

locus for systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). Myeloid cells and B cells expressing OX40L have been demonstrated to support Tfh cell development, contributing to SLE disease pathogenesis. OX40L-OX40 signaling also contributes to the pathogenesis of autoimmune disease by dysregulating T regulatory cells (Tregs or T<sub>regs</sub>). Foxp3+ Tregs play an important role in establishing immunological tolerance by suppressing over-activated T effector (Teff, T<sub>eff</sub>, or T<sub>effector</sub>) cells. In human SLE, OX40L-OX40 signaling inhibits Foxp3 expression in Tregs and negatively impacts their suppressive function.

#### SUMMARY OF THE DISCLOSURE

**[0011]** The disclosure generally relates to proteins capable of modulating T cell costimulatory signaling, and uses of the same in the treatment of autoimmune diseases/disorders.

**[0011a]** In one aspect, the disclosure relates to a protein comprising an extracellular domain of CTLA4 or functional fragment thereof and a polypeptide or complex of two or more polypeptides that specifically binds OX40L, wherein the polypeptide or complex of two or more polypeptides that specifically binds OX40L comprises an antigen-binding site.

**[0011b]** In another aspect, the disclosure relates to a formulation comprising the protein of the disclosure and a pharmaceutically acceptable carrier.

**[0011c]** In another aspect, the disclosure relates to a nucleic acid encoding the protein of the disclosure.

**[0011d]** In another aspect, the disclosure relates to a cell comprising one or more nucleic acids encoding the protein of the disclosure.

**[0011e]** In another aspect, the disclosure relates to a use of the protein of the disclosure in the manufacture of a medicament for treating an autoimmune disease.

**[0011f]** In another aspect, the disclosure relates to a use of the protein of the disclosure in the manufacture of a medicament for treating graft versus host disease (GVHD).

**[0011g]** In another aspect, the disclosure relates to an antibody or functional fragment thereof comprising:

- (i) a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of

- IIYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN, and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83) (according to the IMGT unique numbering scheme); or
- (ii) a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a VLCDR1 comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a VLCDR2 comprising an amino acid sequence of GKD, and a VLCDR3 comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99) (according to the IMGT unique numbering scheme); or
- (iii)a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91) (according to the IMGT unique numbering scheme); or
- (iv) a VHCDR1 comprising an amino acid sequence of GGSISSSSYY (SEQ ID NO: 101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91) (according to the IMGT unique numbering scheme); or
- (v) a VHCDR1 comprising an amino acid sequence of GGSISSSSYY (SEQ ID NO: 109), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 110), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid

sequence of QVWDSNTVI (SEQ ID NO: 115) (according to the IMGT unique numbering scheme); or

5 (vi) a VHCDR1 comprising an amino acid sequence of GGSIDTSSQY (SEQ ID NO: 117), a VHCDR2 comprising an amino acid sequence of IYFSGST (SEQ ID NO: 118), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDT, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVI (SEQ ID NO: 123) (according to the IMGT unique numbering scheme); or

10 (vii) a VHCDR1 comprising an amino acid sequence of GGSISSGSFY (SEQ ID NO: 125), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 126), a VHCDR3 comprising an amino acid sequence of ARERSSSWYPFDY (SEQ ID NO: 127), a VLCDR1 comprising an amino acid sequence of SLRNYF (SEQ ID NO: 129), a VLCDR2 comprising an amino acid sequence of GKN, and a VLCDR3 comprising an amino acid sequence of NSRDSSGYHVV (SEQ ID NO: 131) (according to the IMGT unique numbering scheme); or

15 (viii) a VHCDR1 comprising an amino acid sequence of GFTFSNYA (SEQ ID NO: 133), a VHCDR2 comprising an amino acid sequence of ISGSGDST (SEQ ID NO: 134), a VHCDR3 comprising an amino acid sequence of AKDRTPVYGLDV (SEQ ID NO: 135), a VLCDR1 comprising an amino acid sequence of NIGRKN (SEQ ID NO: 137), a VLCDR2 comprising an amino acid sequence of GDS, and a VLCDR3 comprising an amino acid sequence of QVWDSSTV (SEQ ID NO: 139) (according to the IMGT unique numbering scheme); or

20 (ix) a VHCDR1 comprising an amino acid sequence of GFTFSSYA (SEQ ID NO: 141), a VHCDR2 comprising an amino acid sequence of ISGSGGST (SEQ ID NO: 142), a VHCDR3 comprising an amino acid sequence of AKDLGFYSTWDTDY (SEQ ID NO: 143), a VLCDR1 comprising an amino acid sequence of QGIRND (SEQ ID NO: 145), a VLCDR2 comprising an amino acid sequence of AAS, and a VLCDR3 comprising an amino acid sequence of LQHNTYPWT (SEQ ID NO: 147) (according to the IMGT unique numbering scheme); or

30 (x) a VHCDR1 comprising an amino acid sequence of GASISSSNHYWG (SEQ ID NO: 149), a VHCDR2 comprising an amino acid sequence of IYYSGNT (SEQ ID NO: 150), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDH (SEQ ID NO: 151), a

VLCDR1 comprising an amino acid sequence of NIGDKN (SEQ ID NO: 153), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSSTVV (SEQ ID NO: 155) (according to the IMGT unique numbering scheme); or

5 (xi) a VHCDR1 comprising an amino acid sequence of GDSVSSNSAV (SEQ ID NO: 157), a VHCDR2 comprising an amino acid sequence of TDYRSKWNN (SEQ ID NO: 158), a VHCDR3 comprising an amino acid sequence of ARGDAGMASFDY (SEQ ID NO: 159), a VLCDR1 comprising an amino acid sequence of KLGDKY (SEQ ID NO: 161), a VLCDR2 comprising an amino acid sequence of QDR, and a VLCDR3 comprising an amino acid

10 sequence of QTWDRRTAV (SEQ ID NO: 163) (according to the IMGT unique numbering scheme); or

(xii) a VHCDR1 comprising an amino acid sequence of GGSFSDYY (SEQ ID NO: 165), a VHCDR2 comprising an amino acid sequence of INHSGST (SEQ ID NO: 166), a VHCDR3 comprising an amino acid sequence of ARKRGANFFDD (SEQ ID NO: 167), a

15 VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSSTVV (SEQ ID NO: 155) (according to the IMGT unique numbering scheme); and

**[0012]** optionally wherein the antibody is a human IgG1 antibody. In one example the present

20 disclosure provides a protein comprising a polypeptide or complex of two or more polypeptides that specifically binds CD80 and/or CD86, and a polypeptide or complex of two or more polypeptides that specifically binds OX40L. In some examples, the polypeptide or complex of two or more polypeptides that specifically binds CD80 and/or CD86 is a polypeptide comprising a CTLA4 extracellular domain or functional fragment thereof; a polypeptide comprising a CD28

25 extracellular domain or functional fragment thereof; an antibody; a Fab; a Fab', a F(ab')<sub>2</sub>, a single-chain variable fragment (scFv); a minibody; or a nanobody (VHH). In some examples the polypeptide or complex of two or more polypeptides that specifically binds CD80 and/or CD86 comprises an extracellular domain of CTLA4 or functional fragment thereof consisting of or comprising a sequence having at least 90% sequence identity to SEQ ID NO: 29, SEQ ID NO:

30 173, or SEQ ID NO: 174. In some examples, the polypeptide or complex of two or more polypeptides that specifically binds CD80 and/or CD86 inhibits CD28 costimulatory signaling in T cells.

**[0013]** In another example of the present disclosure, the polypeptide or complex of two or more polypeptides that specifically binds OX40L inhibits binding of endogenous OX40L to endogenous OX40. In some examples, the polypeptide or complex of two or more polypeptides that specifically binds OX40L comprises an antigen-binding site. In some examples, the antigen  
5 binding site is an antibody, a Fab, a Fab', a F(ab')<sub>2</sub>, a single-chain variable fragment (scFv), a minibody, or a nanobody (VHH). In some examples, the antigen-binding site is a Fab comprising a polypeptide comprising the sequence of SEQ ID NO: 336 connected to the C-terminus of the Fab heavy chain CH1 domain. In other examples,

the polypeptide or complex of two or more polypeptides that specifically binds OX40L is an extracellular domain of OX40 or functional fragment thereof.

**[0014]** In some examples, proteins of the present disclosure further comprise a bridging moiety. In some examples, the bridging moiety is functional or non-functional. In some examples, the bridging moiety comprises polypeptide of an immunoglobulin Fc domain or functional fragment thereof, a human serum albumin (HSA) polypeptide or functional fragment thereof, a polypeptide linker, or a polypeptide hinge. In some examples, the bridging moiety comprises a polypeptide of a human IgG1, IgG2, IgG3, or IgG4 Fc domain. In some examples, the polypeptide of a human IgG1 Fc domain comprises a sequence having at least 90% or 100% sequence identity to an amino acid sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240. In some examples, the polypeptide of a human IgG1 Fc domain comprises one or more than one effector function silencing mutation. In certain examples, the hinge polypeptide comprises mutations at positions 234 and 235 from leucine to alanine.

**[0015]** In some examples, the bridging moiety further comprises a hinge polypeptide comprising an amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 242, SEQ ID NO: 176, SEQ ID NO: 249, SEQ ID NO: 177, SEQ ID NO: 243, SEQ ID NO: 212, SEQ ID NO: 244, SEQ ID NO: 213, SEQ ID NO: 245, SEQ ID NO: 247, and SEQ ID NO: 248.

