

CLAIMS

What is claimed is:

1. An isolated antibody or an antigen-binding fragment thereof, comprising:
 - (a) a heavy chain variable domain (VH) comprising,
 - i. a heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:71-82;
 - ii. a heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:83-94, respectively, wherein SEQ ID NO:87 is optionally replaced with any one of SEQ ID NOs: 95-97; and
 - iii. a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:98-109, respectively, and
 - (b) a light chain variable domain (VL) comprising, respectively,
 - i. a light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:110-121, wherein SEQ ID NO:111 is optionally replaced with SEQ ID NO:122, and SEQ ID NO:114 is optionally replaced with SEQ ID NO:123;
 - ii. a light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:124-135, respectively; and
 - iii. a light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:136-147, respectively,

wherein the antibody or antigen-binding fragment is capable of specifically binding to a PD-L1, preferably a human PD-L1.
2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein:
 - (1) the VH comprises the heavy chain CDR1, CDR2 and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 75, 87 and 102, respectively, and the VL comprises the light chain CDR1, CDR2 and CDR3 having the amino acid sequences of SEQ ID NOs: 114, 128 and 140, respectively, wherein SEQ ID NO:87 is optionally replaced with any one of SEQ ID NOs: 95-97, and SEQ ID NO:114 is optionally replaced with SEQ ID NO:123; or
 - (2) the VH comprises the heavy chain CDR1, CDR2 and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 72, 84 and 99, respectively, and the VL comprises the light chain CDR1, CDR2 and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 111, 125 and 137, respectively, wherein SEQ ID NO:111 is optionally replaced with SEQ ID NO:122.
3. The isolated antibody or antigen-binding fragment thereof of claim 4, wherein: the VH comprises the heavy chain CDR1, CDR2 and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 75,

97 and 102, respectively, and the VL comprises the light chain CDR1, CDR2 and CDR3 having the amino acid sequences of SEQ ID NOs: 123, 128 and 140, respectively.

4. The isolated antibody or antigen-binding fragment thereof of claim 4, wherein the VH comprises the heavy chain CDR1, CDR2 and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 72, 84 and 99, respectively, and the VL comprises the light chain CDR1, CDR2 and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 122, 125 and 137, respectively.

5. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the VH comprises an amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NOs: 1-44, and the VL comprises an amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NOs: 45-70, respectively.

6. The isolated antibody or antigen-binding fragment thereof of claim 5, wherein the VH comprises the amino acid sequence of any one of SEQ ID NOs: 1-44, or a variant thereof comprising up to about 3 amino acid substitutions in the VH; and the VL comprises the amino acid sequence of any one of SEQ ID NOs: 45-70, or a variant thereof comprising up to about 3 amino acid substitutions in the VL.

7. The isolated antibody or antigen-binding fragment thereof of claim 5 or 6, wherein:

- (1) the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 13, 14, 15 and 21-44, and the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 49, 58, 62-64 and 68-70; or
- (2) the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 16-20, and the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 46, 57, 59-61 and 65-67.

8. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the VH comprises the amino acid sequence of SEQ ID NO: 21, 25, 27 or 31, and the VL comprises the amino acid sequence of SEQ ID NO: 68.

9. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the VH comprises the amino acid sequence of SEQ ID NO: 16 or 19, and the VL comprises the amino acid sequence of SEQ ID NO: 65.

10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the VH is fused to a heavy chain constant region of an immunoglobulin.

11. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-10, wherein the VL is fused to a light chain constant region (CL) of an immunoglobulin.

12. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-11, wherein the K_D of the binding between the antibody or antigen-binding fragment thereof and the PD-L1 is 10^{-7} M to about 10^{-12} M, preferably about 10^{-8} M to about 10^{-12} M, more preferably about 10^{-9} M to about 10^{-12} M.

13. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-12, being rodent, chimeric, human, partially humanized, or fully humanized.
14. The isolated antibody of claim 13, further comprising a constant domain of a human IgG1.
15. The isolated antibody of claim 14, comprising a heavy chain amino acid sequence of any one of SEQ ID NOs:278-321 and 348-391, and a light chain amino acid sequence of any one of SEQ ID NOs:322-347.
16. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-15, further comprising a second antibody moiety, wherein the second antibody moiety is capable of specifically binds to a second antigen.
17. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the second antibody moiety is a Fab, a Fab', a (Fab')₂, an Fv, a single chain Fv (scFv), an scFv-scFv, a minibody, a diabody, a sdAb, or an antibody mimetics.
18. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the second antibody moiety is a sdAb.
19. The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to CTLA-4, preferably, the second antibody moiety is an sdAb capable of specifically binding to CTLA-4.
20. The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to TIGIT, preferably, the second antibody moiety is an sdAb capable of specifically binding to TIGIT.
21. The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to TIM-3, preferably, the second antibody moiety is an sdAb capable of specifically binding to TIM-3.
22. The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to LAG-3, preferably, the second antibody moiety is an sdAb capable of specifically binding to LAG-3.
23. The isolated antibody or antigen-binding fragment thereof of any one of claims 19-22, wherein the amino-terminus of the heavy chain or light chain of a full-length IgG capable of specifically recognizing PD-L1 is fused, optionally via a peptide linker, to the carboxyl-terminus of the sdAb capable of specifically binding to CTLA-4, TIGIT, TIM-3 or LAG-3.
24. The isolated antibody or antigen-binding fragment thereof of any one of claims 19-22, wherein the carboxyl-terminus of the heavy chain or light chain of a full-length IgG capable of specifically recognizing PD-L1 is fused, optionally via a peptide linker, to the amino-terminus of the sdAb capable of specifically binding to CTLA-4, TIGIT, TIM-3 or LAG-3.

25. The isolated antibody or antigen-binding fragment thereof of claim 23 or 24, wherein the full-length IgG capable of specifically recognizing PD-L1 is fused to the sdAb capable of specifically binding to CTLA-4, TIGIT, TIM-3 or LAG-3 via a peptide linker having the amino acid sequence of one of SEQ ID NOs:397-399.
26. A second isolated antibody or antigen-binding fragment thereof capable of specifically binding to PD-L1 competitively with the isolated antibody or antigen-binding fragment thereof of any one of claims 1-25.
27. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1-25 or the second isolated antibody or antigen-binding fragment thereof of claim 26, and a pharmaceutical acceptable carrier.
28. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-25, the second isolated antibody or antigen-binding fragment thereof of claim 26 or the pharmaceutical composition of claim 27, for use in treating a PD-L1 related disease in a subject in need thereof.
29. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 28, wherein the PD-L1 related disease is a cancer.
30. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 29, wherein the cancer is a solid tumor.
31. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 29, wherein the cancer is a colon cancer.
32. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-31 in combination with an additional cancer therapy.
33. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 32, wherein the additional cancer therapy is a surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or a combination thereof.
34. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 28, wherein the PD-L1 related disease is a pathogenic infection.
35. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-34, wherein the isolated antibody or antigen-binding fragment or pharmaceutical composition is for systemic or local administration.
36. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-34, wherein the isolated antibody or antigen-binding fragment or pharmaceutical composition is for intravenous administration.

37. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-34, wherein the isolated antibody or antigen-binding fragment or pharmaceutical composition is for intratumoral administration.
38. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-37, wherein the subject is a human.