Claims

What is claimed is:

1. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the light chain and heavy chain of said antibody comprise the three complementarity determining regions (CDRs) found in SEQ ID NOs: 9 and 22, respectively.

2. A monoclonal anti-human CD52 antibody, or an antigen-binding portion thereof, that binds to the same epitope on human CD52 as the monoclonal antibody or antigen-binding portion of claim 1.

3. The monoclonal antibody or antigen-binding portion of claim 1 or 2, wherein the antibody is a humanized antibody, a mouse antibody, or a chimeric antibody.

4. The monoclonal antibody or antigen-binding portion of claim 1, wherein the framework regions of the heavy chain utilize a VH3-72 or VH3-23 human germline sequence, and wherein the framework regions of the light chain utilize a VK2 A18b human germline sequence.

5. The monoclonal antibody or antigen-binding portion of claim 1, wherein the antibody comprises heavy chain (H)-CDR1, H-CDR2, H-CDR3, and light chain (L)-CDR1, L-CDR2, and L-CDR3 whose amino acid sequences are SEQ ID NOs: 53, 63, 71, 31, 36, and 44, respectively.

6. The monoclonal antibody or antigen-binding portion of claim 1, wherein the light chain and heavy chain of said antibody comprise the amino acid sequences of SEQ ID NOs: 9 and 22, respectively.

7. The monoclonal antibody or antigen-binding portion according to claim 1, wherein said heavy chain and light chain comprise the amino acid sequences of
   a) SEQ ID NOs: 149 and 155, respectively; or
   b) SEQ ID NOs: 149 and 156, respectively.

8. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the heavy chain and the light chain of said antibody comprise the amino acid sequences of SEQ ID NOs: 279 and 280, respectively, without the signal sequences.

9. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the light chain of said antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 153-157.

10. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the light chain of said antibody comprises an amino acid sequence of SEQ ID NO: 280, without the signal sequence.

11. An antibody light chain or a portion thereof, comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 153-157 and 280, without the signal sequence if present.

12. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the heavy chain of said antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 149-152.

13. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the heavy chain of said antibody comprises an amino acid sequence of SEQ ID NO: 279, without the signal sequence.

14. An antibody heavy chain or a portion thereof, comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 149-152and 279, without the signal sequences if present.

15. The monoclonal antibody of any one of claims 1-7, 9, 10, and 12, wherein said antibody is an IgG1, IgG2, IgG3, or IgG4 molecule.

16. The antigen-binding portion of any one of claims 1-10, 12, and 13, wherein said portion is a single chain antibody, Fv, Fab, Fab', $F(ab')_2$, Fd, single chain Fv molecule (scFv), bispecific single chain Fv dimer, diabody, domain-deleted antibody or single domain antibody (dAb).

17. The monoclonal antibody or antigen-binding portion of claim 1 or 2, wherein said antibody or portion binds to an amino acid sequence comprising SEQ ID NO: 104, and optionally, the binding of said antibody or portion to SEQ ID NO: 104 is reduced by an alanine substitution at one or more of residues 4, 7, 8, and 11 of SEQ ID NO: 104.

18. The monoclonal antibody or antigen-binding portion according to any one of claims 1-10, 12, and 13, wherein said antibody or antigen-binding portion has one or more properties selected from the group consisting of:
    a) depletes T or B lymphocytes, or both;
    b) preferentially depletes T lymphocytes as compared to B lymphocytes;
    c) increases circulating serum levels of TNF-alpha, IL-6, or MCP-1;
    d) mediates antibody-dependent cell mediated cytotoxicity (ADCC) of CD52-expressing cells;
    e) mediates complement-dependent cytotoxicity (CDC) of CD52-expressing cells;
    f) binds to human CD52 in the presence of neutralizing antibodies to alemtuzumab; and
    g) promotes intracellular signaling in human T or B lymphocytes, or both.

