

BTLA. The '694 patent describes an ongoing need to develop treatments that exploit the inhibitory role of BTLA in lymphocyte responses, while allowing for BTLA-HVEM binding. However, there is a lack of BTLA agonist antibodies that mimic the binding of HVEM to BTLA for the treatment of autoimmune diseases. An antibody "mimics"

5 HVEM binding to BTLA if the antibody has an epitope that significantly overlaps the binding site of HVEM, and there is structural similarity between the antibody and HVEM. There is also a lack of BTLA agonist antibodies that bind human BTLA and are useful to study in *in vivo* pre-clinical models of autoimmune diseases such as murine and cynomolgus monkey models. Thus, there remains a need for alternative BTLA agonist
10 antibodies.

Summary

In one aspect, the present disclosure refers to an antibody that binds BTLA, comprising HCDR1 having the amino acid sequence of SEQ ID NO: 13, HCDR2 having the amino acid sequence of SEQ ID NO: 16, HCDR3 having the amino acid sequence of
15 SEQ ID NO: 19, LCDR1 having the amino acid sequence of SEQ ID NO: 22, LCDR2 having the amino acid sequence of SEQ ID NO: 25, and LCDR3 having the amino acid sequence of SEQ ID NO: 28.

In another aspect, the present disclosure refers to an antibody that binds BTLA, comprising HCDR1 having the amino acid sequence of SEQ ID NO: 14, HCDR2 having
20 the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 20, LCDR1 having the amino acid sequence of SEQ ID NO: 23, LCDR2 having the amino acid sequence of SEQ ID NO: 26, and LCDR3 having the amino acid sequence of SEQ ID NO: 29.

In yet another aspect, the present disclosure refers to an antibody that binds
25 BTLA, comprising HCDR1 having the amino acid sequence of SEQ ID NO: 15, HCDR2 having the amino acid sequence of SEQ ID NO: 18, HCDR3 having the amino acid sequence of SEQ ID NO: 21, LCDR1 having the amino acid sequence of SEQ ID NO: 24, LCDR2 having the amino acid sequence of SEQ ID NO: 27, and LCDR3 having the amino acid sequence of SEQ ID NO: 30.

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

In another aspect, the present disclosure refers to the antibody or the pharmaceutical composition disclosed herein for use in therapy.

In another aspect, the present disclosure refers to a use of the antibody as disclosed herein in the manufacture of a medicament for the treatment of one or more of rheumatic, 5 neural, and dermatology disease.

In yet another aspect, the present disclosure refers to a DNA molecule comprising a polynucleotide that encodes the amino acid sequence of SEQ ID NO: 1, 2, 5, 6, 9 or 10.

In a further aspect, the present disclosure refers to a DNA molecule comprising a polynucleotide sequence that encodes the antibody heavy chain having the amino acid 10 sequence of SEQ ID NO: 1, 5, or 9 and a polynucleotide sequence that encodes the antibody light chain having the amino acid sequence of SEQ ID NO: 2, 6, or 10.

In another aspect, the present disclosure refers to a mammalian cell comprising the DNA molecule as disclosed herein.

In yet another aspect, the present disclosure refers to a process for producing an 15 antibody, the process comprises: a) cultivating the mammalian cell as disclosed herein under conditions such that the antibody is expressed, and b) recovering the expressed antibody.

Description

The antibodies of the present invention seek to provide alternative BTLA agonist antibodies. Such BTLA agonist antibodies may be useful in the treatment of autoimmune 20 diseases such as lupus. Such BTLA agonist antibodies are able to bind BTLA from multiple species such as human, cynomolgus monkey, and/or murine BTLA. In addition, such BTLA agonist antibodies demonstrate increased *in vitro* activity compared to an antibody having the same heavy chain variable region and light chain variable region as Mab8D5. The antibodies of the present inventions possess at least one of these desirable characteristics.

25 One such BTLA agonist antibody is able to bind human, cynomolgus monkey, and murine BTLA. Surprisingly, this antibody has this desired cross-reactivity because it mimics HVEM binding to BTLA. This antibody also has a higher binding affinity to BTLA as compared to HVEM binding BTLA. This may provide a benefit for patients having disease states with transient levels of HVEM, wherein it may desirable to have a BTLA-mimicking 30 agonist antibody on-board during times when the patient has a reduction in HVEM.

