

CLAIMS

1. A binding member having a binding specificity to PD-L1, the binding member having one or more of the following properties:
 - 5 (a) binds human PD-L1 with a binding dissociation equilibrium constant (K_D) of lower than 10 pM as measured by Kinetic Exclusion Assay under the conditions indicated in Example 4 for monovalent or in Example 9 for bivalent format;
 - (b) binds to an epitope on PD-L1 which impedes human PD-L1 interaction with both human PD-1 and human CD80;
 - 10 (c) cross-reacts with monkey PD-L1;
 - (d) binds monkey PD-L1, with a binding affinity at least as strong, or at least twice as strong for monkey PD-L1 as for human PD-L1;
 - (e) does not bind to human PD-L2 or human B7-H3;
 - (f) inhibits tumor growth in an HCC827 human lung cancer model;
 - 15 (g) forms less than 3% of dimers after 1 or 2 weeks of storage at 37°C at a concentration of 10 mg/ml in PBS at pH 7.2 in the scFv format.
2. A binding member having a binding specificity to PD-L1, comprising
 - (i) at least one of the variable heavy chain CDR-H1, CDR-H2 and CDR-H3 sequences as set
 - 20 forth in SEQ ID NOs: 6, 7 and 8; and/or
 - (ii) at least one of the variable light chain CDR-L1, CDR-L2 and CDR-L3 sequences as set forth in SEQ ID NOs: 3, 4 and 5;
 - or variants thereof.
- 25 3. The binding member of claims 1 or 2, being humanized.
4. The binding member of any one of the preceding claims, comprising
 - (i) a variable light chain having at least 90% sequence identity to SEQ ID NO: 1; and/or
 - (ii) a variable heavy chain having at least 90% sequence identity to SEQ ID NO: 2 or
 - 30 variants thereof, respectively.

5. The binding member of any one of the preceding claims, further comprising a linker sequence, wherein the linker sequence is the sequence set forth in SEQ ID NO: 10, or variants thereof.
- 5 6. The binding member of claim 4, comprising SEQ ID NO: 9 or SEQ ID NO: 11 or variants thereof.
7. The binding member of any one of claims 1 to 6, being or comprising
 - (i) an antibody fragment such as a Fab, a Fab', a F(ab)'₂, a scFv, a Fv fragment, a scFab, a
10 nanobody, a VHH or a minimal recognition unit;
 - (ii) a full-length antibody molecule; and/or
 - (iii) a non- antibody scaffold such as an affibody, an affilin molecule, an AdNectin, a lipocalin mutein, a DARPin, a Knottin, a Kunitz-type domain, an Avimer, a Tetranectin or a trans-body.
- 15 8. The binding member of any one of claims 1 to 6, being monovalent or multivalent, wherein the binding member is optionally multispecific, bispecific, a diabody, a single-chain diabody, a DART, a BiTE, or a tandem scFv.
- 20 9. The binding member of any one of claims 1 to 4 or 7, comprising a Fc domain.
10. The binding member of claim 9, wherein the binding member comprises a constant region selected from the group consisting of human IgG1, IgG2, IgG3 or IgG4 isotype.
- 25 11. The binding member of claim 9, wherein the binding member comprises a constant region selected from the group consisting of murine IgG1, IgG2A, IgG2B, IgG3 isotype.
12. The binding member of any one of claims 9 to 11, wherein said Fc domain which is modified such that it does not induce cytotoxic immune responses.
- 30 13. The binding member of any one of the claims 1 to 12, being chemically or biologically modified.

14. The binding member of claim 13, being glycosylated, and/or is labelled with or conjugated to a second moiety.

15. The binding member of claim 14, wherein the binding member is PEGylated or HESylated.

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16. An isolated nucleic acid molecule comprising a sequence encoding the binding member of any one of claims 1 to 15.

17. A vector comprising the sequence of the nucleic acid molecule according to claim 16.

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18. The vector of claim 17, being an expression vector or a cloning vector.

19. A host cell comprising the nucleic acid molecule of claim 16 or the vector of claims 17 or 18.

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20. A composition comprising the binding member of any one of claims 1 to 15, the nucleic acid molecule of claim 16, the vector of claims 17 or 18, or the host cell of claim 19; and further a suitable carrier, diluent or excipient.

20 21. The composition of claim 20, being a cosmetic, a diagnostic or a pharmaceutical composition.

22. The composition of claim 21, being a pharmaceutical composition and the carrier being a pharmaceutically acceptable carrier, diluent or excipient.

