

CLAIMS

1. An antibody capable of specifically binding to PD-1 or a functional fragment thereof, wherein the antibody or the functional fragment thereof comprise a light chain and a heavy chain;

the light chain comprises a light chain CDR consisting of CDR-L1, CDR-L2 and CDR-L3; the heavy chain comprises a heavy chain CDR consisting of CDR-H1, CDR-H2 and CDR-H3;

the amino acid sequences of the CDR-L1, CDR-L2, and CDR-L3 are respectively set forth in SEQ ID NO: 1, 5 and 6, or respectively set forth in SEQ ID NO: 2, 5 and 6, or respectively set forth in SEQ ID NO: 3, 5 and 6, or respectively set forth in SEQ ID NO: 4, 5 and 6; the amino acid sequences of the CDR-H1, CDR-H2, and CDR-H3 are respectively set forth in SEQ ID NO: 7, 8 and 9;

preferably, the antibody or the functional fragment thereof includes a PD-1 chimeric antibody and a functional fragment thereof, and a PD-1 humanized antibody and a functional fragment thereof.

2. The antibody or the functional fragment thereof according to claim 1, wherein the antibody comprises a constant region sequence of any one selected from the group consisting of human IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE and IgD.

3. The antibody or the functional fragment thereof according to claim 1 or 2, wherein the functional fragment comprises one or more selected from the group consisting of F(ab')₂, Fab', Fab, Fv, scFv, bispecific antibody and antibody minimal recognition unit.

4. The antibody or the functional fragment thereof according to any one of claims 1 to 3, wherein the amino acid sequences of light chain variable region and heavy chain variable region of the PD-1 chimeric antibody or the functional fragment thereof are respectively set forth in SEQ ID NO: 10 and SEQ ID NO: 14, or respectively set forth

in SEQ ID NO: 11 and SEQ ID NO:14, or respectively set forth in SEQ ID NO: 12 and SEQ ID NO: 14, or respectively set forth in SEQ ID NO: 13 and SEQ ID NO: 14;

preferably, the amino acid sequences of the light chain constant region and the heavy chain constant region of the PD-1 chimeric antibody or the functional fragment thereof are respectively set forth in SEQ ID NO: 15 and SEQ ID NO: 16.

5. The antibody or the functional fragment thereof according to any one of claims 1 to 3, wherein light chain framework region of the PD-1 humanized antibody or the functional fragment thereof comprises FR-L1, FR-L2, FR-L3 and FR-L4, and heavy chain framework region of the PD-1 humanized antibody or the functional fragment thereof comprises FR-H1, FR-H2, FR-H3 and FR-H4;

the FR-L1 is selected from the amino acid sequence set forth in SEQ ID NO: 17 and the amino sequence having the following substitution or a combination thereof:

the 1st amino acid D is replaced by E;

the 2nd amino acid V is replaced by I;

the 13th amino acid L is replaced by V;

the 19th amino acid A is replaced by V;

the FR-L2 is selected from the amino acid sequence set forth in SEQ ID NO: 18 and the amino sequence having the following substitution or a combination thereof:

the 6th amino acid P is replaced by S;

the 7th amino acid G is replaced by H;

the 9th amino acid A is replaced by S;

the FR-L3 is selected from the amino acid sequence set forth in SEQ ID NO: 19 and the amino sequence having the following substitution or a combination thereof:

the 22th amino acid L is replaced by V;

the 24th amino acid P is replaced by T;

the 28th amino acid A is replaced by G;

the 31th amino acid F is replaced by Y;

the FR-L4 is selected from the amino acid sequence set forth in SEQ ID NO: 20 and the amino sequence having the following substitution or a combination thereof:

the 7th amino acid V is replaced by L;

the FR-H1 is selected from the amino acid sequence set forth in SEQ ID NO: 21;

the FR-H2 is selected from the amino acid sequence set forth in SEQ ID NO: 22

and the amino sequence having the following substitution or a combination thereof:

the 5th amino acid A is replaced by T;

the 14th amino acid A is replaced by S;

the FR-H3 is selected from the amino acid sequence set forth in SEQ ID NO: 23

and the amino sequence having the following substitution or a combination thereof:

the 12th amino acid N is replaced by T;

the 14th amino acid Y is replaced by H;

the 18th amino acid N is replaced by S;