**[0016]** In some examples of proteins of the present disclosure, the bridging moiety is connected to the N-terminus or the C-terminus of the polypeptide or complex of two or more polypeptides that specifically binds CD80 and/or CD86. In some examples, the polypeptide or complex of two or more polypeptides that specifically binds CD80 and/or CD86 is connected to the N-terminus of the bridging moiety. In some examples, the bridging moiety is connected to the N-terminus or the C-terminus of the polypeptide or complex of two or more polypeptides that specifically binds OX40L. In some examples, the polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the C-terminus of the bridging moiety. In some examples, a linker polypeptide comprising a (GGGS)<sub>n</sub> (SEQ ID NO: 181) sequence, wherein n is 1 to 12, connects the polypeptide or complex of two or more polypeptides that specifically binds OX40L to the bridging moiety.

**[0017]** In some examples, proteins of the present disclosure comprise a second polypeptide or complex of two or more polypeptides that specifically binds OX40L. In some examples, the bridging moiety is a polypeptide of a human IgG1 Fc domain and the polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the C-terminus of the polypeptide of the human IgG1 Fc domain and the second polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the C-terminus of a second polypeptide of a human IgG1 Fc domain. In some examples, the first and/or the second polypeptide or complex of two or more polypeptides that specifically binds OX40L comprises an antigen-binding site, for example a Fab, or an extracellular domain of OX40 or functional fragment thereof. In some examples, the second polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the bridging moiety by a linker polypeptide comprising a (GGGGS)<sub>n</sub> (SEQ ID NO: 181) sequence, wherein n is 1 to 12.

**[0018]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence of (a) ARHRGX<sub>1</sub>YX<sub>2</sub>FDX<sub>3</sub> (SEQ ID NO: 220), wherein X<sub>1</sub> is S or I, X<sub>2</sub> is F or H, and X<sub>3</sub> is I or Y; or (b) ARERSX<sub>1</sub>X<sub>2</sub>WYPX<sub>3</sub>DY (SEQ ID NO: 221) wherein X<sub>1</sub> is N or S, X<sub>2</sub> is N, D, G or S, and X<sub>3</sub> is I or F.

**[0019]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising (a) a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence GX<sub>1</sub>SX<sub>2</sub>X<sub>3</sub>X<sub>4</sub>SX<sub>5</sub>YY (SEQ ID NO: 222), wherein X<sub>1</sub> is A, G, or V, X<sub>2</sub> is V, or I, X<sub>3</sub> is S or R, X<sub>4</sub> is S, or T, and X<sub>5</sub> is S, or G; (b) a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of: (1) IX<sub>1</sub>YX<sub>2</sub>GST (SEQ ID NO: 223) wherein X<sub>1</sub> is Y, or N, and X<sub>2</sub> is S, or G, (2) X<sub>1</sub>DYSGT (SEQ ID NO: 224) wherein X<sub>1</sub> is I or M, or (3) IGSVDYSGX<sub>1</sub>T (SEQ ID NO: 225), wherein X<sub>1</sub> is N, A, or S; and (c) a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of: (1) ARHRGX<sub>1</sub>YX<sub>2</sub>FDX<sub>3</sub> (SEQ ID NO: 220), wherein X<sub>1</sub> is S or I, X<sub>2</sub> is F or H, and X<sub>3</sub> is I or Y; or (2) ARERSX<sub>1</sub>X<sub>2</sub>WYPX<sub>3</sub>DY (SEQ ID NO: 221), wherein X<sub>1</sub> is N or S, X<sub>2</sub> is N, D, G or S, and X<sub>3</sub> is I or F.

**[0020]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising (a) a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of: (1) X<sub>1</sub>IENKN (SEQ ID NO: 226), wherein X<sub>1</sub> is N or D, or (2) SX<sub>1</sub>RX<sub>2</sub>X<sub>3</sub>X<sub>4</sub> (SEQ ID NO: 227), wherein X<sub>1</sub> is V or L, X<sub>2</sub> is R or N, X<sub>3</sub> is F or Y, and X<sub>4</sub> is F or Y; (b) a light chain variable complementarity-determining region 2 (VLCDR2)

comprising an amino acid sequence of: RDN (SEQ ID NO: 82), GKD (SEQ ID NO: 228), or RDS (SEQ ID NO: 90); and (c) a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of: (1) QVX<sub>1</sub>DSX<sub>2</sub>X<sub>3</sub>VV (SEQ ID NO: 231), wherein X<sub>1</sub> is R or W, X<sub>2</sub> is N, T, or A, and X<sub>3</sub> is I, T, or A, or (2) NSRDSSGYX<sub>1</sub>VX<sub>2</sub> (SEQ ID NO: 232), wherein X<sub>1</sub> is L or H, and X<sub>2</sub> is L or V.

**[0021]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising (i) (a) a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence GX<sub>1</sub>SX<sub>2</sub>X<sub>3</sub>X<sub>4</sub>SX<sub>5</sub>YY (SEQ ID NO: 222), wherein X<sub>1</sub> is A, G, or V, X<sub>2</sub> is V, or I, X<sub>3</sub> is S or R, X<sub>4</sub> is S, or T, and X<sub>5</sub> is S, or G; and (b) a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence IX<sub>1</sub>YX<sub>2</sub>GST (SEQ ID NO: 223), wherein X<sub>1</sub> is Y, or N, and X<sub>2</sub> is S, or G; and (c) a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence ARHRGX<sub>1</sub>YX<sub>2</sub>FDX<sub>3</sub> (SEQ ID NO: 220), wherein X<sub>1</sub> is S or I, X<sub>2</sub> is F or H, and X<sub>3</sub> is I or Y; and (ii) (a) a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence X<sub>1</sub>IENKN (SEQ ID NO: 226), wherein X<sub>1</sub> is N or D; (b) a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence RDN (SEQ ID NO: 82); and (c) a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence QVX<sub>1</sub>DSX<sub>2</sub>X<sub>3</sub>VV (SEQ ID NO: 231), wherein X<sub>1</sub> is R or W, X<sub>2</sub> is N, T, or A, and X<sub>3</sub> is I, T, or A.

**[0022]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising (i) (a) a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence GX<sub>1</sub>SX<sub>2</sub>X<sub>3</sub>X<sub>4</sub>SX<sub>5</sub>YY (SEQ ID NO: 222), wherein X<sub>1</sub> is A, G, or V, X<sub>2</sub> is V, or I, X<sub>3</sub> is S or R, X<sub>4</sub> is S, or T, and X<sub>5</sub> is S, or G; and (b) a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence X<sub>1</sub>DYSGT (SEQ ID NO: 224), wherein X<sub>1</sub> is I or M; and (c) a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence ARERSX<sub>1</sub>X<sub>2</sub>WYPX<sub>3</sub>DY (SEQ ID NO: 221), wherein X<sub>1</sub> is N or S, X<sub>2</sub> is N, D, G or S, and X<sub>3</sub> is I or F; and (ii) (a) a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence SX<sub>1</sub>R X<sub>2</sub>X<sub>3</sub>X<sub>4</sub> (SEQ ID NO: 227), wherein X<sub>1</sub> is V or L, X<sub>2</sub> is R or N, X<sub>3</sub> is F or Y, and X<sub>4</sub> is F or Y; (b) a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence GKD (SEQ ID NO: 229); and (c) a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence NSRDSSGYX<sub>1</sub>VX<sub>2</sub> (SEQ ID NO: 232) wherein X<sub>1</sub> is L or H, and X<sub>2</sub> is L or V.

[0023] In some examples, proteins of the present disclosure comprise antigen-binding sites comprising a heavy chain complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83).

[0024] In some examples, proteins of the present disclosure comprise antigen-binding sites comprising a heavy chain complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a heavy chain complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a heavy chain complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a light chain complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a light chain complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of GKD (SEQ ID NO: 98), and a light chain complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99).

[0025] In some examples, proteins of the present disclosure comprise antigen-binding sites comprising a heavy chain complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a heavy chain complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a heavy chain complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a light chain complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91).

[0026] In some examples, proteins of the present disclosure comprise antigen-binding sites comprising a heavy chain complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISSSSYY (SEQ ID NO: 101), a heavy chain complementarity-

determining region 2 (VHCDR2) comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a heavy chain complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a light chain complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91).

**[0027]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 76, SEQ ID NO: 92, SEQ ID NO: 84, or SEQ ID NO: 100, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 80, SEQ ID NO: 96, SEQ ID NO: 88, or SEQ ID NO: 104.

**[0028]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 76, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 80.

**[0029]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 92, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 96.

**[0030]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 14, or SEQ ID NO: 18, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 7, SEQ ID NO: 15, SEQ ID NO: 13, or SEQ ID NO: 17.

**[0031]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 8, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 7.

**[0032]** In some examples, proteins of the present disclosure comprise antigen-binding sites comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 16, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 15.

30

**[0033]** In some examples, proteins of the present disclosure comprise antigen-binding sites that bind at position 60 and/or 83 of the extracellular domain of human OX40L. In some examples, the antigen-binding site binds at position 17, 18, 19, 20, 21, 23, 26, 28, 60, 83, 110, 111, 112, 113, and 114 of the extracellular domain of human OX40L. In some examples, the antigen-binding site binds at position 58, 59, 60, 61, 62, 63, 81, 82, and 83 of the extracellular domain of human OX40L.

**[0034]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a bridging moiety comprising a sequence comprising of SEQ ID NO: 177 and a sequence comprising of SEQ ID NO: 179; and (iii) an antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83).

**[0035]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 177 and a sequence comprising of SEQ ID NO: 179; and (iii) a first antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83), and the second arm comprising: (i) a

second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 177 and a sequence comprising of SEQ ID NO: 179; and (iii) a second antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83), wherein the first arm and the second arm dimerize with each other.

**[0036]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) an antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of GKD (SEQ ID NO: 98), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99).

