CLAIMS

1. An isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof, comprising the first arm specifically binding to PD-1 and the second arm specifically binding to CD3, wherein

(A)(I)(i) a VH of the first arm specifically binding to PD-1 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 6,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 7, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 8, and

(ii) a VH of the second arm specifically binding to CD3 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 37,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 38, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 39,

(II)(i) a VH of the first arm specifically binding to PD-1 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 9,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 10, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 11, and

(ii) a VH of the second arm specifically binding to CD3 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 37,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 38, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 39,

(III)(i) a VH of the first arm specifically binding to PD-1 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 12,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 13, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 14, and

(ii) a VH of the second arm specifically binding to CD3 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 37,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 38, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 39,

(IV)(i) a VH of the first arm specifically binding to PD-1 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 15,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 16, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 17, and

(ii) a VH of the second arm specifically binding to CD3 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 37,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 38, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 39, or

(V)(i) a VH of the first arm specifically binding to PD-1 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 18,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 19, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 20, and

(ii) a VH of the second arm specifically binding to CD3 has:

(a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 37,

(b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 38, and

(c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 39, and

(B) the first arm specifically binding to PD-1 and the second arm specifically binding to CD3 have a VL having:

(a) a VL-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 26,

(b) a VL-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 27, and

(c) a VL-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 28, respectively.

2. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the FR1, FR2 and FR3 regions of the VH of the first arm specifically binding to PD-1 correspond to the amino acid sequence encoded by the germ-line V gene IGHV7-4-1 with somatic mutation(s), respectively, and the framework 4 region comprises the amino acid sequence encoded by the germ-line J gene JH6c with somatic mutation(s) (excluding the amino acid sequence included in the VH-CDR3 region).

3. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1 or 2, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, and SEQ ID No. 5, or an amino acid sequence having at least 80% identity to VH amino acid sequence thereof.

4. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 3, wherein the VH of the second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36, or an amino acid sequence having an identity of at least 80% to VH amino acid sequence thereof.

5. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, and SEQ ID No. 5; and the VH of the

second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36.

6. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 1; and the VH of the second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36.

7. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 2; and the VH of the second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36.

8. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 3; and the VH of the second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36.

9. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 4; and the VH of the second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36.

10. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 1, wherein the VH of the first arm specifically binding to PD-

1 comprises the amino acid sequence set forth in SEQ ID No. 5; and the VH of the second arm specifically binding to CD3 comprises the amino acid sequence set forth in SEQ ID No. 36.

11. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 10, wherein the first arm specifically binding to PD-1 and the second arm specifically binding to CD3 have the VL comprising the amino acid sequence set forth in SEQ ID No. 25.

12. An isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof, having the first arm specifically binding to PD-1 and the second arm specifically binding to CD3, wherein

(A) the first arm specifically binding to PD-1 has the VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, and SEQ ID No. 5, and the VL comprising the amino acid sequence set forth in SEQ ID No. 25; and

(B) the second arm specifically binding to CD3 has the VH comprising the amino acid sequence set forth in SEQ ID No. 36; and the VL comprising the amino acid sequence set forth in SEQ ID No. 25.

13. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 12, wherein the first arm specifically binding to PD-1 allows interaction between the PD-1 and PD-L1.

14. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 13, wherein cytokine production is sufficiently reduced.

15. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment

thereof according to claim 14, wherein the cytokine is at least IL-2, IFN-γ, or TNF-α.

16. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 15, wherein the PD-1/CD3 bispecific monoclonal antibody is an IgG antibody.

17. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 16, which is an IgG_1 antibody or an IgG_4 antibody.

18. The isolated PD-1/CD3 bispecific monoclonal antibody or an antibody fragment thereof according to claim 16, which is an IgG_1 antibody.

19. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 18, wherein the binding to an Fc receptor is eliminated or reduced.

20. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 19, wherein in two heavy chain constant regions of the PD-1/CD3 bispecific monoclonal IgG_1 antibody, leucine at position 235 according to the EU numbering system is substituted with glycine, and/or glycine at position 236 according to the EU numbering system is substituted with arginine.

21. The isolated PD-1/CD3 bispecific monoclonal antibody or an antibody fragment thereof according to any one of claims 18 to 20, wherein in a constant region of a heavy chain having a VH of the first arm specifically binding to PD-1, leucine at position 351 according to the EU numbering system is substituted with lysine and threonine at position 366 according to the EU numbering system is substituted with lysine; and in a constant region of a heavy chain having a VH of the second arm specifically binding to CD3, leucine at position 351 according to the EU numbering system is substituted with aspartic acid and leucine at position 368 according to the EU

numbering system is substituted with glutamic acid.

22. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 18 to 20, wherein in a constant region of a heavy chain having a VH of the first arm specifically binding to PD-1, leucine at position 351 according to the EU numbering system is substituted with aspartic acid, and leucine at position 368 is substituted with glutamic acid, and in a constant region of a heavy chain having a VH of the second arm specifically binding to CD3, leucine at position 351 according to the EU numbering system is substituted with lysine, and threonine at position 366 according to the EU numbering system is substituted with lysine.

23. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 18 to 22, wherein in two heavy chain constant regions of the PD-1/CD3 bispecific monoclonal antibody, lysine at position 447 according to the EU numbering system is deleted.

24. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to claim 17, wherein the isolated PD-1/CD3 bispecific monoclonal antibody is an IgG_4 antibody, and in two heavy chain constant regions, serine at position 228 according to the EU numbering system is substituted with proline, respectively.

25. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 19, wherein the heavy chain having the VH of the first arm specifically binding to PD-1 has a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 23.

26. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 19 and 25, wherein the heavy chain having the VH of the second arm specifically binding to CD3 has a heavy chain constant region

comprising the amino acid sequence set forth in SEQ ID No. 24.

27. The isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 26, wherein the light chain having the VL of the first arm specifically binding to PD-1 and/or the light chain having VL of the second arm specifically binding to CD3 have a light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29.

28. An isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof, having the first arm specifically binding to PD-1 and the second arm specifically binding to CD3, wherein:

(A) a heavy chain having the VH of the first arm specifically binding to PD-1 has the VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, and SEQ ID No. 5, and the heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 23;

(B) a light chain having the VL of the first arm specifically binding to PD-1 has the VL comprising the amino acid sequence set forth in SEQ ID No. 25, and the light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29;

(C) a heavy chain having the VH of the second arm specifically binding to CD3, has the VH comprising the amino acid sequence set forth in SEQ ID No. 36, and the heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 24; and

(D) a light chain having the VL of the second arm specifically binding to CD3 has the VL comprising the amino acid sequence set forth in SEQ ID No. 25, and the light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29.

29. A pharmaceutical composition comprising the isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof selected from any one of claims 1 to

28, and a pharmaceutically acceptable carrier.

30. Use of an isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any one of claims 1 to 28 as an active ingredient in the manufacture of a pharmaceutical agent for suppressing symptom progression or recurrence of, and/or treating autoimmune diseases.

31. The use according to claim 30, wherein the autoimmune diseases include Behcet's disease, systemic lupus erythematosus, chronic discoid lupus erythematosus, multiple sclerosis, scleroderma, polymyositis, dermatomyositis, periarteritis nodosa, aortitis syndrome, malignant rheumatoid arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthritis, mixed connective tissue disease, Sjogren's syndrome, adult Still's disease, vasculitis, allergic granulomatous vasculitis, hypersensitivity vasculitis, rheumatoid vasculitis, large vessel vasculitis, ANCA associated vasculitis, Cogan's syndrome, RS3PE, temporal arteritis, polymyalgia rheumatica, fibromyalgia, antiphospholipid antibody syndrome, eosinophilic fasciitis, IgG4-related disease, Guillain-Barre syndrome, myasthenia gravis, chronic atrophic gastritis, autoimmune hepatitis, non-alcoholic steatohepatitis, primary biliary cirrhosis, Goodpasture's syndrome, rapidly progressive glomerulonephritis, megaloblastic anemia, autoimmune hemolytic anemia, pernicious anemia, autoimmune neutropenia, idiopathic thrombocytopenic purpura, Basedow disease, Hashimoto disease, autoimmune adrenal insufficiency, primary hypothyroidism, Addison's disease, idiopathic Addison's disease, type I diabetes mellitus, slowly progressive type I diabetes mellitus, focal scleroderma, psoriasis, psoriatic arthritis, bullous pemphigoid, pemphigus, pemphigoid, gestational herpes, linear IgA bullous dermatosis, acquired epidermolysis bullosa, alopecia areata, vitiligo, vitiligo vulgaris, neuromyelitis optica, chronic inflammatory demyelinating

polyneuropathy, multifocal motor neuropathy, sarcoidosis, giant cell arteritis, amyotrophic lateral sclerosis, Harada disease, autoimmune optic neuropathy, idiopathic azoospermia, habitual abortion, inflammatory bowel disease, celiac disease, ankylosing spondylitis, severe asthma, chronic urticarial, transplantation immunity, familial mediterranean fever, eosinophilic chronic rhinosinusitis, dilated cardiomyopathy, systemic mastocytosis, or inclusion body myositis.

32. The use according to claim 30 or 31, wherein the pharmaceutical agent is to be administered together with one or more agents selected from an insulin formulation, sulfonylurea agent, quick-acting insulin secretion promoter, biguanide preparation, insulin resistance improving agent, α-glucosidase inhibitor, diabetic neuropathy therapeutic agent, GLP-1 analog preparation, and DPP-4 inhibitor, steroid agent, interferon β-1a, interferon β-1b, glatiramer acetate, mitoxantrone, azathioprine, cyclophosphamide, cyclosporin, methotrexate, cladribine, adrenocorticotropic hormone (ACTH), corticotropin, mizoribine, tacrolimus, fingolimod, alemtuzumab, immunosuppressive agent, belimumab, anti-rheumatic drug, anti-cytokine drug, and abatacept.

33. Use of the isolated PD-1/CD3 bispecific monoclonal antibody or antibody fragment thereof according to any of claims 1 to 28, as an active ingredient in the manufacture of a pharmaceutical agent for suppressing symptom progression or recurrence of, and/or treating graft-versus-host disease (GVHD).