CLAIMS

1. A method for rescuing immune cells from exhaustion by contacting the immune cells with a first binding agent that binds human PD-1 but does not block the interaction of PD-1 and PD-L1.

2. The method of claim 1 further comprising contacting the immune cells with a second binding agent that binds human PD-1 and blocks the interaction of PD-1 and PD-L1.

3. The method of claim 1 or 2 wherein first binding agent is a polypeptide comprising SEQ ID NOS. 17, 40, 63, 86, 109, and 132 and/or a conservatively substituted derivative thereof.

4. The method of any one of claims 1-3 wherein the second binding agent is a polypeptide comprising SEQ ID NOS. 8, 31, 54, 77, 100, and 123 and/or a conservatively substituted derivative thereof; and/or lambrolizumab.

5. The method of claim 3 wherein the second binding agent is a polypeptide comprising SEQ ID NOS. 8, 31, 54, 77, 100, and 123 and/or a conservatively substituted derivative thereof.

6. The method of claim 3 wherein the second binding agent is lambrolizumab.

7. The method of any one of claims 1-6 wherein the first binding agent and/or the second binding agent 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, canelid antibody and combinations thereof.

8. A polypeptide that binds to human PD-1 protein, the polypeptide comprising SEQ ID NOS. 17, 49, 63, 86, 109, and/or 132; and/or a conservatively substituted derivative thereof.

9. A polypeptide that binds to human PD-1 protein, the polypeptide comprising SEQ ID NOS. 8, 31, 54, 77, 100, and/or 123; and/or a conservatively substituted derivative thereof.

10. The polypeptide of claim 8 or 9 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, canelid antibody and combinations thereof.

11. The polypeptide of claim 10 wherein the polypeptide is a humanized antibody.

12. A pharmaceutical composition comprising a polypeptide of any one of claims 8-11, and a pharmaceutically acceptable excipient.

13. A combination comprising a first binding agent of that does not block the interaction of PD-1 and PD-L1 and a second binding agent that blocks the interaction of PD-1 and PD-L1, wherein the first binding agent and the second binding agent each bind human PD-1.

14. The combination of the claim 13, wherein:
    a) the first binding agent is polypeptide comprising SEQ ID NOS. 17, 49, 63, 86, 109, and/or 132; and/or a conservatively substituted derivative thereof; and,
    b) the second binding agent is a polypeptide comprising SEQ ID NOS. 8, 31, 54, 77, 100, and/or 123; and/or a conservatively substituted derivative thereof; or the second binding agent is lambrolizumab.

15. The combination of claim 13 or 14 wherein at least one of the polypeptides 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, canelid antibody and combinations thereof.

16. The combination of any one of claims 13-15, wherein at least one of the polypeptides is a humanized antibody.

17. A pharmaceutical composition comprising the combination of any one of claims 13-16 and a pharmaceutically acceptable excipient.

18. Use of a pharmaceutically effective amount of the polypeptide of any of claims 8-11, the combination of any one of claims 13-16, or the pharmaceutical composition of claim 12 or 17, in the preparation of a medicament for treating disease in a mammal.

19. The use of claim 18 wherein the disease is selected from the group consisting of cancer, autoimmunity, and infection by human immunodeficiency disease (HIV).

20. The use of claim 19 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.