

immune system (e.g., corticosteroids and cyclophosphamide). However, PD-1 is expressed mostly on activated immune cells. Therefore, anti-PD-1 antibodies have the potential to selectively target cells that are activated during the time of treatment, leaving the rest of the immune cell repertoire intact.

5 The field has struggled to deliver PD-1 agonistic antibodies (Sharpe, A. and Pauken, E., *Nature Reviews Immunology* (2017)). The difficulty, at least partly, is thought to be the result of the complex cellular interactions required to achieve PD-1 agonism in physiological settings *in vitro* or *in vivo*. Therefore, the context of the assay or model used to identify therapeutic antibodies is clearly important when assessing PD-1
10 agonist antibody activity.

 United States Patent Application Publication US20170088618 discloses anti-human PD-1 antibodies, which, in some embodiments, and in certain *in vitro* assays, behave as agonists with rates of association and dissociation with respect to the PD-1 extracellular domain resulting in K_D values of between 19-22 nM (as determined by
15 surface plasmon resonance (SPR) using a BIAcore®T200).

 Thus, there exists a need for alternative anti-human PD-1 antibodies that 1) bind human PD-1 with desirable association and dissociation rates for optimal agonist activity, 2) agonize human PD-1 in an immunologically relevant context to achieve *in vivo* efficacy, 3) display sufficient potency as a monotherapy for the treatment and/or
20 prevention of autoimmune disorders or the prevention of transplant rejection, 4) display desired activity as part of a combination therapy with other therapeutics for the treatment and/or prevention of autoimmune disorders or the prevention of transplant rejection, and/or 5) offers an effective alternative for drug switching when, during the treatment of an autoimmune disorder with another anti-human PD-1 agonist antibody,
25 therapy is suspended because of at least one adverse event and/or inefficacy (particularly, anti-drug antibody (ADA) mediated reduction in efficacy).

Summary

In one aspect, the present disclosure refers to an antibody that binds human PD-1, comprising: 1) a heavy chain variable region (HCVR); and 2) a light chain variable region (LCVR), wherein the HCVR comprises a HCDR1, HCDR2, and HCDR3, and the LCVR comprises a LCDR1, LCDR2, and LCDR3, wherein the amino acid sequence of
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the HCDR1 is SEQ ID NO:5, the amino acid sequence of the HCDR2 is SEQ ID NO:6, and the amino acid sequence of the HCDR3 is SEQ ID NO:7, the amino acid sequence of the LCDR1 is SEQ ID NO:8, the amino acid sequence of the LCDR2 is SEQ ID NO:9, and the amino acid sequence of the LCDR3 is SEQ ID NO:10, and wherein the antibody is an IgG1.

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In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody disclosed herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

In yet another aspect, the present disclosure refers to a use of the antibody disclosed herein in the manufacture of a medicament for treating an autoimmune disease.

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In a further aspect, the present disclosure refers to an antibody disclosed herein for use in treating an autoimmune disease.

Description

Accordingly, the present invention provides novel humanized anti-human PD-1 agonist IgG1 antibodies. The antibodies of the present invention are particularly advantageous over prior art anti-PD-1 antibodies for various reasons, including, but not limited to, the following: 1) they bind human PD-1 (as well as cynomolgus monkey PD-1) with desirable association and dissociation rates, 2) they may be therapeutically effective at lower doses or less frequent dosing, 3) they inhibit primary human T cell

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WE CLAIM:

1. An antibody that binds human PD-1, comprising: 1) a heavy chain variable region (HCVR); and 2) a light chain variable region (LCVR), wherein the HCVR
5 comprises a HCDR1, HCDR2, and HCDR3, and the LCVR comprises a LCDR1, LCDR2, and LCDR3, wherein the amino acid sequence of the HCDR1 is SEQ ID NO:5, the amino acid sequence of the HCDR2 is SEQ ID NO:6, and the amino acid sequence of the HCDR3 is SEQ ID NO:7, the amino acid sequence of the LCDR1 is SEQ ID NO:8, the amino acid sequence of the LCDR2 is SEQ ID
10 NO:9, and the amino acid sequence of the LCDR3 is SEQ ID NO:10, and wherein the antibody is an IgG1.
2. The antibody of Claim 1, wherein the amino acid sequence of the HCVR is SEQ ID NO:3 and the amino acid sequence of the LCVR is SEQ ID NO:4.
3. The antibody of Claim 2 comprising: 1) a HC; and 2) a LC, wherein the amino
15 acid sequence of the HC is SEQ ID NO:1, and the amino acid sequence of the LC is SEQ ID NO:2.
4. The antibody of Claim 3 comprising two HCs and two LCs, wherein the amino acid sequence of each of the HCs is SEQ ID NO:1, and the amino acid sequence of each of the LCs is SEQ ID NO:2.
- 20 5. The antibody of ~~any one of Claims 1-4~~1, wherein the antibody is an agonist of human PD-1 as determined in an in vivo model of an autoimmune disorder or transplant rejection.
6. The antibody of Claim 5 wherein the in vivo model is a model for GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA,
25 IBD, UC, AS, SjS, autoimmune hepatitis, or scleroderma.
7. The antibody of Claim 5 wherein the in vivo model is a mouse model for GVHD and/or lupus nephritis.
8. A pharmaceutical composition comprising the antibody of ~~any one~~any one Claims ~~1-7~~1-7, and one or more pharmaceutically acceptable carriers, diluents, or excipients.
- 30 9. Use of the antibody of Claim 1 in the manufacture of a medicament for method of treating an autoimmune disease, comprising administering to a patient in need thereof, an effective amount of the antibody of any one of Claims 1-7.