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23. The composition of claim 21 or 22, being in a form suitable for parenteral, oral, rectal, systemic, intravenous, subcutaneous, urogenital, topical, intravitreal, intraocular, otic, intranasal, transdermal, intradermal, dermal, sublingual, intracranial, intramuscular, intraperitoneal, or buccal administration.

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24. Use of the binding member of any one of claims 1 to 15, the nucleic acid molecule of claim 16, the vector of claims 17 or 18, or the host cell of claim 19, in the manufacture of a medicament for the treatment, prevention or delay of progression of an PD-L1-mediated disease.

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25. The use of claim 24, wherein the PD-L1-mediated disease is cancer; or wherein said disease is systemic lupus erythematosus, or wherein said disease is systemic lupus erythematosus, sepsis, stroke, pathogen infection or an autoimmune disorder.

10 26. The use according to claim 25, wherein the cancer is selected from the group consisting of: NSCLC (non-small cell lung carcinoma), urothelial cancer, melanoma, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, ovarian cancer, gastrointestinal cancer, hepatocellular cancer, glioma, breast cancer, lymphoma, small cell
15 lung carcinoma, myelodysplastic syndromes, prostate cancer, bladder cancer, cervical cancer, non-clear cell kidney cancer, colorectal cancer, sarcomas, colon cancer, kidney cancer, lung cancer, pancreatic cancer or gastric cancer, skin cancer, uterine cancer, glioblastoma, leukemia, carcinoma, Merkel cell carcinoma or renal cell carcinoma (RCC), blood cancer, multiple myeloma, lymphoblastic leukemia (ALL), B cell leukemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and ovarian cancer.

27. The use of any one of claims 24 to 26, wherein the binding member is administered in combination with one or more therapies selected from the group of antibody therapy, chemotherapy, cytokine therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy, radiation therapy or vaccine therapy.

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28. The binding member of any one of claims 1 to 15, the nucleic acid molecule of claim 16, the vector of claims 17 or 18, or the host cell of claim 19,

(i) for use as medicament, in particular in the treatment of an PD-L1 mediated disease;

(ii) for use in diagnostics;

10 (iii) for use in cosmetics; and/or

(iv) for detection purposes.

29. An *in vitro* method of inhibiting growth of a tumor or a tumor cell, comprising the step of contacting the tumor or tumor cell with a therapeutically effective amount of the binding member of any one of claims 1 to 15.

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30. A method of producing the binding member of any one of claims 1 to 15, the method comprising:

(i) cultivating the host cell of claim 19, thereby allowing the binding member to be expressed;

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(ii) recovering the binding member; and

(iii) optionally purifying the binding member.

31. A method of producing the binding member of any one of claims 1 to 15, the method comprising:

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(a) contacting a cell-free expression system with a nucleic acid product template, the nucleic acid product template encoding the binding member according to any one of claims 1 to 15;

(b) allowing transcription and translation of the nucleic acid product template to occur, thereby allowing a reaction mixture to be formed;

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(c) recovering the binding member from the reaction mixture; and

(d) optionally purifying the binding member.

32. The method of producing the binding member of any one of claims 30 or 31, wherein producing the binding member comprises a step of chemical synthesis.

33. An *in vitro* method of detecting the presence of PD-L1 in a biological sample, the method comprising:

(a) contacting the biological sample with the binding member of any one of claims 1 to 15 under conditions permissive for specific binding of the binding member to PD-L1, and

(b) detecting whether a complex between the binding member and PD-L1 is formed.

34. The *in vitro* method of claim 33, wherein the biological sample is of human origin.

35. The *in vitro* method of any one of claims 33 to 34, wherein the biological sample is at least one of a blood sample, a urine sample, a cerebrospinal fluid sample, a biopsy sample and/or a lymph sample.

36. The method of any one of claims 33 to 35, wherein the method is a method for selecting subjects eligible for therapy with the binding member of any one of claims 1 to 15.

37. An *in vitro* method of inhibiting the interaction between PD-L1 and the receptor complex of PD-1 subunits comprising the step of

(a) providing PD-L1 as well as said receptor complex; and

(b) contacting PD-L1 with a binding member according to any one of claims 1 to 15.

38. An *in vitro* method of inhibiting PD-L1 biological activity comprising the step of

(a) providing PD-L1; and

(b) contacting PD-L1 with a binding member according to any one of claims 1 to 15.

39. A kit comprising the binding member of any one of claims 1 to 15 together with a packaged combination of reagents with instructions.