the FR-H4 is selected from the amino acid sequence set forth in SEQ ID NO: 24;

preferably, light chain variable region sequence of the PD-1 humanized antibody or the functional fragment thereof is one selected from SEQ ID NO: 25 to 36;

preferably, heavy chain variable region sequence of the PD-1 humanized antibody or the functional fragment thereof is one selected from SEQ ID NO: 37 to 42;

more preferably, the light chain variable region sequence of the PD-1 humanized antibody or the functional fragment thereof is set forth in SEQ ID NO: 25; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 37;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 25; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 38;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 29; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 38;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 30; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 38;

alternatively, the light chain variable region sequence of the PD-1 humanized

antibody and functional fragment thereof is set forth in SEQ ID NO: 31; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 38;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 26; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 38;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 28; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 40;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 25; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 40;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 29; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 40;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 30; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 40;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 31; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 40;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 28; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 38;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 27; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 39;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 32; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 39;

alternatively, the light chain variable region sequence of the PD-1 humanized

antibody and functional fragment thereof is set forth in SEQ ID NO: 33; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 39;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 34; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 39;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 35; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 41;

alternatively, the light chain variable region sequence of the PD-1 humanized antibody and functional fragment thereof is set forth in SEQ ID NO: 36; the corresponding heavy chain variable region sequence is set forth in SEQ ID NO: 42;

more preferably, the amino acid sequences of the light chain constant region sequence and the heavy chain constant region sequence of the PD-1 humanized antibody or the functional fragment thereof are set forth in SEQ ID NO: 15 and SEQ ID NO: 16, respectively.

6. An isolated nucleic acid molecule selected from:

A) DNA or RNA, encoding the antibody or the functional fragment thereof according to any one of claims 1 to 5; and

B) a nucleic acid complementary to the nucleic acid as defined in A).

7. A composition, comprising the antibody and/or the functional fragment thereof according to any one of claims 1 to 5, or a compound of the antibody and other components, or a compound of the antibody functional fragment and other components, as an active ingredient.

8. The composition according to claim 7, wherein the antibody or the functional fragment thereof are coupled to at least one diagnostic agent and/or therapeutic agent to form an immunoconjugate.

9. The composition according to claim 8, wherein the diagnostic agent is one or more selected from the group consisting of a radionuclide, a radioactive contrast agent, a paramagnetic ion, a metal, a fluorescent label, a chemiluminescent label, an ultrasound contrast agent, and a photosensitizer;

preferably, the radionuclide is one or more selected from the group consisting of ^{110}In , ^{111}In , ^{177}Lu , ^{18}F , ^{52}Fe , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , ^{86}Y , ^{90}Y , ^{89}Zr , $^{94\text{m}}\text{Tc}$, ^{94}Tc , $^{99\text{m}}\text{Tc}$, ^{120}I , ^{123}I , ^{124}I , ^{125}I , ^{131}I , $^{154-158}\text{Gd}$, ^{32}P , ^{11}C , ^{13}N , ^{15}O , ^{186}Re , ^{188}Re , ^{51}Mn , $^{52\text{m}}\text{Mn}$, ^{55}Co , ^{72}As , ^{75}Br , ^{76}Br , $^{82\text{m}}\text{Rb}$ and ^{83}Sr ;

preferably, the paramagnetic ion is one or more selected from the group consisting of chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and erbium (III);

preferably, the fluorescent label is one or more selected from the group consisting of Alexa 350, Alexa 405, Alexa 430, Alexa 488, Alexa 555, Alexa 647, AMCA, aminoacridine, BODIPY 630/650, BODIPY 650/665, BODIPY-FL, BODIPY-R6G, BODIPY-TMR, BODIPY-TRX, 5-carboxy-4',5'-dichloro-2',7'-dimethoxyfluorescence, 5-carboxy-2',4',5',7'-tetrachlorofluorescein, 5-carboxyfluorescein, 5-carboxyrhodamine, 6-carboxyrhodamine, 6-carboxytetramethylrhodamine, Cascade Blue, Cy2, Cy3, Cy5, Cy7, 6-FAM, dansyl chloride, fluorescein, HEX, 6-JOE, NBD (7-nitrobenzo-2-oxa-1,3-diazole), Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, phthalic acid, terephthalic acid, isophthalic acid, cresyl fast violet, cresyl violet, brilliant cresyl blue, 4-aminobenzoic acid, erythrosine, phthalocyanine, azomethine, cyanine, xanthine, succinyl fluorescein, rare earth metal cryptate, tri-bipyridyldiamine europium, europium cryptate compound or chelate, diamine, dicyanine, La Jolla blue dye, allophycocyanin, allococyanin B, phycocyanin C, phycocyanin R, thiamine, R-phycoerythrin, C-Phycocyanin, phycoerythrin R, REG, rhodamine green, rhodamine isothiocyanate, rhodamine red, ROX, TAMRA, TET, TRIT (tetramethylrhodamine isothiol), tetramethylrhodamine and Texas Red.

