

CLAIMS

1. An isolated monoclonal antibody, or antigen-binding portion thereof, comprising:
 - a) a heavy chain variable region CDR1 comprising amino acids having the
5 sequence set forth in SEQ ID NO: 18;
 - b) a heavy chain variable region CDR2 comprising amino acids having the
sequence set forth in SEQ ID NO: 25;
 - c) a heavy chain variable region CDR3 comprising amino acids having the
sequence set forth in SEQ ID NO: 32;
 - 10 d) a light chain variable region CDR1 comprising amino acids having the sequence
set forth in SEQ ID NO: 39;
 - e) a light chain variable region CDR2 comprising amino acids having the sequence
set forth in SEQ ID NO: 46; and
 - f) a light chain variable region CDR3 comprising amino acids having the sequence
15 set forth in SEQ ID NO: 53;wherein the antibody specifically binds human Programmed Death 1 (PD-1)
protein.
2. The antibody of claim 1, comprising:
 - 20 a) a heavy chain variable region comprising amino acids having the sequence set
forth in SEQ ID NO: 4; and
 - b) a light chain variable region comprising amino acids having the sequence set
forth in SEQ ID NO: 11;wherein the antibody specifically binds human PD-1.
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3. A monoclonal antibody, or antigen binding portion thereof, wherein the antibody
cross-competes for binding to PD-1 with the antibody of claim 1 or 2.
4. The antibody of any one of claims 1 to 3, wherein the antibody
30 a) binds to human PD-1 with a K_D of 5×10^{-9} or less; and
b) binds to neither human ICOS, human CTLA-4 nor human CD28.

5. The monoclonal antibody or antigen-binding portion thereof of any one of claims 1 to 4, which binds to human PD-1 expressed on a cell surface.

6. The antibody of any one of claims 1 to 5, wherein the antibody inhibits the suppression of CD4⁺ CD25⁻ T cells by regulatory T cells.

7. The antibody of any one of claims 1 to 5, wherein the antibody enhances the antigen specific-memory response to a tumor or a pathogen.

8. The antibody of any one of claims 1 to 5, wherein the antibody confers a persistent immunity to tumor relapse.

9. The antibody of any one of claims 1 to 8, wherein the antibody is an IgG₄ isotype.

10. The antibody of claim 9, wherein the antibody has neither ADCC activity nor CDC activity.

11. A composition comprising the antibody, or an antigen-binding portion thereof, of any one of claims 1 to 10, and a pharmaceutically acceptable carrier.

12. The antibody, or an antigen-binding portion thereof, of any one of claims 1 to 10 for use in a method of modulating an immune response.

13. The antibody, or an antigen-binding portion thereof, of any one of claims 1 to 10 for use in a method of inhibiting the growth of tumor cells.

14. The antibody, or an antigen-binding portion thereof, of claim 13, wherein the tumor cells are from a cancer selected from the group consisting of melanoma, renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer.

15. The antibody, or an antigen-binding portion thereof, of claim 13, wherein the tumor cells are from a cancer selected from the group consisting of bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma,

uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

16. The antibody, or an antigen-binding portion thereof, of any one of claims 1 to 10 for use in a method of treating an infectious disease.

17. The antibody, or an antigen-binding portion thereof, of claim 16, wherein the infectious disease is caused by a virus selected from the group consisting of HIV, Influenza, Herpes, Giardia, Malaria, Leishmania, Hepatitis A, B, or C, a herpes virus, VZV, HSV-1, HAV-6, HSV-II, CMV, Epstein Barr virus, adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus, arboviral encephalitis virus, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci, conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, Lyme disease bacteria, Candida albicans, krusei, glabrata, or tropicalis, Cryptococcus neoformans, Aspergillus fumigatus or niger,, Mucorales mucor, absidia or rhizopus, Sporothrix schenckii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis, Histoplasma capsulatum, Entamoeba histolytica, Balantidium coli, Naegleria fowleri, Acanthamoeba sp., Giardialamblia, Cryptosporidium,

Pneumocystis carinii, *Plasmodium vivax*, *Babesia microti*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, *Toxoplasma gondi*, and *Nippostrongylus brasiliensis*.

- 5 18. An immunoconjugate comprising the antibody, or antigen-binding portion thereof, of any one of claims 1 to 10, linked to a therapeutic agent.
19. A composition comprising the immunoconjugate of claim 18 and a pharmaceutically acceptable carrier.
- 10 20. The immunoconjugate of claim 18, wherein the therapeutic agent is a cytotoxin.
21. A composition comprising the immunoconjugate of claim 20 and a pharmaceutically acceptable carrier.
- 15 22. The immunoconjugate of claim 18, wherein the therapeutic agent is a radioactive isotope.
23. A composition comprising the immunoconjugate of claim 22 and a pharmaceutically acceptable carrier.
- 20 24. A bispecific molecule comprising the antibody, or antigen-binding portion thereof, of any one of claims 1 to 10, linked to a second functional moiety having a different binding specificity than said antibody, or antigen-binding portion thereof.
- 25 25. A composition comprising the bispecific molecule of claim 24, and a pharmaceutically acceptable carrier.