**[0037]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) a first antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a heavy

chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of GKD (SEQ ID NO: 98), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99), and the second arm comprising: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) a second antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of GKD (SEQ ID NO: 98), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99), wherein the first arm and the second arm dimerize with each other.

**[0038]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 214; and (iii) an antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain variable complementarity-

determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91).

**[0039]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide complex the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 214; and (iii) a first antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91), and the second arm comprising: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 214; and (iii) a second antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91), wherein the first arm and the second arm dimerize with each other.

**[0040]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of

SEQ ID NO: 216; and (iii) an antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91).

**[0041]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) a first antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91), and the second arm comprising: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) a second antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid

sequence of NIENKN (SEQ ID NO: 89), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91), wherein the first arm and the second arm  
5 dimerize with each other.

**[0042]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) an antigen-binding site comprising, a heavy chain variable  
10 complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining  
15 region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83).

**[0043]** In some examples, proteins of the present disclosure comprise a first arm and a second  
20 arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174; (ii) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) a first antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy  
25 chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-  
30 determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83), and the second arm comprising: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO:

174; (ii) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and (iii) a second antigen-binding site comprising, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83), wherein the first arm and the second arm dimerize with each other.

**[0044]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214; SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) an antigen-binding site comprising a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GFTFSNYA (SEQ ID NO: 133), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of ISGSGGAT (SEQ ID NO: 113), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of TKDRLIMATVRGPYYYYGMDV (SEQ ID NO: 114), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of QSISSY (SEQ ID NO: 121), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of AAS (SEQ ID NO: 146), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QQSHSVSFT (SEQ ID NO: 154).

**[0045]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain

of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID  
NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a  
first bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO:  
175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO:  
5 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237,  
SEQ ID NO: 214; SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and  
SEQ ID NO: 240; and (iii) a first antigen-binding site comprising a heavy chain variable  
complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of  
GFTFSNYA (SEQ ID NO: 133), a heavy chain variable complementarity-determining region 2  
10 (VHCDR2) comprising an amino acid sequence of ISGSGGAT (SEQ ID NO: 113), a heavy  
chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid  
sequence of TKDRLIMATVRGPYYYGMDV (SEQ ID NO: 114), a light chain variable  
complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of  
QSISSY (SEQ ID NO: 121), a light chain variable complementarity-determining region 2  
15 (VLCDR2) comprising an amino acid sequence of AAS (SEQ ID NO: 146), and a light chain  
variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence  
of QQSHSVSFT (SEQ ID NO: 154), and the second arm comprising: (i) a second polypeptide  
comprising the extracellular domain of CTLA4 comprising a sequence selected from a group  
consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID  
20 NO: 234, and SEQ ID NO: 235; (ii) a second bridging moiety comprising a sequence selected  
from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO:  
212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of  
SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214; SEQ ID NO: 216, SEQ ID NO: 179,  
SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a second antigen-binding  
25 site comprising a heavy chain variable complementarity-determining region 1 (VHCDR1)  
comprising an amino acid sequence of GFTFSNYA (SEQ ID NO: 133), a heavy chain variable  
complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of  
ISGSGGAT (SEQ ID NO: 113), a heavy chain variable complementarity-determining region 3  
(VHCDR3) comprising an amino acid sequence of TKDRLIMATVRGPYYYGMDV (SEQ ID  
30 NO: 114), a light chain variable complementarity-determining region 1 (VLCDR1) comprising  
an amino acid sequence of QSISSY (SEQ ID NO: 121), a light chain variable complementarity-  
determining region 2 (VLCDR2) comprising an amino acid sequence of AAS (SEQ ID NO:  
146), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising

an amino acid sequence of QQSHSVSFT (SEQ ID NO: 154), wherein the first arm and the second arm dimerize with each other.

**[0046]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) an antigen-binding site comprising a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of SYAMS (SEQ ID NO: 105), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IISGSGGFTYYADSVK (SEQ ID NO: 106), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of DRLVAPGTFDY (SEQ ID NO: 107), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of RASQGISSWLA (SEQ ID NO: 169), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of AASSLQS (SEQ ID NO: 170), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QQYNSYPYT (SEQ ID NO: 171).

**[0047]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a first bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a first antigen-binding site comprising a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of SYAMS (SEQ ID NO: 105), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IISGSGGFTYYADSVK (SEQ ID NO: 106), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino

acid sequence of DRLVAPGTFDY (SEQ ID NO: 107), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of RASQGISSWLA (SEQ ID NO: 169), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of AASSLQS (SEQ ID NO: 170), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QQYNSYPYT (SEQ ID NO: 171), and the second arm comprises: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a second bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a second antigen-binding site comprising a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of SYAMS (SEQ ID NO: 105), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IISGSGGFTYYADSVK (SEQ ID NO: 106), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of DRLVAPGTFDY (SEQ ID NO: 107), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of RASQGISSWLA (SEQ ID NO: 169), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of AASSLQS (SEQ ID NO: 170), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QQYNSYPYT (SEQ ID NO: 171), wherein the first arm and the second arm dimerize with each other.

**[0048]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) an antigen-binding site comprising, according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence corresponding to

the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain listed in TABLE 3, respectively.

**[0049]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a first bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a first antigen-binding site comprising, according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence corresponding to the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain listed in TABLE 3, respectively, and the second arm comprising: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a second bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a second antigen-binding site comprising, according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence corresponding to the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain listed in TABLE 3, respectively, wherein the first arm and the second arm dimerize with each other.

**[0050]** In some examples, proteins of the present disclosure comprise (i) a polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of

SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214 , SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) an antigen-binding site comprising a polypeptide that specifically binds to OX40L.

**[0051]** In some examples, proteins of the present disclosure comprise a first arm and a second arm, the first arm comprising (i) a first polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a first bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214 , SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a first antigen-binding site comprising a polypeptide that specifically binds to OX40L, and the second arm comprising: (i) a second polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235; (ii) a second bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214 , SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and (iii) a second antigen-binding site comprising a polypeptide that specifically binds to OX40L, wherein the first arm and the second arm dimerize with each other.

**[0052]** In some examples, proteins of the present disclosure comprise an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 40, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 48, SEQ ID NO: 68, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 46, SEQ ID NO: 66, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 50, SEQ ID NO: 70, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 38, SEQ ID NO: 73, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 37, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258, SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, SEQ ID NO:

266, SEQ ID NO: 267, SEQ ID NO: 268, SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271,  
 SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276,  
 SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, SEQ ID NO: 281,  
 SEQ ID NO: 282, SEQ ID NO: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286,  
 5 SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291,  
 SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296,  
 SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301,  
 SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, SEQ ID NO: 306,  
 SEQ ID NO: 307, SEQ ID NO: 308, SEQ ID NO: 309, SEQ ID NO: 310, SEQ ID NO: 311,  
 10 SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 314, SEQ ID NO: 315, SEQ ID NO: 316,  
 SEQ ID NO: 317, SEQ ID NO: 318, SEQ ID NO: 319, SEQ ID NO: 320, SEQ ID NO: 321,  
 SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 324, SEQ ID NO: 325, SEQ ID NO: 326,  
 SEQ ID NO: 327, SEQ ID NO: 328, SEQ ID NO: 329, SEQ ID NO: 330, SEQ ID NO: 331,  
 SEQ ID NO: 332, SEQ ID NO: 333, SEQ ID NO: 334, or SEQ ID NO: 335.

15 **[0053]** In some examples, proteins of the present disclosure comprise polypeptides  
 comprising amino acid sequences at least 90% identical to the amino acid sequences of: SEQ ID  
 NO: 40 and SEQ ID NO: 39; SEQ ID NO: 62 and SEQ ID NO: 61; SEQ ID NO: 64 and SEQ ID  
 NO: 63; SEQ ID NO: 182 and SEQ ID NO: 63; SEQ ID NO: 183 and SEQ ID NO: 63; SEQ ID  
 NO: 184 and SEQ ID NO: 63; SEQ ID NO: 185 and SEQ ID NO: 63; SEQ ID NO: 186 and SEQ  
 20 ID NO: 63; SEQ ID NO: 48 and SEQ ID NO: 47; SEQ ID NO: 68 and SEQ ID NO: 67; SEQ ID  
 NO: 187 and SEQ ID NO: 67; SEQ ID NO: 188 and SEQ ID NO: 67; SEQ ID NO: 189 and SEQ  
 ID NO: 67; SEQ ID NO: 190 and SEQ ID NO: 67; SEQ ID NO: 191 and SEQ ID NO: 67; SEQ  
 ID NO: 46 and SEQ ID NO: 45; SEQ ID NO: 66 and SEQ ID NO: 65; SEQ ID NO: 192 and  
 SEQ ID NO: 65; SEQ ID NO: 193 and SEQ ID NO: 65; SEQ ID NO: 194 and SEQ ID NO: 65;  
 25 SEQ ID NO: 195 and SEQ ID NO: 65; SEQ ID NO: 196 and SEQ ID NO: 65; SEQ ID NO: 50  
 and SEQ ID NO: 49; SEQ ID NO: 70 and SEQ ID NO: 69; SEQ ID NO: 197 and SEQ ID NO:  
 69; SEQ ID NO: 198 and SEQ ID NO: 69; SEQ ID NO: 199 and SEQ ID NO: 69; SEQ ID NO:  
 200 and SEQ ID NO: 69; SEQ ID NO: 201 and SEQ ID NO: 69; SEQ ID NO: 38 and SEQ ID  
 NO: 5; SEQ ID NO: 73 and SEQ ID NO: 5; SEQ ID NO: 42 and SEQ ID NO: 41; SEQ ID NO:  
 30 44 and SEQ ID NO: 43; SEQ ID NO: 52 and SEQ ID NO: 51; SEQ ID NO: 54 and SEQ ID NO:  
 53; SEQ ID NO: 56 and SEQ ID NO: 55; SEQ ID NO: 58 and SEQ ID NO: 57; SEQ ID NO: 60  
 and SEQ ID NO: 59; SEQ ID NO: 37 and SEQ ID NO: 35; SEQ ID NO: 256 and SEQ ID NO:  
 63; SEQ ID NO: 257 and SEQ ID NO: 63; SEQ ID NO: 258 and SEQ ID NO: 63; SEQ ID NO:  
 259 and SEQ ID NO: 63; SEQ ID NO: 260 and SEQ ID NO: 63; SEQ ID NO: 261 and SEQ ID