The present inventions provide antibodies that bind to BTLA and activate and/or enhance BTLA-mediated signaling (BTLA agonist antibodies). The present inventions provide an antibody that comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity

5 determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2, and HCDR3, and wherein the amino acid sequence of LCDR1 is SEQ ID NO: 22, the amino acid sequence of LCDR2 is SEQ ID NO: 25, the amino acid

WE CLAIM:

1. An antibody that binds BTLA, comprising HCDR1 having the amino acid
sequence of SEQ ID NO: 13, HCDR2 having the amino acid sequence of SEQ ID
5 NO: 16, HCDR3 having the amino acid sequence of SEQ ID NO: 19, LCDR1
having the amino acid sequence of SEQ ID NO: 22, LCDR2 having the amino
acid sequence of SEQ ID NO: 25, and LCDR3 having the amino acid sequence of
SEQ ID NO: 28.
2. The antibody of Claim 1, comprising a heavy chain variable region (HCVR)
10 having the amino acid sequence of SEQ ID NO: 3, and a light chain variable
region (LCVR) having the amino acid sequence of SEQ ID NO: 4.
3. The antibody of Claim 1 or 2, comprising a heavy chain (HC) having the amino
acid sequence of SEQ ID NO: 1, and a light chain (LC) having the amino acid
sequence of SEQ ID NO: 2.

4. An antibody that binds BTLA, comprising HCDR1 having the amino acid sequence of SEQ ID NO: 14, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 20, LCDR1 having the amino acid sequence of SEQ ID NO: 23, LCDR2 having the amino acid sequence of SEQ ID NO: 26, and LCDR3 having the amino acid sequence of SEQ ID NO: 29.
5. The antibody of Claim 4, comprising a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 7, and a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 8.

6. The antibody of Claims 4 or 5, comprising a heavy chain (HC) having the amino acid sequence of SEQ ID NO:5, and a light chain (LC) having the amino acid sequence of SEQ ID NO: 6.

7. An antibody that binds BTLA, comprising HCDR1 having the amino acid sequence of SEQ ID NO: 15, HCDR2 having the amino acid sequence of SEQ ID NO: 18, HCDR3 having the amino acid sequence of SEQ ID NO: 21, LCDR1 having the amino acid sequence of SEQ ID NO: 24, LCDR2 having the amino acid sequence of SEQ ID NO: 27, and LCDR3 having the amino acid sequence of SEQ ID NO: 30.
8. The antibody of Claim 7, comprising a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 11, and a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 12.
9. The antibody of Claim 7 or 8, comprising a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 9, and a light chain (LC) having the amino acid sequence of SEQ ID NO: 10.
10. A pharmaceutical composition comprising the antibody of any one of Claims 1 to 9, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

11. The antibody of any one of Claims 1 to 9 or the pharmaceutical composition of Claim 10 for use in therapy.
12. Use of the antibody of any one of Claims 1 to 9 in the manufacture of a medicament for the treatment of one or more of rheumatic, neural, and dermatology disease.
13. The use of the antibody of Claim 12, wherein the rheumatic disease is at least one of lupus nephritis, systemic lupus erythematosus, and rheumatoid arthritis.
14. The use of the antibody of Claim 12, wherein the dermatology disease is at least one of atopic dermatitis and psoriasis.
15. The use of the antibody of Claim 12, wherein the neural disease is multiple sclerosis.

16. A DNA molecule comprising a polynucleotide that encodes the amino acid sequence of SEQ ID NO: 1, 2, 5, 6, 9 or 10.
17. A DNA molecule comprising a polynucleotide sequence that encodes the antibody heavy chain having the amino acid sequence of SEQ ID NO: 1, 5, or 9 and a
5 polynucleotide sequence that encodes the antibody light chain having the amino acid sequence of SEQ ID NO: 2, 6, or 10.
18. A mammalian cell comprising the DNA molecule of Claim 17.
19. A process for producing an antibody, the process comprises: a)

cultivating the mammalian cell of Claim 18 under conditions such that the antibody is expressed, and b) recovering the expressed antibody.