

CLAIMS

1. A humanized monoclonal anti-human-PD-1 antibody or an antigen-binding fragment thereof comprising:

- 5 (i) a heavy chain variable domain comprising HCDR1 comprising or consisting of an amino acid sequence of SEQ ID NO: 1, HCDR2 comprising or consisting of an amino acid sequence of SEQ ID NO: 2 and HCDR3 comprising or consisting of an amino acid sequence of SEQ ID NO: 9, and
- (ii) a light chain variable domain comprising LCDR1 comprising or consisting of an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising or consisting of an amino acid sequence of SEQ ID NO: 13 and LCDR3 comprising or consisting of an amino acid sequence of SEQ ID NO: 14,
- 10 wherein the antibody or antigen binding fragment thereof is an antagonist of the binding of human PD-L1 and/or PD-L2 to human PD-1.

2. A humanized monoclonal anti-human-PD-1 antibody or an antigen-binding fragment thereof of claim 1, comprising: (a) a VH comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 21; and (b) a VL comprising or consisting of an amino acid sequence of SEQ ID NO: 24,

wherein the antibody or antigen binding fragment thereof is an antagonist of the binding of human PD-L1 and/or PD-L2 to human PD-1.

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3. The antibody or antigen-binding fragment thereof of claim 1 or 2, wherein it comprises:

- (a) a heavy chain comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 31, optionally with one, two or three modification(s) selected from substitution(s), addition(s), deletion(s) and any combination thereof at any position but positions 7, 16, 17, 20, 33, 38, 43, 46, 62, 63, 65, 69, 73, 76, 78, 80, 84, 85, 88, 93, 95, 96, 97, 98, 100, 101, 105, 106 and 112 of SEQ ID NO: 31, and (b) a light chain comprising or consisting of an amino acid sequence of SEQ ID NO: 34, optionally with one, two or three modification(s) selected from substitution(s), addition(s), deletion(s) and any combination thereof at any position but positions 3, 4, 7, 14, 17, 18, 28, 29, 33, 34, 39, 42, 44, 50, 81, 88, 94, 97, 99 and 105 of SEQ ID NO: 34.

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4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein it comprises: (a) a heavy chain comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 31, and (b) a light chain comprising or consisting of an amino acid sequence of SEQ ID NO: 34.

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5. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant domain derived from a human kappa light chain constant domain and a heavy chain constant domain derived from a human IgG1, IgG2, IgG3 or IgG4 heavy chain constant domain.
- 5 6. The antibody or antigen-binding fragment thereof of any one of claims 1-3 and 5, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant domain derived from a human kappa light chain constant domain and a heavy chain constant domain derived from a human IgG1 heavy chain constant domain, optionally with a substitution or a combination of substitutions selected from the group consisting of T250Q/M428L; M252Y/S254T/T256E + H433K/N434F; 10 E233P/L234V/L235A/G236A + A327G/A330S/P331S; E333A; S239D/A330L/I332E; P257I/Q311; K326W/E333S; S239D/I332E/G236A; N297A; L234A/L235A; N297A + M252Y/S254T/T256E; K322A and K444A, preferably selected from the group consisting of N297A optionally in combination with M252Y/S254T/T256E, and L234A/L235A.
- 15 7. The antibody or antigen-binding fragment thereof of any one of claims 1-3 and 5, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant domain derived from a human kappa light chain constant domain and a heavy chain constant domain derived from a human IgG4 heavy chain constant domain, optionally with a substitution or a combination of substitutions selected from the group consisting of S228P; L234A/L235A, S228P + M252Y/S254T/T256E and K444A.
- 20 8. The antibody or antigen-binding fragment thereof according to any one of claims 1-7, which specifically binds to human PD-1 with a binding affinity constant (KD) for a human PD-1 equal or lower than 10^{-7} M, the affinity being preferably determined by biosensor analysis.
9. The antibody or antigen-binding fragment thereof according to any one of claims 1-7, which has a humanness (T20) equal or greater than 85%, preferably equal or greater than 88 % and/or which has a high production yield in mammalian cells.
- 25 10. An isolated nucleic acid molecule or a group of isolated nucleic acid molecules encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 9.
11. A vector comprising the isolated nucleic acid molecule or the group of isolated nucleic acid molecules of claim 10.
12. A host cell comprising the isolated nucleic acid molecule and/or the group of isolated nucleic acid 30 molecules of claim 9 and/or the vector according to claim 11.