19. An isolated nucleic acid encoding the heavy chain or an antigen-binding portion thereof, or the light chain or an antigen-binding portion thereof, of an antibody or according to any one of claims 1-10, 12, and 13.

20. The isolated nucleic acid of claim 19, wherein said isolated nucleic acid comprises:
    a) a heavy chain nucleotide sequence of SEQ ID NO: 290, or said nucleotide sequence without the sequence encoding a signal peptide;
    b) a light chain nucleotide sequence selected from the group consisting of SEQ ID NO: 291, or said nucleotide sequence without the sequence encoding a signal peptide; or
    c) the nucleotide sequences of both a) and b).

21. The isolated nucleic acid of claim 20, wherein said isolated nucleic acid comprises a heavy chain nucleotide sequence and a light chain nucleotide sequence of SEQ ID NO: 290 and SEQ ID NO: 291, respectively, both without sequences encoding signal peptides.

22. Use of an isolated nucleic acid comprising a heavy chain nucleotide sequence and an isolated nucleic acid comprising a light chain nucleotide sequence for the manufacture of a medicament for treating a patient in need thereof, wherein said heavy chain nucleotide sequence and light chain nucleotide sequence are SEQ ID NO: 290 and SEQ ID NO: 291, both respectively, without sequences encoding signal peptides.

23. A recombinant vector comprising (1) a nucleic acid sequence encoding the heavy chain or an antigen-binding portion thereof, (2) a nucleic acid sequence encoding the light chain or an antigen-binding portion thereof, or (3) both, of a monoclonal antibody according to any one of claims 1-10, 12, and 13.

24. A host cell comprising a first nucleic acid sequence encoding the heavy chain or an antigen-binding portion thereof of a monoclonal antibody according to any one of claims 1-10, 12, and 13, said first nucleic acid sequence operably linked to an expression control element, and a second nucleic acid sequence encoding the light chain or an antigen-binding portion thereof of said monoclonal antibody, said second nucleic acid sequence operably linked to an expression control element.

25. A method of making an anti-human CD52 antibody or an antigen-binding portion thereof, comprising maintaining the host cell of claim 24 under conditions appropriate for expression of the antibody or portion.

26. The method of claim 25, further comprising isolating the antibody or portion.

27. A composition comprising the monoclonal antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18 and a pharmaceutically acceptable vehicle or carrier.

28. A method for treating a patient in need thereof, comprising administering to the patient an effective amount of the antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18, or a composition of claim 33.

29. The method of claim 28, wherein the patient is receiving a transplantation.

30. A method for treating an autoimmune disease in a patient in need thereof, comprising administering to the patient an effective amount of the antibody or antigen-binding

portion according to any one of claims 1-10, 12, 13, and 15-18, or a composition of claim 27.

31. The method of claim 30, wherein said autoimmune disease is multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, or vasculitis.

32. A method for treating cancer in a patient in need thereof, comprising administering to the patient an effective amount of the monoclonal antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18, or a composition of claim 27.

33. The method of claim 32, wherein said cancer is a leukemia.

34. The method of claim 32, wherein said cancer is a lymphoma.

35. The method of claim 32, wherein said cancer is T cell malignancy, and the antibody or portion preferentially depletes T cells as compared to B cells.

36. The method of claim 32, wherein said cancer is a solid tumor.

37. The method of claim 28, 30, or 32, further comprising administering to the patient a neutrophil or NK cell stimulatory agent.

38. The method of claim 37, wherein the agent is G-CSF or GM-CSF.

39. The method of claim 28, 30, or 32, further comprising administering to the patient a T regulatory cell stimulatory agent.

40. The method of claim 39, wherein the agent is rapamycin.

41. A method of inhibiting angiogenesis in a patient in need thereof, comprising administering an effective amount of the monoclonal antibody or portion of any one of claims 1-10, 12, 13, and 15-18 to the patient.

