PD-L1, B7-H1, CD274, anti-PD-L1, Programmed death ligand, MDX-1105, MED14736, antibody, scFv, Fab, affinity, KD, cancer, lymphoma, tumor, ovarian, colon, breast, lung, myeloma, neuroblastic, leukemia, mast cell, T cell, B-cell, Fab, single chain, CDR, heavy chain, light chain, variable, VH, V

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| A | US 2009/0117095 A1 (MESSMER et al.) 07 May 2009 (07.05.2009), Abstract, and Sequence Listing: SEQ ID NO: 173 | 1-13 |
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| A | US 2011/0020325 A1 (KWON et al.) 27 January 2011 (27.01.2011), para [0014]-[0015], [0017]-[0018], and [0051] | 1-13 |
| A | US 2009/0055944 A1 (KORMAN et al.) 26 February 2009 (26.02.2009), Entire documentation, especially Abstract | 1-13 |

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 19 December 2013 (19.12.2013) | 09 JAN 2014 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/43775

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-13, drawn to a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least 10 -6M, a Fab fully human antibody fragment, a single chain human antibody, or a method for treating a broad spectrum of mammalian cancers or treating inflammatory diseases or autoimmune diseases, comprising administering an effective amount of an anti-PD-LI polypeptide that has a heavy chain variable domain sequence, and that has a light chain variable domain sequence. Since each antibody represented by a pair of heavy chain and light chain sequences, each is structurally different from all other heavy chain and light chain sequences represented by other SEQ ID NOS, respectively, the first named invention is restricted to SEQ ID NO: 1 and SEQ ID NO: 2 (called E6 in claim 2). Group I+ will be searched to the extent that it reads on an antibody has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences of SEQ ID NO: 1, and has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences of SEQ ID NO: 2, without fee.

**********Continuation in the extra sheet**********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-13, limited to SEQ ID NO: 1 and SEQ ID NO: 2

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US 13/43775

Continuation of:
Box No III (unity of invention is lacking)

It is believed that claims 1-13 read on this first named invention. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be: an antibody has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences of SEQ ID NO: 3, and has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences of SEQ ID NO: 4 (claims 1-13).

The inventions listed as Group I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Feature
Group I+ includes the special technical feature of different antibodies that has a heavy chain variable domain sequence, and that has a light chain variable domain sequence represented by a pair of SEQ ID NOS, which is structurally different from all other pair of heavy chain/light chain sequences represented by other SEQ ID NOS.

Common Technical Features
The inventions of Group I+ share the technical feature of a human antibody that binds to a PD-L1 epitope has a heavy chain variable domain sequence, and that has a light chain variable domain sequence;

Claims 1-2 and 8-13 of Group I+ further share the technical feature of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least 10-6M;

Claims 3-4 and 8-13 of Group I+ further share the technical feature of a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain;

Claims 5-6 and 8-13 of Group 1+ further share the technical feature of a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions; and

Claims 8-13 of Group I+ further share the technical feature of a method for treating a broad spectrum of mammalian cancers or treating inflammatory diseases or autoimmune diseases, comprising administering an effective amount of an anti-PD-LI polypeptide.

However, these shared technical features do not represent a contribution over prior art as being being anticipated by WO 2007/005874 A2 to KORMAN et al. (hereinafter 'Korman') as follows:

Korman discloses discloses a fully human antibody of an IgG class that binds to a PD-L1 epitope with a binding affinity of at least 10-6M (pg 1, ln 29 to pg 2, ln 7 - 'isolated monoclonal antibodies, in particular human monoclonal antibodies that bind to PD-L1...(a) binds to human PD-L1 with a Kd of 1x10-7 M or less', wherein ' human monoclonal antibodies' is ' a fully human antibody', and wherein 'a Kd of 1x10-7 M or less' is 10 fold higher than 'a binding affinity of at least 10-6M'; pg 11, ln 29-30 - 'full-length antibodies... an IgG 1 or IgG4 isotype'),
--- that has a heavy chain variable domain sequence, and that has a light chain variable domain sequence (Abstract - 'human monoclonal antibodies that specifically bind to PD-LI with high affinity'; pg 4, ln 15-32 - 'an isolated monoclonal antibody... comprising a heavy chain variable region. ...a light chain variable region ...wherein the antibody specifically binds PD-L1; pg 7, ln 7-10).

Korman further discloses a Fab fully human antibody fragment that binds to a PD-L1 (Abstract - 'human monoclonal antibodies that specifically bind to PD-LI with high affinity'; pg 11, ln 30-31 - 'the antibodies can be antibody fragments, such as Fab ... fragments') having a variable domain region from a heavy chain and a variable domain region from a light chain (pg 22, ln 13-14 - 'a Fab fragment, a monovalent fragment consisting ofthe VL,VH, CL and CHI domains'; pg 4, ln 15-32; pg 7, ln 7-10); and a single chain human antibody that binds to a PD-L1 (Abstract; pg 11, ln 30-31 - 'the antibodies can be... single chain antibodies') having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions (pg 22, ln 16-22 - 'a Fv fragment consisting of the V L and V H domains of a single arm of an antibody... the two domains of the Fv fragment, VL and VH,...can be joined ...by a synthetic linker ... made as a single protein chain in which the VL and VH regions pair to form monovalent molecules... known as single chain Fv (scFv)'; pg 4, ln 15-32; pg 7, ln 7-10).

Furthermore, Korman discloses a method for treating a broad spectrum of mammalian cancers or treating inflammatory diseases or autoimmune diseases (Abstract - 'methods for treating .. cancer and infectious diseases, using anti-PD-LI antibodies'; pg 21, ln 2-5 - 'methods of using the antibodies to modify an immune response ... treat ... cancer or infectious disease, or to stimulate a protective autoimmune response ... by coadministration of anti-PD-L1'),
---comprising administering an effective amount of an anti-PD-LI polypeptide (pg 72, ln 16-18 - 'Pharmaceutical compositions ... administered in combination therapy,... include an anti-PD-L1 antibody'; pg 76, ln 30-31 - 'A "therapeutically effective dosage" of an anti-PD-L1 antibody ... results in a decrease in severity of disease symptoms'). Without a shared special technical feature, the inventions lack unity with one another.

Group I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

IHE155052

# 与 PD-1 结合的抗原结合蛋白

本发明公开了与抗-PD-L1 抗体有关或由抗-PD-L1 抗体衍生的组合物和方法。更具体地，本发明完整地公开了结合 PD-L1 的人抗体、PD-L1 结合片段和这种抗体的衍生物、以及包括这种片段的与 PD-L1 结合的多肽。而且，本发明公开了编码这种抗体、抗体片段和衍生物和多肽的核酸，包括这种多核苷酸的细胞，制备这种抗体、抗体片段和衍生物和多肽的方法，以及使用这种抗体、抗体片段和衍生物和多肽的方法，所述方法包括对患有 PD-L1 相关病症或状况(包括各种炎性病症和各种癌)的受试者进行治疗和诊断的方法。