The field has struggled to deliver therapeutically effective and safe CD200R agonistic antibodies. The difficulty, at least partly, is thought to be the result of the complex cellular interactions required to achieve CD200R agonism with minimal safety concerns (*e.g*. without inducing cytokine release) in physiological settings.

United States Patent 8,212,008 discloses CD200R antibodies, such as Dx182. Dx182 is a humanized IgG1 antibody that agonizes CD200R and blocks binding of CD200 to CD200R. However, Dx182 also binds to and activates cynomolgus monkey CD200RLa (cynomolgus monkey activating form) expressed in murine mast cells, and thereby induces a mast cell degranulation response in these cells via the cynomolgus CD200RLa. WO 2015/057906 also discloses CD200R agonist antibodies, such as H2RM147. H2RM147 is likely to compete with human CD200 for binding to human CD200R1.

Thus, there exists a need for alternative CD200R antibodies that 1) bind human CD200R with desirable association and dissociation rates for optimal agonist activity, 2) agonize human CD200R to achieve immunosuppressive response and *in vivo* efficacy, 3) display sufficient potency as an monotherapy for the treatment and/or prevention of disorders such as autoimmune disorders, allergic disease, asthma, or other inflammatory disorders, 4) do not cause significant cytokine release, 5) do not block binding of human CD200 and human CD200R, 6) do not bind CD200RLa or binds CD200RLa with low affinity. and/or 7) demonstrate low immunogenicity (i.e., sufficiently non-immunogenic in cynomolgus monkeys and/or humans) and *in vivo* stability, physical and chemical stability including, but not limited to, thermal stability, solubility, low self-association, and pharmacokinetic characteristics which are acceptable for development and/or use in the treatment of autoimmune disorders, allergic disease, asthma, or other inflammatory disorders.

Summary

In one aspect of the present disclosure, there is provided an antibody that binds human CD200R, comprising a heavy chain variable region (HCVR) and 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 the HCDR1 is given by SEQ ID NO: 1, the amino acid sequence of the HCDR2 is given by SEQ ID NO: 2, and the amino acid sequence of the HCDR3 is given by SEQ ID NO: 3, the amino acid sequence of the LCDR1 is given by SEQ ID NO: 4, the amino acid sequence of the LCDR2 is given by SEQ ID NO: 5, and the amino acid sequence of the LCDR3 is given by SEQ ID NO: 6.

In another aspect of the present disclosure, there is provided a CD200R agonist antibody, wherein the antibody does not cause significant cytokine release compared to a wild-type IgG1 antibody having the same CDRs as the CD200R agonist antibody.

In a further aspect of the present disclosure, there is provided an antibody disclosed herein, for use in therapy.

In another aspect of the present disclosure, there is provided a use of the antibody disclosed herein, in the manufacture of a medicament for the treatment of a disease, wherein the disease is an autoimmune disease, allergic disease, asthma, atopic dermatitis, or other inflammatory disorders.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody disclosed herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

In another aspect of the present disclosure, there is provided a DNA molecule comprising a polynucleotide that encodes the HC whose amino acid sequence is given by SEQ ID NO: 9 or a polynucleotide that encodes the LC whose amino acid sequence is given by SEQ ID NO: 10.

In a further aspect of the present disclosure, there is provided a mammalian cell transformed with the DNA molecule disclosed herein, which transformed mammalian cell is capable of expressing an antibody comprising two HCs and two LCs, in which the amino acid sequence of each HC is given by SEQ ID NO: 9, and the amino acid sequence of each LC is given by SEQ ID NO: 10.

Description

Accordingly, the present invention provides novel anti-human CD200R agonist antibodies. The antibodies of the present invention are particularly advantageous over prior art CD200R agonist antibodies in view of at least the following properties: 1) desirable association and dissociation rates, 2) agonism of human CD200R to achieve an

immunosuppressive response and *in vivo* efficacy, 3) sufficiently potent as an monotherapy for the treatment and/or prevention of autoimmune disorders, allergic disease, asthma, or other inflammatory disorders 4) no significant cytokine release, 5) no

WE CLAIM:

1. An antibody that binds human CD200R, comprising a heavy chain variable region (HCVR) and 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 the HCDR1 is given by SEQ ID NO: 1, the amino acid sequence of the HCDR2 is given by SEQ ID NO: 2, and the amino acid sequence of the HCDR3 is given by SEQ ID NO: 3, the amino acid sequence of the LCDR1 is given by SEQ ID NO: 4, the amino acid sequence of the LCDR2 is given by SEQ ID NO: 5, and the amino acid sequence of the LCDR3 is given by SEQ ID NO: 6.
2. The antibody of Claim 1, comprising a HCVR and a LCVR, wherein the amino acid sequence of the HCVR is given by SEQ ID NO: 7 and the amino acid sequence of the LCVR is given by SEQ ID NO: 8.
3. The antibody of Claim 2, wherein Xaa at position 1 of SEQ ID NO: 7 is glutamine.
4. The antibody of Claim 2, wherein Xaa at position 1 of SEQ ID NO: 7 is pyroglutamic acid.
5. The antibody of any one of Claims 1-4, wherein the antibody does not cause significant cytokine release.
6. The antibody of any one of Claims 1- 5, wherein the antibody is a CD200R agonist antibody.
7. The antibody of any one of Claims 1- 6, wherein the antibody binds at least three of Fcɣ RI, Fcɣ RIIA_131H, Fcɣ RIIA_131R, Fcɣ RIIb, and Fcɣ RIIIA_158V.
8. The antibody of any one of Claims 1- 7, wherein the antibody binds at least four of Fcɣ RI, Fcɣ RIIA_131H, Fcɣ RIIA_131R, Fcɣ RIIb, and Fcɣ RIIIA_158V.
9. The antibody of any one of Claims 7-8, wherein the binding affinities are:
    (i) about 70 pM to about 500 pM to Fcɣ RI;
    (ii) about 2 µM to about 5 µM to Fcɣ RIIA_131H;