10. The composition according to claim 8 or 9, wherein the therapeutic agent is one or

more selected from the group consisting of a naked antibody, a cytotoxic agent, a drug, a radionuclide, a boron atom, an immunomodulator, an anti-apoptotic agent, a photosensitizing therapeutic, an immunoconjugate and an oligonucleotide;

preferably, the drug is one or more selected from the group consisting of methotrexate, fluorouracil, mercaptopurine, hydroxyurea, cytarabine, nitrogen mustard, cyclophosphamide, thiotepa, cisplatin, mitomycin, bleomycin, camptothecin, podophyllotoxin, actinomycin D, doxorubicin, daunorubicin, vinblastine, paclitaxel, cephalotaxus alkaloids and L-asparaginase;

preferably, the oligonucleotide is one or more selected from the group consisting of shRNA, miRNA and siRNA;

preferably, the immunomodulator is one or more selected from the group consisting of a cytokine, a chemokine, a stem cell growth factor, a lymphotoxin, a hematopoietic factor, a colony stimulating factor (CSF), an interferon, an erythropoietin, a thrombopoietin, a tumor necrosis factor (TNF), an interleukin (IL), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF) and stem cell growth factor;

preferably, the radionuclide is one or more selected from the group consisting of ¹¹¹In, ¹¹¹At, ¹⁷⁷Lu, ²¹¹Bi, ²¹²Bi, ²¹³Bi, ²¹¹At, ⁶²Cu, ⁶⁷Cu, ⁹⁰Y, ¹²⁵I, ¹³¹I, ¹³³I, ³²P, ³³P, ⁴⁷Sc, ¹¹¹Ag, ⁶⁷Ga, ¹⁵³Sm, ¹⁶¹Tb, ¹⁵²Dy, ¹⁶⁶Dy, ¹⁶¹Ho, ¹⁶⁶Ho, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁸⁹Re, ²¹¹Pb, ²¹²Pb, ²²³Ra, ²²⁵Ac, ⁷⁷As, ⁸⁹Sr, ⁹⁹Mo, ¹⁰⁵Rh, ¹⁴⁹Pm, ¹⁶⁹Er, ¹⁹⁴Ir, ⁵⁸Co, ⁸⁰mBr, ⁹⁹mTc, ¹⁰³mRh, ¹⁰⁹Pt, ¹¹⁹Sb, ¹⁸⁹mOs, ¹⁹²Ir, ²¹⁹Rn, ²¹⁵Po, ²²¹Fr, ²⁵⁵Fm, ¹¹C, ¹³N, ¹⁵O, ⁷⁵Br, ¹⁹⁸Au, ¹⁹⁹Au, ²²⁴Ac, ⁷⁷Br, ¹¹³mIn, ⁹⁵Ru, ⁹⁷Ru, ¹⁰³Ru, ¹⁰⁵Ru, ¹⁰⁷Hg, ²⁰³Hg, ¹²¹mTe, ¹²²mTe, ¹²⁵mTe, ¹⁶⁵Tm, ¹⁶⁷Tm, ¹⁶⁸Tm, ¹⁹⁷Pt, ¹⁰⁹Pd, ¹⁴²Pr, ¹⁴³Pr, ¹⁶¹Tb, ⁵⁷Co, ⁵⁸Co, ⁵¹Cr, ⁵⁹Fe, ⁷⁵Se, ²⁰¹Tl, ⁷⁶Br and ¹⁶⁹Yb.