35

NO: 63; SEQ ID NO: 262 and SEQ ID NO: 63; SEQ ID NO: 263 and SEQ ID NO: 63; SEQ ID  
 NO: 264 and SEQ ID NO: 63; SEQ ID NO: 265 and SEQ ID NO: 63; SEQ ID NO: 266 and SEQ

ID NO: 63; SEQ ID NO: 267 and SEQ ID NO: 63; SEQ ID NO: 268 and SEQ ID NO: 63; SEQ ID NO: 269 and SEQ ID NO: 63; SEQ ID NO: 270 and SEQ ID NO: 63; SEQ ID NO: 271 and SEQ ID NO: 63; SEQ ID NO: 272 and SEQ ID NO: 63; SEQ ID NO: 273 and SEQ ID NO: 63; SEQ ID NO: 274 and SEQ ID NO: 63; SEQ ID NO: 275 and SEQ ID NO: 63; SEQ ID NO: 276  
5 and SEQ ID NO: 63; SEQ ID NO: 277 and SEQ ID NO: 63; SEQ ID NO: 278 and SEQ ID NO: 63; SEQ ID NO: 279 and SEQ ID NO: 63; SEQ ID NO: 280 and SEQ ID NO: 63; SEQ ID NO: 281 and SEQ ID NO: 63; SEQ ID NO: 282 and SEQ ID NO: 63; SEQ ID NO: 283 and SEQ ID NO: 63; SEQ ID NO: 284 and SEQ ID NO: 63; SEQ ID NO: 285 and SEQ ID NO: 63; SEQ ID NO: 286 and SEQ ID NO: 63; SEQ ID NO: 287 and SEQ ID NO: 63; SEQ ID NO: 288 and SEQ ID NO: 63; SEQ ID NO: 289 and SEQ ID NO: 63; SEQ ID NO: 290 and SEQ ID NO: 63; SEQ ID NO: 291 and SEQ ID NO: 63; SEQ ID NO: 292 and SEQ ID NO: 63; SEQ ID NO: 293 and SEQ ID NO: 63; SEQ ID NO: 294 and SEQ ID NO: 67; SEQ ID NO: 295 and SEQ ID NO: 67; SEQ ID NO: 296 and SEQ ID NO: 67; SEQ ID NO: 297 and SEQ ID NO: 67; SEQ ID NO: 298, and SEQ ID NO: 67; SEQ ID NO: 299 and SEQ ID NO: 67; SEQ ID NO: 300 and SEQ ID NO: 67; SEQ ID NO: 301 and SEQ ID NO: 67; SEQ ID NO: 302 and SEQ ID NO: 67; SEQ ID NO: 303 and SEQ ID NO: 67; SEQ ID NO: 304 and SEQ ID NO: 67; SEQ ID NO: 305 and SEQ ID NO: 67; SEQ ID NO: 306 and SEQ ID NO: 67; SEQ ID NO: 307 and SEQ ID NO: 67; SEQ ID NO: 308 and SEQ ID NO: 67; SEQ ID NO: 309 and SEQ ID NO: 67; SEQ ID NO: 310 and SEQ ID NO: 67; SEQ ID NO: 311 and SEQ ID NO: 67; SEQ ID NO: 312 and SEQ ID NO: 67; SEQ ID NO: 313 and SEQ ID NO: 67; SEQ ID NO: 314 and SEQ ID NO: 67; SEQ ID NO: 315 and SEQ ID NO: 67; SEQ ID NO: 316 and SEQ ID NO: 67; SEQ ID NO: 317 and SEQ ID NO: 67; SEQ ID NO: 318 and SEQ ID NO: 67; SEQ ID NO: 319 and SEQ ID NO: 67; SEQ ID NO: 320 and SEQ ID NO: 67; SEQ ID NO: 321 and SEQ ID NO: 67; SEQ ID NO: 322 and SEQ ID NO: 67; SEQ ID NO: 323 and SEQ ID NO: 67; SEQ ID NO: 324 and SEQ ID NO: 67; SEQ ID NO: 325 and SEQ ID NO: 67; SEQ ID NO: 326 and SEQ ID NO: 67; SEQ ID NO: 327 and SEQ ID NO: 67; SEQ ID NO: 328 and SEQ ID NO: 67; SEQ ID NO: 329 and SEQ ID NO: 67; SEQ ID NO: 330 and SEQ ID NO: 67; SEQ ID NO: 331 and SEQ ID NO: 67; SEQ ID NO: 332 and SEQ ID NO: 253; SEQ ID NO: 333 and SEQ ID NO: 255; SEQ ID NO: 334 and SEQ ID NO: 253; and SEQ ID NO: 335 or SEQ ID NO: 255.

30 **[0054]** In some examples, proteins of the present disclosure comprise two polypeptides comprising amino acid sequences of SEQ ID NO: 63 and two polypeptides comprising amino

acid sequences of SEQ ID NO: 64, or two polypeptides comprising amino acid sequences of SEQ ID NO: 68 and two polypeptides comprising amino acid sequences of SEQ ID NO: 67.

5 [0055] In some examples, proteins of the present disclosure have an  $IC_{50}$  less than 12 nM, for example 5 nM to 12 nM or 5 nM to 9 nM, as measured in an OX40L neutralization/OX40-HEK reporter assay.

[0056] In some examples, proteins of the present disclosure have an  $IC_{50}$  of 2 nM to 12 nM, for example 2 nM to 9.5 nM, as measured in a primary T cell activation assay.

[0057] In some examples, proteins of the present disclosure have a  $K_D$  for OX40L binding of less than 75 nM, for example 20 nM to 75 nM, as measured in a Biacore assay.

10 [0058] In some examples, a protein of the present disclosure significantly inhibits at least one of IL-2, IFN $\gamma$ , IL-6, and TNF $\alpha$  production by cells in an *in vitro* mixed lymphocyte reaction assay as compared to cells treated under the same conditions but in the absence of protein, or in the presence of a human CTLA4 extracellular domain fused at the N-terminus of a human IgG1 Fc domain (CTLA4-Ig) and an anti-OX40L antibody, presented individually or in combination  
15 of the two proteins presented separately.

[0059] In some examples, a protein of the present disclosure significantly inhibits alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation in an *in vitro* mixed lymphocyte reaction assay as compared to alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody.

20 [0060] In some examples, a protein of the present disclosure preferentially inhibits alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation as compared to regulatory T cell ( $T_{reg}$ ) proliferation in an *in vitro* mixed lymphocyte reaction assay as compared to alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody.

25 [0061] In some examples, a protein of the present disclosure significantly enhances  $T_{reg}$  suppressive function in an *in vitro* mixed lymphocyte reaction assay as compared to  $T_{reg}$  cells treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody.

30 [0062] In some examples, a protein of the present disclosure significantly inhibits alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation in an adoptive transfer assay in humanized mice

as compared to alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells in mice treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody.

**[0063]** In some examples, a protein of the present disclosure significantly inhibits serum IFN $\gamma$  levels in an adoptive transfer assay in humanized mice as compared to mice treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody.

**[0064]** In some examples, a protein of the present disclosure is not significantly internalized into myeloid-derived dendritic cells (MDDCs).

**[0065]** In some examples, a protein of the present disclosure is cross-reactive with cynomolgus OX40L and/or is not cross-reactive with mouse, rabbit, or rat OX40L. In some examples, a protein of the present disclosure is cross reactive with cynomolgus CD80 and CD86.

**[0066]** In another example, the present disclosure provides the use of a heavy chain polypeptide as disclosed herein in the preparation of a protein comprising the heavy chain polypeptide and a light chain polypeptide as disclosed herein.

**[0067]** In another example, the present disclosure provides a formulation comprising a protein as disclosed herein and a pharmaceutically acceptable carrier.

**[0068]** In another example, the present disclosure provides a nucleic acid encoding a protein as disclosed herein.

**[0069]** In yet another example, the present disclosure provides a cell comprising one or more nucleic acids encoding a protein as disclosed herein.

**[0070]** In another example, the present disclosure provides a method of treating an autoimmune disease in a patient comprising administering to the patient a protein or formulation as disclosed herein. For example, autoimmune diseases that can be treated by proteins of the present disclosure include rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, atopic dermatitis, Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis,

Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or

5 Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Cutaneous Lupus, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia,

10 Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, IgA Nephropathy,

15 IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed

20 connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis

25 (peripheral uveitis), Parsonage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA),

30 Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's

arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, and Vogt-Koyanagi-Harada Disease. In another example, the present disclosure provides a method of treating graft versus host disease (GVHD) in a patient, comprising administering to the patient a protein or formulation as disclosed herein.

**[0071]** In still another example, the present disclosure provides an antibody or functional fragment thereof comprising, according to the IMGT unique numbering scheme, a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN (SEQ ID NO: 82), and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83).

**[0072]** In some examples, an antibody of the present disclosure comprises a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 76, and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 80.

