

In one example, the present disclosure refers to an isolated human antibody or an antigen-binding fragment thereof that specifically binds B and T lymphocyte attenuator (BTLA), comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, 387, or 207, with from 0 to 3 amino acid modifications.

In another example, the present disclosure refers to an isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, 143, or 210, respectively, with from 0 to 3 amino acid modifications.

In one aspect, the present disclosure refers to an isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein: (a) the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein (i) CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 205, (ii) CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 387, wherein the amino acid at position 5 is aspartic acid (D) or glutamic acid (E) and the amino acid at position 7 is asparagine (N) or glutamine (Q), and (iii) CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 207, and (b) the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2, and CDRL3, wherein (i) CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 142, (ii) CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 143, with 0 to 1 amino acid modification at position 6 numbered according to SEQ ID NO: 143, wherein the amino acid at position 6 is aspartic acid (D) or glutamic acid (E), and (iii) CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 210, respectively.

In yet another aspect, the present disclosure refers to an isolated nucleic acid which comprises one or more nucleotide sequences encoding polypeptides capable of forming an antibody or antigen-binding fragment as disclosed herein.

In yet another aspect, the present disclosure refers to a host cell comprising the nucleic acid sequence as disclosed herein.

In yet another aspect, the present disclosure refers to a method of producing an antibody or an antigen-binding fragment thereof that binds to BTLA, comprising the step of culturing the host cell as disclosed herein, under conditions for production of said antibody or an antigen-binding fragment thereof, optionally further comprising isolating and/or purifying said antibody or an antigen-binding fragment thereof.

In yet another aspect, the present disclosure refers to a method for preparing a human antibody or antigen-binding fragment thereof that specifically binds BTLA, the method comprising the steps of: 1) providing a host cell comprising one or more nucleic acid molecules encoding the amino acid sequence of a heavy chain and a light chain which when expressed are capable of combining to create an antibody or antigen-binding molecule; 2) culturing the host cell expressing the encoded amino acid sequence; and 3) isolating the antibody or antigen-binding molecule as disclosed herein.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof as disclosed herein and at least one pharmaceutically acceptable excipient.

In yet another aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in therapy.

In yet another aspect, the present disclosure refers to the use of an antibody or antigen-binding fragment thereof as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a BTLA-related disease.

CLAIMS:

What is claimed is:

1. An isolated human antibody or an antigen-binding fragment thereof that specifically binds B and T lymphocyte attenuator (BTLA), comprising a heavy chain and a light chain, wherein:

- (a) the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein
 - (i) CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 205,
 - (ii) CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 387, with 0 to 2 amino acid modifications at positions 5 and 7 numbered according to SEQ ID NO: 387, wherein the amino acid at position 5 is aspartic acid (D) or glutamic acid (E) and the amino acid at position 7 is asparagine (N) or glutamine (Q), and
 - (iii) CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 207, and
- (b) the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2, and CDRL3, wherein
 - (i) CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 142,
 - (ii) CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 143, with 0 to 1 amino acid modification at position 6 numbered according to SEQ ID NO: 143, wherein the amino acid at position 6 is aspartic acid (D) or glutamic acid (E), and
 - (iii) CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 210.

2. The isolated human antibody or an antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NO: 390, with up to 3 amino acid modifications therein; and the light chain variable region comprises an amino acid sequence as set forth in SEQ ID NO: 378, with up to 3 amino acid modifications therein.

3. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein the heavy chain or light chain also comprise a constant region.

4. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein the heavy chain and light chain are connected by a flexible linker to form a single-chain antibody.
5. The antibody or antigen-binding fragment thereof of any of the preceding claims, which binds a residue of BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92.
6. The antibody or antigen-binding fragment thereof of any of the preceding claims, which is an IgG1, IgG2 or IgG4 antibody.
7. The antibody of any of the preceding claims, which is selected from the group consisting of: a human antibody, a humanised antibody, a chimeric antibody and a multispecific antibody (such as a bispecific antibody).
8. The antigen-binding fragment according to any of claims 1 to 6, which is selected from the group consisting of: scFv, sc(Fv)₂, dsFv, Fab, Fab', (Fab')₂ and a diabody.
9. The antibody or antigen-binding fragment thereof of any of the preceding claims, which is monoclonal.
10. The antibody or antigen-binding fragment thereof of any preceding claim, wherein said antibody or antigen-binding fragment thereof agonizes human BTLA expressed on the surface of an immune cell, wherein said immune cell is optionally a T cell.
11. The antibody or antigen-binding fragment thereof of any preceding claim, wherein binding of said antibody or antigen-binding fragment thereof to human BTLA expressed on the surface of an immune cell decreases proliferation of said cell relative to a comparable immune cell not bound by said antibody or antigen-binding fragment thereof, and wherein said cell is optionally a T cell.

