

CLAIMS

1. A method for rescuing immune cells from exhaustion *in vitro* by contacting the immune cells with a first antibody that binds human PD-1 but does not block the interaction of PD-1 and PD-L1, and a second antibody that binds human PD-1 and blocks the interaction of PD-1 and PD-L1; wherein:

the first antibody comprises:

- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 2, 25, and 48, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 71, 94, and 117, respectively;
- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 3, 26, and 49, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 72, 95, and 118, respectively;
- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 7, 30, and 53, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 76, 99, and 122, respectively;
- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 13, 36, and 59, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 82, 105, and 128, respectively;
- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 17, 40, and 63, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 86, 109, and 132, respectively; or
- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 19, 42, and 65, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 88, 111, and 134, respectively;

and,

the second antibody comprises:

- a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 22, 45, and 68, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 91, 114, and 137, respectively;
 - a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 6, 29, and 52, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 75, 98, and 121, respectively;
 - a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 8, 31, and 54, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 77, 100, and 123, respectively;
 - a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 23, 46, and 69, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 92, 115, and 138, respectively; or,
 lambrolizumab.
2. The method of claim 1 wherein the first antibody comprises a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 17, 40, and 63, respectively; and a light chain variable region (VL) comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 86, 109, and 132, respectively.
 3. The method of claim 1 or 2 wherein the second antibody comprises a heavy chain variable region (VH) comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 8, 31, and 54, respectively; and a light chain variable region (VL) comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 77, 100, and 123, respectively; or the second antibody is lambrolizumab.
 4. The method of claim 2 wherein the second antibody comprises a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 8, 31, and 54, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 77, 100, and 123, respectively.
 5. The method of claim 2 wherein the second antibody is lambrolizumab.

6. The method of any one of claims 1-5 wherein the first antibody and/or the second antibody is selected from the group consisting of a human antibody, human IgG, human IgG1, human IgG2, human IgG2a, human IgG2b, human IgG3, human IgG4, human IgM, human IgA, human IgA1, human IgA2, human IgD, human IgE, canine antibody, canine IgGA, canine IgGB, canine IgGC, canine IgGD, chicken antibody, chicken IgA, chicken IgD, chicken IgE, chicken IgG, chicken IgM, chicken IgY, goat antibody, goat IgG, mouse antibody, mouse IgG, pig antibody, rat antibody, a derivative thereof, F_{ab} , F_{ab2} , $F_{ab'}$ single chain antibody, F_v , single chain, mono-specific antibody, bispecific antibody, trimeric antibody, multi-specific antibody, multivalent antibody, chimeric antibody, canine-human chimeric antibody, canine-mouse chimeric antibody, antibody comprising a canine Fc, humanized antibody, human antibody, caninized antibody, CDR-grafted antibody, shark antibody, nanobody, camelid antibody and combinations thereof.
7. A polypeptide that binds to human PD-1 protein, the polypeptide being an antibody comprising a combination of a heavy chain variable region (VH) and a light chain variable region (VL) selected from the group consisting of:
 - (a) a VH comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 17, 40, and 63, respectively; and a VL comprising CDRs 1, 2 and 3 as set forth in SEQ ID NOS: 86, 109, and 132, respectively;
 - (b) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 8, 31, and 54, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 77, 100, and 123, respectively;
 - (c) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 2, 25, and 48, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 71, 94, and 117, respectively;
 - (d) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 3, 26, and 49, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 72, 95, and 118, respectively;
 - (e) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 6, 29, and 52, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 75, 98, and 121, respectively;
 - (f) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 11, 34, and 57, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 80, 103, and 126, respectively;

- (g) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 12, 35, and 58, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 81, 104, and 127, respectively;
 - (h) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 13, 36, and 59, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 82, 105, and 128, respectively;
 - (i) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 19, 42, and 65, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 88, 111, and 134, respectively;
 - (j) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 20, 43, and 66, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 89, 112, and 135, respectively;
 - (k) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 21, 44, and 67, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 90, 113, and 136, respectively;
 - (l) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 22, 45, and 68, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 91, 114, and 137, respectively; and,
 - (m) a VH comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 23, 46, and 69, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 92, 115, and 138, respectively.
8. A polypeptide of claim 7, wherein said polypeptide comprises: SEQ ID NOS. 17, 40, 63, 86, 109, and 132; or, SEQ ID NOS. 8, 31, 54, 77, 100, and 123.
9. The polypeptide of claim 7 or 8 selected from the group consisting of a human antibody, human IgG, human IgG1, human IgG2, human IgG2a, human IgG2b, human IgG3, human IgG4, human IgM, human IgA, human IgA1, human IgA2, human IgD, human IgE, canine antibody, canine IgGA, canine IgGB, canine IgGC, canine IgGD, chicken antibody, chicken IgA, chicken IgD, chicken IgE, chicken IgG, chicken IgM, chicken IgY, goat antibody, goat IgG, mouse antibody, mouse IgG, pig antibody, rat antibody, a derivative thereof, F_{ab}, F_{ab}2, F_{ab}′, single chain antibody, F_v, single chain, mono-specific antibody, bispecific antibody, trimeric antibody, multi-specific antibody, multivalent antibody, chimeric antibody, canine-human chimeric antibody, canine-mouse chimeric antibody, antibody comprising a canine Fc,

humanized antibody, human antibody, caninized antibody, CDR-grafted antibody, shark antibody, nanobody camelid antibody and combinations thereof.

10. The polypeptide of claim 9 wherein the polypeptide is a humanized antibody.
11. A pharmaceutical composition comprising a polypeptide of any one of claims 7-10, and a pharmaceutically acceptable excipient.
12. The pharmaceutical composition of claim 11 comprising a polypeptide comprising SEQ ID NOS. 17, 40, 63, 86, 109, and 132; and a polypeptide comprising SEQ ID NOS. 8, 31, 54, 77, 100, and 123.
13. The pharmaceutical composition of claim 11 comprising:
 - a) the first polypeptide comprises SEQ ID NOS. 17, 40, 63, 86, 109, and/or 132; and,
 - b) the second polypeptide comprises SEQ ID NOS. 8, 31, 54, 77, 100, and/or 123; or the second polypeptide is lambrolizumab.
14. A pharmaceutically effective amount of the polypeptide of any of claims 7-10, or the pharmaceutical composition of any of claims 11-13, for use as a medicament for treating disease in a mammal.
15. The use of a pharmaceutical composition of claim 13 in the preparation of a medicament for treating disease in a mammal wherein the disease is selected from the group consisting of cancer, autoimmunity, and infection by human immunodeficiency disease (HIV).
16. The use of claim 15 wherein the cancer is selected from the group consisting of breast, blood, colon, stomach, rectum, skeletal tissue, skin, brain, lung, bladder, kidney, ovary and liver cancer.
17. An isolated polynucleotide encoding a polypeptide of claim 7, or an expression vector, or host cell, comprising the polynucleotide.