CLAIMS

1. Use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds to PD-1 in the manufacture of a medicament for managing, preventing or treating an immune disorder in a subject, wherein the antibody or antigen-binding fragment thereof comprises

   (a) a light chain variable region (VL) comprising:

   a VL complementarity determining region 1 (CDR1) comprising SEQ ID NO:1 or SEQ ID NO:7,

   VL CDR2 comprising SEQ ID NO:2, and

   a VL CDR3 comprising SEQ ID NO:3; and

   (b) a heavy chain variable region (VH) comprising:

   a VH CDR1 comprising SEQ ID NO:4,

   a VH CDR2 comprising SEQ ID NO:5, and

   a VH CDR3 comprising SEQ ID NO:6.

2. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises

   (a) a VL comprising an amino acid sequence of SEQ ID NO:8;

   (b) a VL comprising an amino acid sequence of SEQ ID NO:9;

   (c) a VL comprising an amino acid sequence of SEQ ID NO:10;

   (d) a VH comprising an amino acid sequence of SEQ ID NO:11;

   (e) a VH comprising an amino acid sequence of SEQ ID NO:12;

   (f) a VH comprising an amino acid sequence of SEQ ID NO:13;

   (g) a VL comprising an amino acid sequence of SEQ ID NO:8; and a VH comprising an amino acid sequence of SEQ ID NO:11;

   (h) a VL comprising an amino acid sequence of SEQ ID NO:9; and a VH comprising an amino acid sequence of SEQ ID NO:11;

(i) a VL comprising an amino acid sequence of SEQ ID NO:10; and a VH comprising an amino acid sequence of SEQ ID NO:11;

(j) a VL comprising an amino acid sequence of SEQ ID NO:8; and a VH comprising an amino acid sequence of SEQ ID NO:12;

(k) a VL comprising an amino acid sequence of SEQ ID NO:9; and a VH comprising an amino acid sequence of SEQ ID NO:12;

(l) a VL comprising an amino acid sequence of SEQ ID NO:10; and a VH comprising an amino acid sequence of SEQ ID NO:12;

(m) a VL comprising an amino acid sequence of SEQ ID NO:8; and a VH comprising an amino acid sequence of SEQ ID NO:13;

(n) a VL comprising an amino acid sequence of SEQ ID NO:9; and a VH comprising an amino acid sequence of SEQ ID NO:13; or

(o) a VL comprising an amino acid sequence of SEQ ID NO:10; and a VH comprising an amino acid sequence of SEQ ID NO:13.

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

(a) a human IgG1 Fc region or a variant thereof;

(b) a human IgG1-K322A Fc region;

(c) a heavy chain Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40; wherein optionally the antibody or antigen-binding fragment thereof further comprises a light chain constant region comprising an amino acid sequence of SEQ ID NO:41; or

(d) a light chain constant region comprising an amino acid sequence of SEQ ID NO:41; and a heavy chain Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40.

4. The use of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof comprises

(a) a light chain comprising an amino acid sequence of SEQ ID NO:31;

(b) a heavy chain comprising an amino acid sequence of SEQ ID NO:32;

(c) a light chain comprising an amino acid sequence of SEQ ID NO:31; and a heavy chain comprising an amino acid sequence of SEQ ID NO:32;

(d) a heavy chain comprising an amino acid sequence of SEQ ID NO:33;

(e) a light chain comprising an amino acid sequence of SEQ ID NO:31; and a heavy chain comprising an amino acid sequence of SEQ ID NO:33;

(f) a heavy chain comprising an amino acid sequence of SEQ ID NO:34;

(g) a light chain comprising an amino acid sequence of SEQ ID NO:31; and a heavy chain comprising an amino acid sequence of SEQ ID NO:34;

(h) a heavy chain comprising an amino acid sequence of SEQ ID NO:35; or

(i) a light chain comprising an amino acid sequence of SEQ ID NO:31; and a heavy chain comprising an amino acid sequence of SEQ ID NO:35.

5. The use of any one of claims 1-4,

wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to at least one of residues 100-109 within an amino acid sequence of SEQ ID NO:42; and

wherein optionally, when bound to PD-1, the antibody or antigen-binding fragment binds to at least one of residues 100-105 within an amino acid sequence of SEQ ID NO:42.

6. The use of any one of claims 1-5, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to at least one residue selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42; and

wherein optionally, when bound to PD-1, the antibody or antigen-binding fragment

(a) binds to N33 within an amino acid sequence of SEQ ID NO:42;

(b) binds to T51 within an amino acid sequence of SEQ ID NO:42;

(c) binds to S57 within an amino acid sequence of SEQ ID NO:42;

(d) binds to L100 within an amino acid sequence of SEQ ID NO:42;

(e) binds to N102 within an amino acid sequence of SEQ ID NO:42;

(f) binds to G103 within an amino acid sequence of SEQ ID NO:42;

(g) binds to R104 within an amino acid sequence of SEQ ID NO:42;

(h) binds to D105 within an amino acid sequence of SEQ ID NO:42;

(i) binds to H107 within an amino acid sequence of SEQ ID NO:42;

(j) binds to S109 within an amino acid sequence of SEQ ID NO:42; or

(k) binds to G103 and R104 within an amino acid sequence of SEQ ID NO:42.