**[0073]** In some examples, an antibody of the present disclosure or functional fragment thereof comprises, according to the IMGT unique numbering scheme, a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a VLCDR1 comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a VLCDR2 comprising an amino acid sequence of GKD (SEQ ID NO: 98), and a VLCDR3 comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99).

**[0074]** In some examples, an antibody of the present disclosure comprises a heavy chain variable domain comprises an amino acid sequence at least 90% identical to SEQ ID NO: 92,

and a light chain variable domain comprises an amino acid sequence at least 90% identical to SEQ ID NO: 96.

5 [0075] In some examples, an antibody of the present disclosure or functional fragment thereof comprises, according to the IMGT unique numbering scheme, a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 10  
91).

[0076] In some examples, an antibody of the present disclosure comprises a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 84, and the light chain variable domain (VL) comprises an amino acid sequence at least 90% identical to SEQ ID NO: 88.

15 [0077] In some examples, an antibody of the present disclosure or functional fragment thereof comprises, according to the IMGT unique numbering scheme, a VHCDR1 comprising an amino acid sequence of GGSISSSSYY (SEQ ID NO: 101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS (SEQ ID NO: 90), and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91).  
20

[0078] In some examples, an antibody of the present disclosure comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to SEQ ID NO: 100, and a light chain variable domain (VL) comprises an amino acid sequence at least 90% identical to SEQ ID NO: 104.  
25

[0079] In some examples, antibodies of the present disclosure, or functional fragments thereof, are human IgG1 antibodies.

[0080] In another example, the present disclosure provides the use of an antibody as disclosed herein or functional fragment thereof, in the preparation of a protein as disclosed herein.  
30

[0081] Other examples and details of the disclosure are presented herein below.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0082] **FIGs. 1A-1W** provide schematic illustrations of various protein designs of fusion proteins with Ig Fc constant domains that bind CD80 and/or CD86, and OX40L. **FIG. 1A** is a schematic illustration of an exemplary fusion protein where Extracellular Domains (ECDs) of CD28 are fused to the N-terminus of an Fc domain and ECDs of OX40 are fused to the C-terminus of the same Fc domain. **FIG. 1B** is a schematic illustration of an exemplary fusion protein where ECDs of OX40 are fused to the N-terminus of an Fc domain and ECDs of CD28 are fused to the C-terminus of the same Fc domain. **FIG. 1C** is a schematic illustration of an exemplary fusion protein where ECDs of CTLA4 are fused to the N-terminus of an Fc domain and ECDs of OX40 are fused to the C-terminus of the same Fc domain. **FIG. 1D** is a schematic illustration of an exemplary fusion protein where ECDs of OX40 are fused to the N-terminus of an Fc domain and ECDs of CTLA4 are fused to the C-terminus of the same Fc domain. **FIG. 1E** is a schematic illustration of an exemplary fusion protein where ECDs of CD28 are each fused in tandem to the N-termini of ECDs of OX40 which are then fused to the N-termini of an Fc domain. **FIG. 1F** is a schematic illustration of an exemplary fusion protein where ECDs of CTLA4 are each fused in tandem to the N-termini of ECDs of OX40 which are then fused to the N-terminus of an Fc domain. **FIG. 1G** is a schematic illustration of an exemplary fusion protein where ECDs of OX40 are each fused in tandem to the N-termini of ECDs of CD28 which are then fused to the N-terminus of an Fc domain. **FIG. 1H** is a schematic illustration of an exemplary fusion protein where an ECD of OX40 is fused in tandem to the N-terminus of an ECD of CTLA4 which is then fused to the N-terminus of an Fc domain. **FIG. 1I** is a schematic illustration of an exemplary fusion protein where any tandem ECD combination of **FIGs. 1E-1H** (labelled here as X and Y) are fused to the C-terminus of an Fc domain. **FIG. 1J** is a schematic illustration of an exemplary fusion protein where an ECD of CD28 is fused to the N-terminus of an Fc domain and an anti-OX40L antibody binding domain is fused to the C-terminus of the same Fc domain. **FIG. 1K** is a schematic illustration of an exemplary fusion protein where ECDs of CTLA4 are fused to the N-terminus of an Fc domain and anti-OX40L antibody binding domains are fused to the C-terminus of the same Fc domain. **FIG. 1L** is a schematic illustration of an exemplary fusion protein where an ECD of OX40 is fused to the N-terminus of an Fc domain and anti-CD80 and anti-CD86 antibody binding domains are fused to the C-terminus of the Fc domain. **FIG. 1M** is a schematic illustration of an exemplary fusion protein where anti-OX40L antibody binding domains are fused to the N-terminus of an Fc domain and anti-CD80

## CLAIMS

### WHAT IS CLAIMED IS

1. A protein comprising  
an extracellular domain of CTLA4 or functional fragment thereof and a polypeptide or  
5 complex of two or more polypeptides that specifically binds OX40L, wherein the polypeptide or  
complex of two or more polypeptides that specifically binds OX40L comprises an antigen-  
binding site.
2. The protein of claim 1, wherein the CTLA4 extracellular domain or functional fragment  
thereof comprises a sequence having at least 90% sequence identity to SEQ ID NO: 29,  
10 SEQ ID NO: 173, or SEQ ID NO: 174.
3. The protein of claim 2, wherein the antigen binding site comprises a Fab or an antibody.
4. The protein of claim 3, wherein the Fab comprises a polypeptide comprising the  
sequence of SEQ ID NO: 336 connected to the C-terminus of the Fab heavy chain CH1  
domain.
- 15 5. The protein of claim 1, further comprising a bridging moiety  
wherein the bridging moiety comprises a polypeptide of a human IgG1 Fc  
domain; optionally wherein the polypeptide of a human IgG1 Fc domain comprises a  
sequence having at least 90% or 100% sequence identity to an amino acid sequence  
selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO:  
20 238, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID  
NO: 239, and SEQ ID NO: 240.
6. The protein of claim 5, wherein the bridging moiety further comprises a hinge  
polypeptide  
comprising an amino acid sequence having at least 90% sequence identity to an amino  
25 acid sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 242,  
SEQ ID NO: 176, SEQ ID NO: 249, SEQ ID NO: 177, SEQ ID NO: 243, SEQ ID NO:  
212, SEQ ID NO: 244, SEQ ID NO: 213, SEQ ID NO: 245, SEQ ID NO: 247, and SEQ  
ID NO: 248.

7. The protein of claim 6, wherein the:
- (a) extracellular domain of CTLA4 or functional fragment thereof is connected to the N-terminus of the bridging moiety; or
  - (b) polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the C-terminus of the bridging moiety;
- optionally wherein a linker polypeptide connects the polypeptide or complex of two or more polypeptides that specifically binds OX40L to the bridging moiety.
8. The protein of claim 7, further comprising a second polypeptide or complex of two or more polypeptides that specifically binds OX40L,
- wherein the bridging moiety is a polypeptide of a human IgG1 Fc domain and the polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the C-terminus of the polypeptide of the human IgG1 Fc domain and the second polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the C-terminus of a second polypeptide of a human IgG1 Fc domain.
9. The protein of claim 8, wherein the second polypeptide or complex of two or more polypeptides that specifically binds OX40L is connected to the bridging moiety by a linker polypeptide;
- optionally wherein the linker polypeptide comprises a (GGGGS)<sub>n</sub> (SEQ ID NO: 181) sequence, wherein n is 1 to 12.
10. The protein of claim 3, wherein the antigen-binding site comprises:
- (a) a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence
- GX<sub>1</sub>SX<sub>2</sub>X<sub>3</sub>X<sub>4</sub>SX<sub>5</sub>YY (SEQ ID NO: 222),
- wherein X<sub>1</sub> is A, G, or V;
- X<sub>2</sub> is V, or I;
- X<sub>3</sub> is S or R;

X<sub>4</sub> is S, or T; and

X<sub>5</sub> is S, or G;

(b) a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence selected from the group consisting of:

5 (1) IX<sub>1</sub>YX<sub>2</sub>GST (SEQ ID NO: 223)

wherein X<sub>1</sub> is Y, or N, and

X<sub>2</sub> is S, or G,

(2) X<sub>1</sub>DYSGT (SEQ ID NO: 224)

wherein X<sub>1</sub> is I or M, and

10 (3) IGSVDYSGX<sub>1</sub>T (SEQ ID NO: 225)

wherein X<sub>1</sub> is N, A, or S;

(c) a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence selected from the group consisting of:

(1) ARHRGX<sub>1</sub>YX<sub>2</sub>FDX<sub>3</sub> (SEQ ID NO: 220)

15 wherein X<sub>1</sub> is S or I,

X<sub>2</sub> is F or H, and

X<sub>3</sub> is I or Y; and

(2) ARERSX<sub>1</sub>X<sub>2</sub>WYPX<sub>3</sub>DY (SEQ ID NO: 221)

wherein X<sub>1</sub> is N or S,

20 X<sub>2</sub> is N, D, G or S, and

X<sub>3</sub> is I or F

(d) a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence selected from the group consisting of:

(1) X<sub>1</sub>IENKN (SEQ ID NO: 226)

wherein X<sub>1</sub> is N or D, and

(2) SX<sub>1</sub>RX<sub>2</sub>X<sub>3</sub>X<sub>4</sub>

wherein X<sub>1</sub> is V or L,

5 X<sub>2</sub> is R or N,

X<sub>3</sub> is F or Y, and

X<sub>4</sub> is F or Y;

(e) a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence selected from the group consisting of

10 RDN, GKD, and RDS;

and

(f) a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence selected from the group consisting of:

(1) QVX<sub>1</sub>DSX<sub>2</sub>X<sub>3</sub>VV (SEQ ID NO: 231)