42. The method of claim 41, wherein the patient has a solid tumor.

43. The method of claim 41, wherein the patient has neovascularization.

44. Use of the monoclonal antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18 for the manufacture of a medicament for treating an autoimmune disease in a patient in need thereof.

45. Use of the antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18 for the manufacture of a medicament for treating cancer in a patient in need thereof.

46. Use of the antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18 for the manufacture of a medicament for treating a patient in need of a transplantation.

47. Use of the antibody or antigen-binding portion according to any one of claims 1-10, 12, 13, and 15-18 for the manufacture of a medicament for treating neovascularization in a patient in need thereof.

48. Use of the antibody or portion of any one of claims 1-10, 12, 13, and 15-18 as a medicament.

CLAIMS

1. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the light chain and heavy chain of said antibody comprise the three complementarity determining regions (CDRs) found in SEQ ID NOs: 9 and 22, respectively.

2. The monoclonal antibody or antigen-binding portion of claim 1, wherein the antibody is a humanized antibody, a mouse antibody, or a chimeric antibody.

3. The monoclonal antibody or antigen-binding portion of claim 1 or 2, wherein the framework regions of the heavy chain utilize a VH3-72 human germline sequence, and wherein the framework regions of the light chain utilize a VK2 A18b human germline sequence.

4. The monoclonal antibody or antigen-binding portion of any one of claims 1-3, wherein the antibody comprises heavy chain (H)-CDR1, H-CDR2, H-CDR3, and light chain (L)-CDR1, L-CDR2, and L-CDR3 whose amino acid sequences are SEQ ID NOs: 53, 63, 71, 31, 36, and 44, respectively.

5. The monoclonal antibody or antigen-binding portion of any one of claims 1-4, wherein the light chain and heavy chain of said antibody comprise the amino acid sequences of SEQ ID NOs: 9 and 22, respectively.

6. The monoclonal antibody or antigen-binding portion according to any one of claims 1-4, wherein said heavy chain and light chain comprise the amino acid sequences of
   a) SEQ ID NOs: 149 and 155, respectively; or
   b) SEQ ID NOs: 149 and 156, respectively.

7. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the heavy chain and the light chain of said antibody comprise the amino acid sequences of SEQ ID NOs: 279 and 280, respectively, without the signal sequences.

8. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the light chain of said antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 153-157.

9. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the light chain of said antibody comprises an amino acid sequence of SEQ ID NO: 280, without the signal sequence.

10. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the heavy chain of said antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 149-152.

11. A monoclonal anti-human CD52 antibody or an antigen-binding portion thereof, wherein the heavy chain of said antibody comprises an amino acid sequence of SEQ ID NO: 279, without the signal sequence.

12. The monoclonal antibody of any one of claims 1-6, and 8-10, wherein said antibody is an IgG1, IgG2, IgG3, or IgG4 molecule.

13. The antigen-binding portion of any one of claims 1-11, wherein said portion is a single chain antibody, Fv, Fab, Fab', $F(ab')_2$, Fd, single chain Fv molecule (scFv), bispecific single chain Fv dimer, diabody, domain-deleted antibody or single domain antibody (dAb).

14. The monoclonal antibody or antigen-binding portion of any one of claims 1-13, wherein said antibody or portion binds to an amino acid sequence comprising SEQ ID NO: 104, and optionally, the binding of said antibody or portion to SEQ ID NO: 104 is reduced by an alanine substitution at one or more of residues 4, 7, 8, and 11 of SEQ ID NO: 104.

15. The monoclonal antibody or antigen-binding portion according to any one of claims 1-14, wherein said antibody or antigen-binding portion has one or more properties selected from the group consisting of:

a) depletes T or B lymphocytes, or both;

b) preferentially depletes T lymphocytes as compared to B lymphocytes;

c) increases circulating serum levels of TNF-alpha, IL-6, or MCP-1;

d) mediates antibody-dependent cell mediated cytotoxicity (ADCC) of CD52-expressing cells;

e) mediates complement-dependent cytotoxicity (CDC) of CD52-expressing cells;

f) binds to human CD52 in the presence of neutralizing antibodies to alemtuzumab; and

g) promotes intracellular signaling in human T or B lymphocytes, or both.