(iii) about 1 µM to about 5 µM to Fcɣ RIIA_131R;

(iv) about 1 µM to about 4 µM to Fcɣ RIIb;

(v) about 1 µM to about 6 µM to Fcɣ RIIIA_158V; and

(vi) greater than 9 µM to Fcɣ RIIIA_158F.

10. The antibody of any one of Claims 7-9, wherein the binding affinities are:

(i) about 400 pM to Fcɣ RI;

(ii) about 4 µM to Fcɣ RIIA_131H;

(iii) about 2 µM to Fcɣ RIIA_131R;

(iv) about 2 µM to Fcɣ RIIb;

(v) about 4 µM to Fcɣ RIIIA_158V; and

(vi) greater than 10 µM to Fcɣ RIIIA_158F.

11. The antibody of any one of Claims 9-10, wherein the binding affinity is determined by Surface Plasmon Resonance at 25°C.

12. The antibody of any one of Claims 1-11, wherein the antibody does not bind C1q.

13. The antibody of Claim 12, wherein binding to C1q is determined by ELISA.

14. The antibody of any one of Claims 1-13, wherein the antibody is an IgG4P.

15. The antibody of Claim 1 or Claim 2, comprising a heavy chain (HC) and a light chain (LC), wherein the amino acid sequence of the HC is given by SEQ ID NO: 9 and the amino acid sequence of the LC is given by SEQ ID NO: 10.

16. The antibody of Claim 15, wherein Xaa at position 1 of SEQ ID NO: 9 is glutamine and Xaa at position 446 of SEQ ID NO: 9 is glycine.

17. The antibody of Claim 15, wherein Xaa at position 1 of SEQ ID NO: 9 is pyroglutamic acid and Xaa at position 446 of SEQ ID NO: 9 is glycine.

18. The antibody of Claim 15, wherein Xaa at position 1 of SEQ ID NO: 9 is glutamine and Xaa at position 446 of SEQ ID NO: 9 is absent.

19. The antibody of Claim 15, wherein Xaa at position 1 of SEQ ID NO: 9 is pyroglutamic acid and Xaa at position 446 of SEQ ID NO: 9 is absent.

20. A CD200R agonist antibody, wherein the antibody does not cause significant cytokine release compared to a wild-type IgG1 antibody having the same CDRs as the CD200R agonist antibody.

21. The antibody of Claim 20, comprising a heavy chain variable region (HCVR) and 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 the HCDR1 is given by SEQ ID NO: 1, the amino acid sequence of the HCDR2 is given by SEQ ID NO: 2, and the amino acid sequence of the HCDR3 is given by SEQ ID NO: 3, the amino acid sequence of the LCDR1 is given by SEQ ID NO: 4, the amino acid sequence of the LCDR2 is given by SEQ ID NO: 5, and the amino acid sequence of the LCDR3 is given by SEQ ID NO: 6, and wherein binding of antibody to Fcɣ RI, Fcɣ RIIA_131H, Fcɣ RIIA_131R, Fcɣ RIIb, and Fcɣ RIIIA_158V, Fcɣ RIIIA_158F, or C1q does not cause significant cytokine release compared to a wild-type IgG1 antibody having the same CDRs as the CD200R agonist antibody.

22. The antibody of any one of Claims 20-21, wherein the antibody does not bind Fcɣ RIIIA_158F or C1q.

23. The antibody of any one of Claims 1-22, for use in therapy.

24. The use of the antibody of any one of Claims 1-22 in the manufacture of a medicament for the treatment of a disease, wherein the disease is an autoimmune disease, allergic disease, asthma, atopic dermatitis, or other inflammatory disorders.

25. A pharmaceutical composition comprising the antibody of any one of Claims 1-22, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

26. A DNA molecule comprising a polynucleotide that encodes the HC whose amino acid sequence is given by SEQ ID NO: 9 or a polynucleotide that encodes the LC whose amino acid sequence is given by SEQ ID NO: 10.

27. The DNA molecule of Claim 26, in which the sequence of the polynucleotide that encodes the HC is given by SEQ ID NO: 12 or the

sequence of the polynucleotide that encodes the LC is given by SEQ ID NO: 13.

28. The DNA molecule of Claim 26 comprising 1) a polynucleotide that encodes the HC whose amino acid sequence is given by SEQ ID NO: 9, and 2) a polynucleotide that encodes the LC whose amino acid sequence is given by SEQ ID NO: 10.

29. The DNA molecule of Claim 28, wherein the sequence of the polynucleotide that encodes the HC is given by SEQ ID NO: 12, and the sequence of the polynucleotide that encodes the LC is given by SEQ ID NO: 13.

30. A mammalian cell transformed with the DNA molecule of Claim 29, which transformed mammalian cell is capable of expressing an antibody comprising two HCs and two LCs, in which the amino acid sequence of each HC is given by SEQ ID NO: 9, and the amino acid sequence of each LC is given by SEQ ID NO: 10.