15 wherein X<sub>1</sub> is R or W,

X<sub>2</sub> is N, T, or A, and

X<sub>3</sub> is I, T, or A, and

(2) NSRDSSGYX<sub>1</sub>VX<sub>2</sub> (SEQ ID NO: 232)

wherein X<sub>1</sub> is L or H, and

20 X<sub>2</sub> is L or V.

11. The protein of claim 3, wherein the antigen-binding site comprises:

(i) (a) a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a

- VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a  
VLCDR2 comprising an amino acid sequence of RDN, and a VLCDR3 comprising an  
amino acid sequence of QVRDSNIVV (SEQ ID NO: 83);
- (b) a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO:  
5 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a  
VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO:  
95), a VLCDR1 comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a  
VLCDR2 comprising an amino acid sequence of GKD, and a VLCDR3 comprising an  
amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99);
- (c) a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85),  
10 a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a  
VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a  
VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a  
VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an  
15 amino acid sequence of QVWDSNTVV (SEQ ID NO: 91);
- (d) a VHCDR1 comprising an amino acid sequence of GGSISSSSYY (SEQ ID NO:  
101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO:  
102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO:  
103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a  
20 VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an  
amino acid sequence of QVWDSNTVV (SEQ ID NO: 91); or
- (e) according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3,  
VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence  
corresponding to the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and  
25 VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain  
listed in TABLE 3, respectively; and/or
- (ii) (a) an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 76,  
SEQ ID NO: 92, SEQ ID NO: 84, or SEQ ID NO: 100, and an amino acid sequence  
having at least 90% sequence identity to SEQ ID NO: 80, SEQ ID NO: 96, SEQ ID NO:  
30 88, or SEQ ID NO: 104;

- (b) an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 76, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 80;
- (c) an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 92, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 96; or
- 5 (d) according to the IMGT unique numbering scheme, a heavy chain variable domain and a light chain variable domain each comprising an amino acid sequence corresponding to the heavy chain variable domain and light chain variable domain sequences of a heavy chain variable domain and light chain variable domain listed in TABLE 3, respectively; and/or
- 10 (iii) (a) an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 14, or SEQ ID NO: 18, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 7, SEQ ID NO: 15, SEQ ID NO: 13, or SEQ ID NO: 17;
- (b) an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 8, and
- 15 an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 7;
- (c) an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 16, and an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 15; or
- (d) according to the IMGT unique numbering scheme, a heavy chain and a light chain each comprising an amino acid sequence corresponding to the heavy chain and light
- 20 chain sequences of a heavy chain and light chain listed in TABLE 3, respectively.
12. The protein of claim 3, wherein the antigen-binding site binds at:
- (i) position 60 and/or 83 of the extracellular domain of human OX40L;
- (ii) position 17, 18, 19, 20, 21, 23, 26, 28, 60, 83, 110, 111, 112, 113, and 114 of the extracellular domain of human OX40L; or
- 25 (iii) position 58, 59, 60, 61, 62, 63, 81, 82, and 83 of the extracellular domain of human OX40L.
13. The protein of claim 3 comprising:

- (i) (a) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- (b) a bridging moiety comprising a sequence comprising of SEQ ID NO: 177 and a sequence comprising of SEQ ID NO: 179; and
- 5 (c) an antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a VLCDR2 comprising an amino acid sequence of RDN, and a VLCDR3 comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83)
- 10 or
- (ii) a first arm and a second arm, the first arm comprising:
- (a) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- 15 (b) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 177 and a sequence comprising of SEQ ID NO: 179; and
- (c) a first antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a VLCDR2 comprising an amino acid sequence of RDN , and a VLCDR3 comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83), and
- 20 the second arm comprising:
- (a) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- 25 (b) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 177 and a sequence comprising of SEQ ID NO: 179; and

(c) a second antigen-binding site comprising a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a VLCDR2 comprising an amino acid sequence of RDN, and a VLCDR3 comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83);

wherein the first arm and the second arm dimerize with each other.

14. The protein of claim 3 comprising:

(i) (a) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

(b) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and

(c) an antigen-binding site comprising a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a VLCDR1 comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a VLCDR2 comprising an amino acid sequence of GKD, and a VLCDR3 comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99);

(ii) a first arm and a second arm, the first arm comprising:

(a) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

(b) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and

(c) a first antigen-binding site comprising a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a VLCDR1 comprising an amino

acid sequence of SVRRFF (SEQ ID NO: 97), a VLCDR2 comprising an amino acid sequence of GKD, and a VLCDR3 comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99); and

the second arm comprising:

5 (a) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

(b) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and

10 (c) a second antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a VLCDR1 comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a VLCDR2 comprising an amino acid sequence of GKD, and a VLCDR3 comprising an amino acid sequence of  
15 NSRDSSGYLVL (SEQ ID NO: 99),

wherein the first arm and the second arm dimerize with each other;

(iii) (a) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

20 (b) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 214; and

(c) an antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a VLCDR1 comprising an amino acid sequence of  
25 NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91);

(iv) a first arm and a second arm, the first arm comprising:

- (a) a first polypeptide complex the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- (b) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 214; and
- 5 (c) a first antigen-binding site comprising a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91), and
- 10 the second arm comprising:
- (a) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- 15 (b) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 214; and
- (c) a second antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91),
- 20 wherein the first arm and the second arm dimerize with each other;
- 25 (v) (a) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- (b) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and

- 5 (c) an antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91);
- (vi) a first arm and a second arm, the first arm comprising:
- 10 (a) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- (b) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and
- 15 (c) a first antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91), and
- 20 the second arm comprising:
- (a) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;
- (b) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and
- 25 (c) a second antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence

of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91),

wherein the first arm and the second arm dimerize with each other;

5 (vii) (a) a polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

(b) a bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and

10 (c) an antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a VLCDR2 comprising an amino acid sequence of RDN, and a VLCDR3 comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83);

(viii) a first arm and a second arm, the first arm comprising:

15 (a) a first polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

(b) a first bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and

20 (c) a first antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a VLCDR2 comprising an amino acid sequence of RDN, and a VLCDR3 comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83), and

the second arm comprising:

(a) a second polypeptide comprising the extracellular domain of CTLA4 comprising SEQ ID NO: 174;

- (b) a second bridging moiety comprising a sequence comprising of SEQ ID NO: 213 and a sequence comprising of SEQ ID NO: 216; and
- (c) a second antigen-binding site comprising, a VHCDR1 comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a VHCDR2 comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a VLCDR1 comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a VLCDR2 comprising an amino acid sequence of RDN, and a VLCDR3 comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83),
- wherein the first arm and the second arm dimerize with each other;
- (ix) (a) a polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235;
- (b) a bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and
- (c) an antigen-binding site comprising, according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence corresponding to the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain listed in TABLE 3, respectively; or
- (x) a first arm and a second arm, the first arm comprising:
- (a) a first polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235;
- (b) a first bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID

NO: 178, SEQ ID NO: 237, SEQ ID NO: 214 , SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and

5 (c) a first antigen-binding site comprising, according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence corresponding to the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain listed in TABLE 3, respectively, and

the second arm comprising:

10 (a) a second polypeptide comprising the extracellular domain of CTLA4 comprising a sequence selected from a group consisting of SEQ ID NO: 174, SEQ ID NO: 119, SEQ ID NO: 215, SEQ ID NO: 233, SEQ ID NO: 234, and SEQ ID NO: 235;

(b) a second bridging moiety comprising a sequence selected from a group consisting of SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 212, SEQ ID NO: 213, and SEQ ID NO: 248, and a sequence selected from a group consisting of SEQ ID NO: 178, SEQ ID NO: 237, SEQ ID NO: 214 , SEQ ID NO: 216, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 239, and SEQ ID NO: 240; and

15 (c) a second antigen-binding site comprising, according to the IMGT unique numbering scheme, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 each comprising an amino acid sequence corresponding to the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 sequences of a heavy chain variable domain and a light chain variable domain listed in TABLE 3, respectively,

wherein the first arm and the second arm dimerize with each other.

15. The protein of claim 15, wherein:

25 (i) the antigen-binding site further comprises a partial hinge polypeptide comprising the sequence of SEQ ID NO: 336; or

(ii) the first antigen-binding site and second antigen-binding site both further comprise a partial hinge polypeptide comprising the sequence of SEQ ID NO: 336.