16. An isolated nucleic acid encoding the heavy chain or an antigen-binding portion thereof, and the light chain or an antigen-binding portion thereof, of an antibody or according to any one of claims 1-12, 14, and 15.

17. The isolated nucleic acid of claim 16, wherein said isolated nucleic acid comprises:

a) a heavy chain nucleotide sequence of SEQ ID NO: 290, or said nucleotide sequence without the sequence encoding a signal peptide; and

b) a light chain nucleotide sequence selected from the group consisting of SEQ ID NO: 291, or said nucleotide sequence without the sequence encoding a signal peptide.

18. The isolated nucleic acid of claim 17, wherein said isolated nucleic acid comprises a heavy chain nucleotide sequence and a light chain nucleotide sequence of SEQ ID NO: 290 and SEQ ID NO: 291, respectively, both without sequences encoding signal peptides.

19. Use of an isolated nucleic acid comprising a heavy chain nucleotide sequence and an isolated nucleic acid comprising a light chain nucleotide sequence for the manufacture of a medicament for treating a patient in need thereof, wherein said heavy chain nucleotide sequence and light chain nucleotide sequence are SEQ ID NO: 290 and SEQ ID NO: 291, respectively, without sequences encoding signal peptides.

20. A recombinant vector comprising (1) a nucleic acid sequence encoding the heavy chain or an antigen-binding portion thereof, and (2) a nucleic acid sequence encoding the light

chain or an antigen-binding portion thereof, of a monoclonal antibody according to any one of claims 1-12, 14, and 15.

21. A host cell comprising a first nucleic acid sequence encoding the heavy chain or an antigen-binding portion thereof of a monoclonal antibody according to any one of claims 1-12, 14, and 15, said first nucleic acid sequence operably linked to an expression control element, and a second nucleic acid sequence encoding the light chain or an antigen-binding portion thereof of said monoclonal antibody, said second nucleic acid sequence operably linked to an expression control element.

22. A method of making an anti-human CD52 antibody or an antigen-binding portion thereof, comprising maintaining the host cell of claim 21 under conditions appropriate for expression of the antibody or portion.

23. The method of claim 22, further comprising isolating the antibody or portion.

24. A composition comprising the monoclonal antibody or antigen-binding portion according to any one of claims 1-15 and a pharmaceutically acceptable vehicle or carrier.

25. Use of the monoclonal antibody or antigen-binding portion according to any one of claims 1-15 for the manufacture of a medicament for treating an autoimmune disease in a patient in need thereof.

26. The method of claim 25, wherein said autoimmune disease is multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, or vasculitis.

27. Use of the antibody or antigen-binding portion according to any one of claims 1-15 for the manufacture of a medicament for treating cancer in a patient in need thereof.

28. The method of claim 27, wherein said cancer is a leukemia.

29. The method of claim 27, wherein said cancer is a lymphoma.

30. The method of claim 27, wherein said cancer is T cell malignancy, and the antibody or portion preferentially depletes T cells as compared to B cells.

31. The method of claim 27, wherein said cancer is a solid tumor.

32. Use of the antibody or antigen-binding portion according to any one of claims 1-15 for the manufacture of a medicament for treating a patient in need of a transplantation.

33. Use of the antibody or antigen-binding portion according to any one of claims 1-15 for the manufacture of a medicament for treating neovascularization in a patient in need thereof.

34. Use of the antibody or antigen-binding portion according to any one of claims 1-15 for the manufacture of a medicament for inhibiting angiogenesis in a patient in need thereof.

35. The method of claim 33, wherein the patient has a solid tumor.

36. Use of the antibody or portion of any one of claims 1-15 for the manufacture of a medicament.