13. A method for producing the antibody or antigen-binding fragment thereof of any one of claims 1-9, comprising a step of culturing a host cell according to claim 12 and optionally a step of isolating the antibody or antigen-binding fragment.
14. A pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof
5 according to any one of claims 1-9 and/or the isolated nucleic acid molecule and/or a group of isolated nucleic acid molecules according to claim 10 and/or the vector according to claim 11 and/or the host cell according to claim 12 and a pharmaceutically acceptable carrier.
15. The pharmaceutical composition according to claim 14, wherein it further comprises an additional therapeutic agent, preferably selected in the group consisting of alkylating agents, angiogenesis
10 inhibitors, antibodies, in particular anti-tumor targeting antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-2 family inhibitors), activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors,
15 DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-
20 steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, hypomethylating agents, checkpoints inhibitors,
25 peptide vaccine and the like, epitopes or neoepitopes from tumor antigens, as well as combinations of one or more of these agents.
16. The antibody or antigen-binding fragment thereof according to any one of claims 1-10, the pharmaceutical composition of claim 14 or 15, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules of claim 10, the vector according to claim 11, or the host cell according
30 to claim 12 for use as a medicament.
17. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to claim 16 in the prevention or treatment of cancer.

18. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to claim 17, wherein the cancer is selected from the group consisting of a hematologic malignancy or a solid tumor with expression of PD-1 and/or PD-L1 such as a cancer selected from the group consisting of hematolymphoid neoplasms, angioimmunoblastic T cell lymphoma, myelodysplastic syndrome, and acute myeloid leukemia, a cancer induced by virus or associated with immunodeficiency such as a cancer selected from the group consisting of Kaposi sarcoma (e.g., associated with Kaposi sarcoma herpes virus); cervical, anal, penile and vulvar squamous cell cancer and oropharyngeal cancers (e.g., associated with human papilloma virus); B cell non-Hodgkin lymphomas (NHL) including diffuse large B-cell lymphoma, Burkitt lymphoma, plasmablastic lymphoma, primary central nervous system lymphoma, HHV-8 primary effusion lymphoma, classic Hodgkin lymphoma, and lymphoproliferative disorders (e.g., associated with Epstein-Barr virus (EBV) and/or Kaposi sarcoma herpes virus); hepatocellular carcinoma (e.g., associated with hepatitis B and/or C viruses); Merkel cell carcinoma (e.g., associated with Merkel cell polyoma virus (MPV)); and cancer associated with human immunodeficiency virus infection (HIV) infection, and a cancer selected from the group consisting of metastatic or not metastatic, Melanoma, malignant mesothelioma, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Hodgkin's Lymphoma, Head and Neck Cancer, Urothelial Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Small Cell Lung Cancer, Metastatic Merkel Cell Carcinoma, Gastric or Gastroesophageal cancers and Cervical Cancer.
19. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to claim 17, wherein the cancer has tumor cells which are PD-L1 negative.
20. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to any one of claims 16-19, for use in combination with radiotherapy or an additional therapeutic agent, preferably selected in the group consisting of alkylating agents, angiogenesis inhibitors, antibodies, in particular anti-tumor targeting antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-2 family inhibitors), activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase

- inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3
- 5 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, hypomethylating agents, checkpoints inhibitors, peptide vaccine and the like, epitopes or neoepitopes from tumor antigens, as well as combinations of one or more of these agents.
- 10 21. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to claim 16 in the prevention or treatment of an infectious disease, preferably a chronic infectious disease, even more preferably caused by a virus selected from the group consisting of HIV, hepatitis virus, herpes virus, adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie
- 15 virus, coronavirus, 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 and arboviral encephalitis virus.
22. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for
- 20 use according to claim 16 in the prevention or treatment of patients with lymphopenic disorder.
23. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to any one of claims 16-22, wherein the subject to be treated is immunosuppressed, immunocompromised or immunodepressed.
- 25 24. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to any one of claims 16-22, wherein the subject has a high mutation burden and neoantigen density.