16. The protein of claim 3 comprising:

(i) an amino acid sequence at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NO: 40, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 48, SEQ ID NO: 68, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 46, SEQ ID NO: 66, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 50, SEQ ID NO: 70, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 38, SEQ ID NO: 73, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 37, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258, SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, SEQ ID NO: 266, SEQ ID NO: 267, SEQ ID NO: 268, SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, SEQ ID NO: 281, SEQ ID NO: 282, SEQ ID NO: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, SEQ ID NO: 306, SEQ ID NO: 307, SEQ ID NO: 308, SEQ ID NO: 309, SEQ ID NO: 310, SEQ ID NO: 311, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 314, SEQ ID NO: 315, SEQ ID NO: 316, SEQ ID NO: 317, SEQ ID NO: 318, SEQ ID NO: 319, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 324, SEQ ID NO: 325, SEQ ID NO: 326, SEQ ID NO: 327, SEQ ID NO: 328, SEQ ID NO: 329, SEQ ID NO: 330, SEQ ID NO: 331, SEQ ID NO: 332, SEQ ID NO: 333, SEQ ID NO: 334, and SEQ ID NO: 335; or

(ii) polypeptides comprising amino acid sequences at least 90% identical to the amino acid sequences of:

SEQ ID NO: 40 and SEQ ID NO: 39;

SEQ ID NO: 62 and SEQ ID NO: 61;

SEQ ID NO: 64 and SEQ ID NO: 63;

SEQ ID NO: 182 and SEQ ID NO: 63;

SEQ ID NO: 183 and SEQ ID NO: 63;

SEQ ID NO: 184 and SEQ ID NO: 63;

SEQ ID NO: 185 and SEQ ID NO: 63;

5 SEQ ID NO: 186 and SEQ ID NO: 63;

SEQ ID NO: 48 and SEQ ID NO: 47;

SEQ ID NO: 68 and SEQ ID NO: 67;

SEQ ID NO: 187 and SEQ ID NO: 67;

SEQ ID NO: 188 and SEQ ID NO: 67;

10 SEQ ID NO: 189 and SEQ ID NO: 67;

SEQ ID NO: 190 and SEQ ID NO: 67;

SEQ ID NO: 191 and SEQ ID NO: 67;

SEQ ID NO: 46 and SEQ ID NO: 45;

SEQ ID NO: 66 and SEQ ID NO: 65;

15 SEQ ID NO: 192 and SEQ ID NO: 65;

SEQ ID NO: 193 and SEQ ID NO: 65;

SEQ ID NO: 194 and SEQ ID NO: 65;

SEQ ID NO: 195 and SEQ ID NO: 65;

SEQ ID NO: 196 and SEQ ID NO: 65;

20 SEQ ID NO: 50 and SEQ ID NO: 49;

SEQ ID NO: 70 and SEQ ID NO: 69;

SEQ ID NO: 197 and SEQ ID NO: 69;

SEQ ID NO: 198 and SEQ ID NO: 69;

SEQ ID NO: 199 and SEQ ID NO: 69;

SEQ ID NO: 200 and SEQ ID NO: 69;

SEQ ID NO: 201 and SEQ ID NO: 69;

5 SEQ ID NO: 38 and SEQ ID NO: 5;

SEQ ID NO: 73 and SEQ ID NO: 5;

SEQ ID NO: 42 and SEQ ID NO: 41;

SEQ ID NO: 44 and SEQ ID NO: 43;

SEQ ID NO: 52 and SEQ ID NO: 51;

10 SEQ ID NO: 54 and SEQ ID NO: 53;

SEQ ID NO: 56 and SEQ ID NO: 55;

SEQ ID NO: 58 and SEQ ID NO: 57;

SEQ ID NO: 60 and SEQ ID NO: 59;

SEQ ID NO: 37 and SEQ ID NO: 35;

15 SEQ ID NO: 256 and SEQ ID NO: 63;

SEQ ID NO: 257 and SEQ ID NO: 63;

SEQ ID NO: 258 and SEQ ID NO: 63;

SEQ ID NO: 259 and SEQ ID NO: 63;

SEQ ID NO: 260 and SEQ ID NO: 63;

20 SEQ ID NO: 261 and SEQ ID NO: 63;

SEQ ID NO: 262 and SEQ ID NO: 63;

SEQ ID NO: 263 and SEQ ID NO: 63;

SEQ ID NO: 264 and SEQ ID NO: 63;

SEQ ID NO: 265 and SEQ ID NO: 63;

SEQ ID NO: 266 and SEQ ID NO: 63;

SEQ ID NO: 267 and SEQ ID NO: 63;

5 SEQ ID NO: 268 and SEQ ID NO: 63;

SEQ ID NO: 269 and SEQ ID NO: 63;

SEQ ID NO: 270 and SEQ ID NO: 63;

SEQ ID NO: 271 and SEQ ID NO: 63;

SEQ ID NO: 272 and SEQ ID NO: 63;

10 SEQ ID NO: 273 and SEQ ID NO: 63;

SEQ ID NO: 274 and SEQ ID NO: 63;

SEQ ID NO: 275 and SEQ ID NO: 63;

SEQ ID NO: 276 and SEQ ID NO: 63;

SEQ ID NO: 277 and SEQ ID NO: 63;

15 SEQ ID NO: 278 and SEQ ID NO: 63;

SEQ ID NO: 279 and SEQ ID NO: 63;

SEQ ID NO: 280 and SEQ ID NO: 63;

SEQ ID NO: 281 and SEQ ID NO: 63;

SEQ ID NO: 282 and SEQ ID NO: 63;

20 SEQ ID NO: 283 and SEQ ID NO: 63;

SEQ ID NO: 284 and SEQ ID NO: 63;

SEQ ID NO: 285 and SEQ ID NO: 63;

SEQ ID NO: 286 and SEQ ID NO: 63;

SEQ ID NO: 287 and SEQ ID NO: 63;

SEQ ID NO: 288 and SEQ ID NO: 63;

SEQ ID NO: 289 and SEQ ID NO: 63;

5 SEQ ID NO: 290 and SEQ ID NO: 63;

SEQ ID NO: 291 and SEQ ID NO: 63;

SEQ ID NO: 292 and SEQ ID NO: 63;

SEQ ID NO: 293 and SEQ ID NO: 63;

SEQ ID NO: 294 and SEQ ID NO: 67;

10 SEQ ID NO: 295 and SEQ ID NO: 67;

SEQ ID NO: 296 and SEQ ID NO: 67;

SEQ ID NO: 297 and SEQ ID NO: 67;

SEQ ID NO: 298, and SEQ ID NO: 67;

SEQ ID NO: 299 and SEQ ID NO: 67;

15 SEQ ID NO: 300 and SEQ ID NO: 67;

SEQ ID NO: 301 and SEQ ID NO: 67;

SEQ ID NO: 302 and SEQ ID NO: 67;

SEQ ID NO: 303 and SEQ ID NO: 67;

SEQ ID NO: 304 and SEQ ID NO: 67;

20 SEQ ID NO: 305 and SEQ ID NO: 67;

SEQ ID NO: 306 and SEQ ID NO: 67;

SEQ ID NO: 307 and SEQ ID NO: 67;

SEQ ID NO: 308 and SEQ ID NO: 67;

SEQ ID NO: 309 and SEQ ID NO: 67;

SEQ ID NO: 310 and SEQ ID NO: 67;

SEQ ID NO: 311 and SEQ ID NO: 67;

5 SEQ ID NO: 312 and SEQ ID NO: 67;

SEQ ID NO: 313 and SEQ ID NO: 67;

SEQ ID NO: 314 and SEQ ID NO: 67;

SEQ ID NO: 315 and SEQ ID NO: 67;

SEQ ID NO: 316 and SEQ ID NO: 67;

10 SEQ ID NO: 317 and SEQ ID NO: 67;

SEQ ID NO: 318 and SEQ ID NO: 67;

SEQ ID NO: 319 and SEQ ID NO: 67;

SEQ ID NO: 320 and SEQ ID NO: 67;

SEQ ID NO: 321 and SEQ ID NO: 67;

15 SEQ ID NO: 322 and SEQ ID NO: 67;

SEQ ID NO: 323 and SEQ ID NO: 67;

SEQ ID NO: 324 and SEQ ID NO: 67;

SEQ ID NO: 325 and SEQ ID NO: 67;

SEQ ID NO: 326 and SEQ ID NO: 67;

20 SEQ ID NO: 327 and SEQ ID NO: 67;

SEQ ID NO: 328 and SEQ ID NO: 67;

SEQ ID NO: 329 and SEQ ID NO: 67;

SEQ ID NO: 330 and SEQ ID NO: 67;

SEQ ID NO: 331 and SEQ ID NO: 67;

SEQ ID NO: 332 and SEQ ID NO: 253;

SEQ ID NO: 333 and SEQ ID NO: 255;

5 SEQ ID NO: 334 and SEQ ID NO: 253; or

SEQ ID NO: 335 and SEQ ID NO: 255.

17. The protein of claim 3 comprising:

(i) polypeptides comprising amino acid sequences of SEQ ID NO: 62 and SEQ ID NO: 61;

10 (ii) two polypeptides comprising amino acid sequences of SEQ ID NO: 62 and two polypeptides comprising amino acid sequences of SEQ ID NO: 61;

(iii) polypeptides comprising amino acid sequences of SEQ ID NO: 63 and SEQ ID NO: 64;

15 (iv) two polypeptides comprising amino acid sequences of SEQ ID NO: 63 and two polypeptides comprising amino acid sequences of SEQ ID NO: 64;

(v) polypeptides comprising amino acid sequences of SEQ ID NO: 68 and SEQ ID NO: 67; or

(vi) two polypeptides comprising amino acid sequences of SEQ ID NO: 68 and two polypeptides comprising amino acid sequences of SEQ ID NO: 67.