10. The ~~method-use~~ of Claim 9, wherein the autoimmune disease is GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA, IBD, UC, AS, SjS, autoimmune hepatitis, scleroderma, celiac disease, Addison's disease, Hashimoto's disease, Graves' disease, atrophic gastritis/pernicious anemia, acquired hypogonadism/infertility, hypoparathyroidism, Coombs positive-hemolytic anemia, chronic allergic diseases (such as asthma, hay fever, or allergic rhinitis), Crohn's disease, male or female infertility, Behcet's, Wegener's granulomatosis, myocarditis, myositis, PMR, spontaneous abortion, vitiligo, atherosclerosis, autoimmune pancreatitis, bullous pemphigoid, chronic viral infections, or myasthenia gravis.
11. The ~~method-use~~ of Claim 10, wherein the autoimmune disease is GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA, IBD, UC, AS, SjS, autoimmune hepatitis, or scleroderma.
12. The ~~method-use~~ of ~~any one of Claims 9-11~~10, wherein the antibody is to be administered in combination with another therapeutic agent effective for the treatment of an autoimmune disease.
13. An antibody of Claim 1 for use in treating an autoimmune disease.
- ~~13. The antibody of any one of Claims 1-7, for use in therapy.~~
- ~~14. The antibody of any one of Claims 1-7, for use in treating an autoimmune disease.~~
15. ~~The antibody for use of Claim 14, wherein the autoimmune disease is GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA, IBD, UC, AS, SjS, autoimmune hepatitis, scleroderma, celiac disease, Addison's disease, Hashimoto's disease, Graves' disease, atrophic gastritis/pernicious anemia, acquired hypogonadism/infertility, hypoparathyroidism, Coombs positive hemolytic anemia, chronic allergic diseases (such as asthma, hay fever, or allergic rhinitis), Crohn's disease, male or female infertility, Behcet's, Wegener's granulomatosis, myocarditis, myositis, PMR, spontaneous abortion, vitiligo, atherosclerosis, autoimmune pancreatitis, bullous pemphigoid, chronic viral infections, or myasthenia gravis.~~
16. ~~The antibody for use of Claim 15 wherein the autoimmune disease is GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA, IBD, UC, AS, SjS, autoimmune hepatitis, or scleroderma.~~

17. — ~~The antibody for use of any one of Claims 14-16 wherein the antibody is administered in simultaneous, separate, or sequential combination with another therapeutic agent effective for the treatment of an autoimmune disease.~~
18. — ~~The use of the antibody of any one of Claims 1-7 for the manufacture of a medicament for the treatment of an autoimmune disease.~~
19. — ~~The use of Claim 18, wherein the autoimmune disease is GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA, IBD, UC, AS, SjS, autoimmune hepatitis, scleroderma, celiac disease, Addison's disease, Hashimoto's disease, Graves' disease, atrophic gastritis/pernicious anemia, acquired hypogonadism/infertility, hypoparathyroidism, Coombs positive hemolytic anemia, chronic allergic diseases (such as asthma, hay fever, or allergic rhinitis), Crohn's disease, male or female infertility, Behcet's, Wegener's granulomatosis, myocarditis, myositis, PMR, spontaneous abortion, vitiligo, atherosclerosis, autoimmune pancreatitis, bullous pemphigoid, chronic viral infections, or myasthenia gravis.~~
20. — ~~The use of Claim 19, wherein the autoimmune disease is GVHD, solid organ transplantation rejection, vasculitis, SLE, T1DM, MS, GCA, PsO, PsA, RA, IBD, UC, AS, SjS, autoimmune hepatitis, or scleroderma.~~
21. — ~~The use of any one of Claims 18-19 wherein the antibody is administered in simultaneous, separate, or sequential combination with another therapeutic agent effective for the treatment of an autoimmune disease.~~