11. Use of the composition according to any one of claims 7 to 10 for the manufacture of a medicament in prevention and/or treatment of an autoimmune disease, an immune response against transplant, an allergy, an infection, a neurodegenerative disease, or a tumor;

preferably, the autoimmune disease is one or more selected from the group

consisting of arthritis, rheumatoid arthritis, psoriasis, multiple sclerosis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, glomerulonephritis, dilatation cardiomyopathy-like disease, Sjogren's syndrome, allergic contact dermatitis, polymyositis, scleroderma, periarterial polyarteritis, rheumatic fever, vitiligo, insulin-dependent diabetes mellitus, Behcet's syndrome and chronic thyroiditis;

preferably, the neurodegenerative disease is one or more selected from the group consisting of Parkinson's disease, Huntington's disease, Machado-Joseph disease, amyotrophic lateral sclerosis and Creutzfeldt-Jakob disease;

preferably, the tumor is one or more selected from the group consisting of leukemia, lymphoma, myeloma, brain tumor, head and neck squamous cell carcinoma, non-small cell lung cancer, nasopharyngeal carcinoma, esophageal cancer, gastric cancer, pancreatic cancer, gallbladder cancer, liver cancer, colorectal cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, uterine sarcoma, prostate cancer, bladder cancer, renal cell carcinoma, and melanoma.

12. Use of the antibody or the functional fragment thereof according to any one of claims 1 to 5 for the manufacture of a medicament in prevention and/or treatment of an autoimmune disease, an immune response against transplant, an allergy, an infection, a neurodegenerative disease, or a tumor;

preferably, the autoimmune disease is one or more selected from the group consisting of arthritis, rheumatoid arthritis, psoriasis, multiple sclerosis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, glomerulonephritis, dilatation cardiomyopathy-like disease, Sjogren's syndrome, allergic contact dermatitis, polymyositis, scleroderma, periarterial polyarteritis, rheumatic fever, vitiligo, insulin-dependent diabetes mellitus, Behcet's syndrome and chronic thyroiditis;

preferably, the neurodegenerative disease is one or more selected from the group consisting of Parkinson's disease, Huntington's disease, Machado-Joseph disease, amyotrophic lateral sclerosis and Creutzfeldt-Jakob disease;

preferably, the tumor is one or more selected from the group consisting of leukemia, lymphoma, myeloma, brain tumor, head and neck squamous cell carcinoma,

non-small cell lung cancer, nasopharyngeal carcinoma, esophageal cancer, gastric cancer, pancreatic cancer, gallbladder cancer, liver cancer, colorectal cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, uterine sarcoma, prostate cancer, bladder cancer, renal cell carcinoma, and melanoma.

13. A drug for prevention and/or treatment of an autoimmune disease, an immune response against transplant, an allergy, an infection, a neurodegenerative disease, or a tumor, comprising the antibody capable of specifically binding to PD-1 or the functional fragment capable of specifically binding to PD-1 thereof according to any one of claims 1 to 5, and a pharmaceutically acceptable carrier;

alternatively, the drug comprises the composition according to any one of claims 7 to 10 and a pharmaceutically acceptable carrier;

preferably, the autoimmune disease is one or more selected from the group consisting of arthritis, rheumatoid arthritis, psoriasis, multiple sclerosis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, glomerulonephritis, dilatation cardiomyopathy-like disease, Sjogren's syndrome, allergic contact dermatitis, polymyositis, scleroderma, periarterial polyarteritis, rheumatic fever, vitiligo, insulin-dependent diabetes mellitus, Behcet's syndrome and chronic thyroiditis;

preferably, the neurodegenerative disease is one or more selected from the group consisting of Parkinson's disease, Huntington's disease, Machado-Joseph disease, amyotrophic lateral sclerosis and Creutzfeldt-Jakob disease;

preferably, the tumor is one or more selected from the group consisting of leukemia, lymphoma, myeloma, brain tumor, head and neck squamous cell carcinoma, non-small cell lung cancer, nasopharyngeal carcinoma, esophageal cancer, gastric cancer, pancreatic cancer, gallbladder cancer, liver cancer, colorectal cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, uterine sarcoma, prostate cancer, bladder cancer, renal cell carcinoma, and melanoma.

14. Use of the drug according to claim 13 for the manufacture of a medicament in prevention and/or treatment of an autoimmune disease, an immune response against a transplant, an allergy, an infection, a neurodegenerative disease or a tumor.