7. The use of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof:

(a) attenuates T cell activity; wherein optionally the attenuation of T cell activity is measured by inhibition of cytokine production; and/or

(b) downregulates PD-1 expression on the surface of T cells; wherein optionally the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the treatment with the antibody or antigen-binding fragment thereof; and/or is concurrent with or precedes cytokine inhibition.

8. The use of claim 7, wherein the cytokine that is inhibited by the antibody or antigen-binding fragment thereof comprises IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, TNF-α, IFN-γ, or any combination thereof; and

wherein optionally

(a) the cytokine is IL-1;

(b) the cytokine is IL-2;

(c) the cytokine is IL-6;

(d) the cytokine is IL-12;

(e) the cytokine is IL-17;

(f) the cytokine is IL-22;

(g) the cytokine is IL-23;

(h) the cytokine is GM-CSF;

(i) the cytokine is TNF-α; or

(j) the cytokine is IFN-γ.

9. The use of claim 7 or 8, wherein the attenuation of T cell activity is measured by

(a) inhibition of T cell proliferation;

(b) upregulation of expression of an inhibitory receptor on the surface of T cells, wherein the inhibitory receptor is not PD-1; wherein optionally the inhibitory receptor is selected from the group consisting of LAG-3, CTLA-4, and TIM-3;

(c) inhibition of T cell recall response;

(d) increase of T cell exhaustion; or

(e) increase of regulatory T cells.

10. The use of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof

(a) specifically binds to human PD-1 and/or monkey PD-1, but not rodent PD-1; wherein optionally the K_D for binding to purified human PD-1 is from about 100 pM to about 10 nM, and the K_D for binding to human PD-1 expressed on cell surface and monkey PD-1 expressed on cell surface is from about 100 pM to about 10 nM; or

(b) has attenuated ADCC activity and/or attenuated CDC activity.

11. The use of claim 7, wherein

(a) the EC50 for attenuating T cell activity is from about 1 pM to about 10 pM, from about 10 pM to about 100 pM, from about 100 pM to about 1 nM, from about 1 nM to about 10 nM, or from about 10 nM to about 100 nM;

(b) the maximal percent attenuation of T cell activity is at least about 10%, 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%; or

(c) the maximal percent downregulation of PD-1 expression is at least about 10%, 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

12. The use of any one of claims 1-11, wherein

(a) the antibody is a monoclonal antibody; wherein optionally the antibody is a humanized, human, or chimeric antibody; and wherein optionally the humanized antibody is a deimmunized antibody or a composite human antibody; or

(b) the antibody or antigen-binding fragment thereof is a Fab, a Fab', a $F(ab')_2$, a Fv, a scFv, a dsFv, a diabody, a triabody, a tetrabody, or a multispecific antibody formed from antibody fragments.

13. The use of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof is conjugated to an agent; and wherein optionally the agent is selected from the group consisting of a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound, and a chemiluminescent compound.

14. The use of anyone of claims 1-13, wherein the immune disorder is an inflammatory disease; and wherein optionally the inflammatory disease is uveitis.

15. The use of anyone of claims 1-13, wherein the immune disorder is a hypersensitivity disease; wherein optionally the hypersensitivity disease is selected from the group consisting of allergy, atopic dermatitis, and hypersensitivity vasculitis; and wherein optionally

(a) the hypersensitivity disease is allergy;

(b) the hypersensitivity disease is atopic dermatitis; or

(c) the hypersensitivity disease is hypersensitivity vasculitis.

16. The use of anyone of claims 1-13, wherein the immune disorder is an autoimmune disease; wherein optionally the autoimmune disease is selected from the group consisting of rheumatoid arthritis, Crohn's disease, psoriasis, psoriatic arthritis, multiple sclerosis, lupus, ankylosing spondylitis, type I diabetes, Sjögren's syndrome, ulcerative colitis, neuromyelitis optica, celiac disease, scleroderma, and temporal arteritis; and wherein optionally,

(a) the autoimmune disease is rheumatoid arthritis;

(b) the autoimmune disease is Crohn's disease;

(c) the autoimmune disease is psoriasis;

(d) the autoimmune disease is psoriatic arthritis;

(e) the autoimmune disease is multiple sclerosis;

(f) the autoimmune disease is lupus; wherein optionally the lupus is systemic lupus erythematosus, cutaneous lupus erythematosus, or lupus nephritis;

(g) the autoimmune disease is ankylosing spondylitis;

(h) the autoimmune disease is type I diabetes;

(i) the autoimmune disease is Sjögren's syndrome;

(j) the autoimmune disease is ulcerative colitis;

(k) the autoimmune disease is neuromyelitis optica;

(l) the autoimmune disease is celiac disease;

(m) the autoimmune disease is temporal arteritis; or

(n) the autoimmune disease is scleroderma.

17. The use of any one of claims 1-13, wherein

(a) the immune cells in the subject express PD-1; or

(b) the antibody or antigen-binding fragment thereof further comprises a pharmaceutically acceptable carrier.