20 18. The protein of claim 1, wherein:

(i) the protein has an  $IC_{50}$  less than 12 nM as measured in an OX40L neutralization/OX40-HEK reporter assay;

optionally wherein the protein has an  $IC_{50}$  of 5 nM to 12 nM as measured in an OX40L neutralization/OX40-HEK reporter assay;

further optionally wherein the protein has an IC<sub>50</sub> of 5 nM to 9 nM as measured in an OX40L neutralization/OX40-HEK reporter assay; and/or

(ii) the protein has an IC<sub>50</sub> of 2 nM to 12 nM as measured in a primary T cell activation assay;

5 optionally wherein the protein has an IC<sub>50</sub> of 2 nM to 9.5 nM as measured in a primary T cell activation assay; and/or

(iii) the protein has a K<sub>D</sub> for OX40L binding of less than 75 nM as measured in a Biacore assay;

10 optionally the protein has a K<sub>D</sub> for OX40L binding of 20 nM to 75 nM as measured in a Biacore assay; and/or

(iv) the protein significantly inhibits at least one of IL-2, IFN $\gamma$ , IL-6, and TNF $\alpha$  production by cells in an *in vitro* mixed lymphocyte reaction assay as compared to cells treated under the same conditions but in the absence of protein, or in the presence of a human CTLA4 extracellular domain fused at the N-terminus of a human IgG1 Fc domain (CTLA4-Ig) and an anti-OX40L antibody, presented individually or in combination of the two proteins presented separately; and/or

15

(v) the protein significantly inhibits alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation in an *in vitro* mixed lymphocyte reaction assay as compared to alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody; and/or

20

(vi) the protein preferentially inhibits alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation as compared to regulatory T cell (T<sub>reg</sub>) proliferation in an *in vitro* mixed lymphocyte reaction assay as compared to alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody; and/or

25

(vii) the protein significantly enhances T<sub>reg</sub> suppressive function in an *in vitro* mixed lymphocyte reaction assay as compared to T<sub>reg</sub> cells treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody; and/or

- (viii) the protein significantly inhibits alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell proliferation in an adoptive transfer assay in humanized mice as compared to alloreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells in mice treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody; and/or
- 5 (ix) the protein significantly inhibits serum IFN $\gamma$  levels in an adoptive transfer assay in humanized mice as compared to mice treated under the same conditions but in the absence of protein, or in the presence of a CTLA4-Ig and/or an anti-OX40L antibody; and/or
- 10 (x) the protein is not significantly internalized into myeloid-derived dendritic cells (MDDCs); and/or
- (xi) the protein is cross-reactive with cynomolgus OX40L; and/or
- (xii) the protein is not cross-reactive with mouse, rabbit, or rat OX40L; and/or
- (xiii) the protein is cross reactive with cynomolgus CD80 and CD86.
- 15 19. A formulation comprising the protein of claim 1 and a pharmaceutically acceptable carrier.
20. A nucleic acid encoding the protein of claim 1.
21. A cell comprising one or more nucleic acids encoding the protein of claim 1.
22. Use of the protein of claim 1 in the manufacture of a medicament for treating an autoimmune disease.
- 20 23. The use of claim 23, wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, atopic dermatitis, Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia,
- 25 Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas

disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Cocksackie myocarditis, CREST syndrome, Crohn's disease, Cutaneous Lupus, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis,

Thrombocytopenic purpura (TTP), Thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, and Vogt-Koyanagi-Harada Disease.

5        24. Use of the protein of claim 1 in the manufacture of a medicament for treating graft versus host disease (GVHD).

25. An antibody or functional fragment thereof comprising:

10        (i) a heavy chain variable complementarity-determining region 1 (VHCDR1) comprising an amino acid sequence of GGSISTSSYY (SEQ ID NO: 77), a heavy chain variable complementarity-determining region 2 (VHCDR2) comprising an amino acid sequence of IYYSGST (SEQ ID NO: 78), a heavy chain variable complementarity-determining region 3 (VHCDR3) comprising an amino acid sequence of ARHRGSYFFDI (SEQ ID NO: 79), a light chain variable complementarity-determining region 1 (VLCDR1) comprising an amino acid sequence of DIENKN (SEQ ID NO: 81), a light chain variable complementarity-determining region 2 (VLCDR2) comprising an amino acid sequence of RDN, and a light chain variable complementarity-determining region 3 (VLCDR3) comprising an amino acid sequence of QVRDSNIVV (SEQ ID NO: 83) (according to the IMGT unique numbering scheme); or

20        (ii) a VHCDR1 comprising an amino acid sequence of GVSIRSNGYY (SEQ ID NO: 93), a VHCDR2 comprising an amino acid sequence of MDYSGT (SEQ ID NO: 94), a VHCDR3 comprising an amino acid sequence of ARERSNNWYPIDY (SEQ ID NO: 95), a VLCDR1 comprising an amino acid sequence of SVRRFF (SEQ ID NO: 97), a VLCDR2 comprising an amino acid sequence of GKD, and a VLCDR3 comprising an amino acid sequence of NSRDSSGYLVL (SEQ ID NO: 99) (according to the IMGT unique numbering scheme); or

25        (iii) a VHCDR1 comprising an amino acid sequence of GASVSSSSYY (SEQ ID NO: 85), a VHCDR2 comprising an amino acid sequence of INYGGST (SEQ ID NO: 86), a VHCDR3 comprising an amino acid sequence of ARHRGIYHFDY (SEQ ID NO: 87), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91) (according to the IMGT unique numbering scheme); or

- (iv) a VHCDR1 comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 101), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 102), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a  
5 VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVV (SEQ ID NO: 91) (according to the IMGT unique numbering scheme); or
- (v) a VHCDR1 comprising an amino acid sequence of GGSISSSSY (SEQ ID NO: 109), a VHCDR2 comprising an amino acid sequence of IGSVDYSGNT (SEQ ID NO: 110), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a  
10 VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVI (SEQ ID NO: 115) (according to the IMGT unique numbering scheme); or
- (vi) a VHCDR1 comprising an amino acid sequence of GGSIDTSSQY (SEQ ID NO: 117), a VHCDR2 comprising an amino acid sequence of IYFSGST (SEQ ID NO: 118), a VHCDR3 comprising an amino acid sequence of ARHRGIYFFDY (SEQ ID NO: 103), a  
15 VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDT, and a VLCDR3 comprising an amino acid sequence of QVWDSNTVI (SEQ ID NO: 123) (according to the IMGT unique numbering scheme); or
- (vii) a VHCDR1 comprising an amino acid sequence of GGSISSGSFY (SEQ ID NO: 125), a VHCDR2 comprising an amino acid sequence of IYYS GST (SEQ ID NO: 126), a VHCDR3 comprising an amino acid sequence of ARERSSSWYPFDY (SEQ ID NO: 127), a VLCDR1 comprising an amino acid sequence of SLRNYF (SEQ ID NO: 129), a  
20 VLCDR2 comprising an amino acid sequence of GKN, and a VLCDR3 comprising an amino acid sequence of NSRDSSGYHVV (SEQ ID NO: 131) (according to the IMGT unique numbering scheme); or
- (viii) a VHCDR1 comprising an amino acid sequence of GFTFSNYA (SEQ ID NO: 133), a VHCDR2 comprising an amino acid sequence of ISGSGDST (SEQ ID NO: 134), a VHCDR3 comprising an amino acid sequence of AKDRTPVYGLDV (SEQ ID NO: 135), a VLCDR1 comprising an amino acid sequence of NIGRKN (SEQ ID NO: 137), a  
30

VLCDR2 comprising an amino acid sequence of GDS, and a VLCDR3 comprising an amino acid sequence of QVWDSSTV (SEQ ID NO: 139) (according to the IMGT unique numbering scheme); or

5 (ix) a VHCDR1 comprising an amino acid sequence of GFTFSSYA (SEQ ID NO: 141), a VHCDR2 comprising an amino acid sequence of ISGSGGST (SEQ ID NO: 142), a VHCDR3 comprising an amino acid sequence of AKDLGFYSTWDTDY (SEQ ID NO: 143), a VLCDR1 comprising an amino acid sequence of QGIRND (SEQ ID NO: 145), a VLCDR2 comprising an amino acid sequence of AAS, and a VLCDR3 comprising an amino acid sequence of LQHNTYPWT (SEQ ID NO: 147) (according to the IMGT unique numbering scheme); or

10 (x) a VHCDR1 comprising an amino acid sequence of GASISSNHYWG (SEQ ID NO: 149), a VHCDR2 comprising an amino acid sequence of IYYSGNT (SEQ ID NO: 150), a VHCDR3 comprising an amino acid sequence of ARHRGSYFFDH (SEQ ID NO: 151), a VLCDR1 comprising an amino acid sequence of NIGDKN (SEQ ID NO: 153), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSSTVV (SEQ ID NO: 155) (according to the IMGT unique numbering scheme); or

15 (xi) a VHCDR1 comprising an amino acid sequence of GDSVSSNSAV (SEQ ID NO: 157), a VHCDR2 comprising an amino acid sequence of TDYRSKWNN (SEQ ID NO: 158), a VHCDR3 comprising an amino acid sequence of ARGDAGMASFDY (SEQ ID NO: 159), a VLCDR1 comprising an amino acid sequence of KLGDKY (SEQ ID NO: 161), a VLCDR2 comprising an amino acid sequence of QDR, and a VLCDR3 comprising an amino acid sequence of QTWDRRTAV (SEQ ID NO: 163) (according to the IMGT unique numbering scheme); or

20 (xii) a VHCDR1 comprising an amino acid sequence of GGSFSDYY (SEQ ID NO: 165), a VHCDR2 comprising an amino acid sequence of INHSGST (SEQ ID NO: 166), a VHCDR3 comprising an amino acid sequence of ARKRGANFFDD (SEQ ID NO: 167), a VLCDR1 comprising an amino acid sequence of NIENKN (SEQ ID NO: 89), a VLCDR2 comprising an amino acid sequence of RDS, and a VLCDR3 comprising an amino acid sequence of QVWDSSTVV (SEQ ID NO: 155) (according to the IMGT unique numbering scheme); and

optionally wherein the antibody is a human IgG1 antibody.

26. The antibody of claim 25, wherein:
- (i) the heavy chain variable domain (VH) comprises an amino acid sequence at least 90% identical to SEQ ID NO: 76, and the light chain variable domain (VL) comprises an amino acid sequence at least 90% identical to SEQ ID NO: 80; or
  - 5 (ii) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 92, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 96; or
  - (iii) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 84, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 88; or
  - (iv) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 100,  
10 and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 104; or
  - (v) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 108, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 112; or
  - (vi) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 116, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 120; or
  - 15 (vii) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 124, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 128; or
  - (viii) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 132, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 136; or
  - (ix) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 140,  
20 and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 144; or
  - (x) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 148, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 152; or
  - (xi) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 156, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 160; or
  - 25 (xii) the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO: 164, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO: 168; optionally wherein the antibody is a human IgG1 antibody.