12. The antibody or antigen-binding fragment thereof of claim 11, wherein said decrease in cell proliferation is measured by an assay described in Example 8 or Example 9.
13. The antibody or antigen-binding fragment thereof of claim 11 or 12, wherein said decrease in cell proliferation is measured in vitro or in vivo.
14. The antibody or antigen-binding fragment thereof of any one of claims 11-13, wherein said decrease in cell proliferation is at least 10%, 15%, 20%, 25%, 30%, 40%, or 50%.
15. The antibody or antigen-binding fragment thereof of any one of claims 11-13, wherein said decrease in cell proliferation is from 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 10% to 15%, 20% to 50%, 20% to 40%, or 20% to 30%.
16. The antibody or antigen-binding fragment thereof of any preceding claim, wherein said antibody or antigen-binding fragment thereof comprises a domain that binds to an Fc receptor.
17. The antibody or antigen-binding fragment thereof of claim 16, wherein said Fc receptor is expressed on the surface of an immune cell.
18. The antibody or antigen-binding fragment thereof of claim 17, wherein said immune cell is an antigen presenting cell.
19. The antibody or antigen-binding fragment thereof of claim 18, wherein said antigen presenting cell is a dendritic cell, macrophage, monocyte, or neutrophil.
20. The antibody or antigen-binding fragment thereof of any one of claims 16-19, wherein said antibody or antigen-binding fragment thereof binds to human BTLA expressed on the surface of a T cell.
21. The antibody or antigen-binding fragment thereof of any one of claims 16-20, wherein said Fc receptor is FcγRIIB.

22. The antibody or antigen-binding fragment thereof of any preceding claim, wherein binding of said antibody or antigen-binding fragment thereof to human BTLA expressed on the surface of an immune cell decreases NF κ B signaling of said immune cell relative to a comparable immune cell not bound by said antibody or antigen-binding fragment thereof, and wherein said immune cell is optionally a T cell.

23. The antibody or antigen-binding fragment thereof of claim 22, wherein said decrease in NF κ B signaling of said immune cell is measured by an assay described in Example 10.

24. The antibody or antigen-binding fragment thereof of claim 22 or 23, wherein said decrease in NF κ B signaling of said immune cell is at least 10%, 15%, 20%, 25%, 30%, or 40%.

25. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, each as determined by surface plasmon resonance (SPR) at 37°C.

26. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C.

27. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, each as determined by surface plasmon resonance (SPR) at 37°C, and wherein said antibody binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C; does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.

28. The antibody or antigen-binding fragment thereof of claim 27, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms) at 37°C.

29. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms) , as determined by surface plasmon resonance (SPR) at 37°C, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and wherein said antibody inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.

30. The antibody or antigen-binding fragment thereof of claim 29, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C.

31. The antibody or antigen-binding fragment thereof of claim 29 or 30, wherein said antibody or antigen-binding fragment thereof wherein said antibody binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C.

32. An isolated nucleic acid which comprises one or more nucleotide sequences encoding polypeptides capable of forming an antibody or antigen-binding fragment as claimed in any of claims 1 to 31.

33. A host cell comprising the nucleic acid sequence according to claim 32.

34. A method of producing an antibody or an antigen-binding fragment thereof that binds to BTLA, comprising the step of culturing the host cell of claim 33, under conditions for production of said antibody or an antigen-binding fragment thereof, optionally further comprising isolating and/or purifying said antibody or an antigen-binding fragment thereof.

35. A method for preparing a human antibody or antigen-binding fragment thereof that specifically binds BTLA, the method comprising the steps of:

- 1) providing a host cell comprising one or more nucleic acid molecules encoding the amino acid sequence of a heavy chain and a light chain which when expressed are capable of combining to create an antibody or antigen-binding molecule;
- 2) culturing the host cell expressing the encoded amino acid sequence; and
- 3) isolating the antibody or antigen-binding molecule of any of claims 1 to 31.

36. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any of claims 1 to 31 and at least one pharmaceutically acceptable excipient.

37. An antibody or antigen-binding fragment thereof in accordance with any of claims 1 to 31, or the pharmaceutical composition in accordance with claim 36, for use in therapy.

38. Use of an antibody or antigen-binding fragment thereof in accordance with any of claims 1 to 31, or the pharmaceutical composition in accordance with claim 36, in the manufacture of a medicament for the treatment of a BTLA-related disease.

39. The use in accordance with claim 38, wherein the BTLA-related disease is one caused by decreased expression and/or activity of BTLA in a subject.

40. The use in accordance with claim 38 or 39, wherein the BTLA-related disease is an inflammatory or autoimmune disease, or a disorder of excessive immune cell proliferation.

41. The use in accordance with claim 40, wherein the disease or condition comprises Addison's disease, allergy, alopecia areata, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-phospholipid syndrome, asthma, autoimmune haemolytic anaemia, autoimmune hepatitis, autoimmune pancreatitis, autoimmune polyendocrine syndrome, Behcet's disease, bullous pemphigoid, cerebral malaria, chronic inflammatory demyelinating polyneuropathy, coeliac disease, Crohn's disease, Cushing's Syndrome, dermatomyositis, diabetes mellitus type 1,

eosinophilic granulomatosis with polyangiitis, graft versus host disease, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hidradenitis Suppurativa, inflammatory fibrosis, inflammatory bowel disease, juvenile arthritis, Kawasaki disease, leukemia, lymphoma, lymphoproliferative disorders, multiple sclerosis, myasthenia gravis, myeloma, neuromyelitis optica, pemphigus, polymyositis, primary biliary cholangitis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, transplant rejection, transverse myelitis, ulcerative colitis, uveitis, vasculitis, vitiligo, or Vogt-Koyanagi-Harada Disease.

42. The use in accordance with claim 40, wherein the disease or condition comprises vasculitis, systemic lupus erythematosus, ulcerative colitis, inflammatory bowel disease, graft versus host disease, rheumatoid arthritis, juvenile arthritis or psoriatic arthritis.