CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and an anti-CD200 antibody comprising an altered Fc constant region, wherein said anti-CD200 antibody inhibits the interaction between CD200 and CD200R, and wherein said altered Fc constant region exhibits decreased effector function relative to the effector function of the corresponding native Fc constant region.

2. The pharmaceutical composition of claim 1, wherein the effector function comprises one or more of the following:

(a) antibody-dependent cell-mediated cytotoxicity (ADCC);

(b) complement dependent cytotoxicity (CDC); or

(c) binding to one or more Fc receptors.

3. The pharmaceutical composition of claim 1, wherein the anti-CD200 antibody is a murine antibody, a chimeric antibody, a humanized antibody, a deimmunized antibody, or a human antibody.

4. The pharmaceutical composition of claim 1, wherein the altered Fc constant region is an altered form of a native constant region selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgA, IgD, and IgE.

5. The pharmaceutical composition of claim 1, wherein the altered Fc constant region comprises at least one amino acid substitution, insertion, or deletion, relative to the corresponding native constant region.

6. The pharmaceutical composition of claim 1, wherein:

(a) the altered Fc constant region is a G2/G4 constant region; or

(b) relative to the native Fc constant region, said altered Fc constant region comprises:

(i) altered glycosylation;

(ii) an Ala-Ala mutation;

(iii) the CH1 and hinge regions of an IgG2 antibody; or

(iv) the CH2 and CH3 regions of an IgG4 antibody.

7. The pharmaceutical composition of claim 6, wherein the altered glycosylation comprises one or more of the following: (i) a change in one or more sugar components; (ii) presence of one or more additional sugar components; and (iii) absence of one or more sugar components.

8. The pharmaceutical composition of claim 7, wherein said antibody is expressed in a host cell selected from the group consisting of a mammalian cell, a bacterial cell, and a plant cell.

9. The pharmaceutical composition of claim 8, wherein the host cell is *E. coli*.

10. The pharmaceutical composition of claim 8, wherein the host cell is a rat-hybridoma cell.

11. The pharmaceutical composition of claim 8, wherein the host cell is a CHO cell.

12. The pharmaceutical composition of claim 1, wherein the anti-CD200 antibody comprises:

(a) a light chain polypeptide comprising:

(i) a light chain variable domain comprising a light chain CDR1 having the amino acid sequence set forth in residues 44 to 51 of SEQ ID NO:47; a light chain CDR2 having the amino acid sequence set forth in residues 70 to 76 of SEQ ID NO:47; and a light chain CDR3 having the amino acid sequence set forth in residues 109 to 117 of SEQ ID NO:47;

(ii) a light chain variable domain having an amino acid sequence comprising residues 19 to 128 of SEQ ID NO:47; or

(iii) an amino acid sequence comprising residues 19 to 240 of SEQ ID NO:47; and

(b) a heavy chain polypeptide comprising:

(iv) a heavy chain variable domain comprising: a heavy chain CDR1 having the amino acid sequence set forth in residues 46 to 55 of SEQ ID NO:15; a heavy chain CDR2 having the amino acid sequence set forth in residues 70 to 86 of SEQ ID NO:15; and a heavy chain CDR3 having the amino acid sequence set forth in residues 119 to 126 of SEQ ID NO:15;

(v) a heavy chain variable domain having an amino acid sequence comprising residues 20 to 137 of SEQ ID NO:15; or

(vi) an amino acid sequence comprising residues 20 to 463 of SEQ ID NO:15.

13. The pharmaceutical composition of claim 1, wherein the anti-CD200 antibody comprises:

(a) a light chain polypeptide comprising:

(i) a light chain variable domain comprising: a light chain CDR1 having the amino acid sequence set forth in residues 44 to 54 of SEQ ID NO:32; a light chain CDR2 having the amino acid sequence set forth in residues 70 to 76 of SEQ ID NO:32; and a light chain CDR3 having the amino acid sequence set forth in residues 109 to 117 of SEQ ID NO:32;

(ii) a light chain variable domain having an amino acid sequence comprising residues 21 to 127 of SEQ ID NO:32; or

(iii) an amino acid sequence comprising residues 21 to 234 of SEQ ID NO:32; and

(b) a heavy chain polypeptide comprising:

(iv) a heavy chain CDR1 having the amino acid sequence set forth in residues 46 to 55 of SEQ ID NO:20; a heavy chain CDR2 having the amino acid sequence set forth in residues 70 to 86 of SEQ ID NO:20; and a heavy chain CDR3 having the amino acid sequence set forth in residues 119 to 131 of SEQ ID NO:20; or

(v) a heavy chain variable domain having an amino acid sequence comprising residues 21 to 142 of SEQ ID NO:20.

14. The pharmaceutical composition of claim 1, wherein the anti-CD200 antibody comprises:

(a) a light chain polypeptide comprising:

(i) a light chain variable domain having an amino acid sequence comprising residues 23 to 129 of SEQ ID NO:28; or

(ii) an amino acid sequence comprising residues 23 to 236 of SEQ ID NO:28; and

(b) a heavy chain polypeptide comprising:

(iii) a heavy chain variable domain having an amino acid sequence comprising residues 20 to 136 of SEQ ID NO:13; or

(iv) an amino acid sequence comprising residues 20 to 462 of SEQ ID NO:13.

15. The pharmaceutical composition of claim 1, wherein the altered Fc constant region has 0 to 20% of the FcR binding of the corresponding native Fc constant region.

16. The pharmaceutical composition of claim 1, wherein the altered Fc constant region has no effector function as compared to the corresponding native Fc constant region.

17. The pharmaceutical composition of claim 1, wherein the altered Fc constant region has reduced or no ADCC or CDC activity as compared to the corresponding native Fc constant region.

18. An anti-CD200 antibody comprising an altered Fc constant region, wherein said anti-CD200 antibody inhibits the interaction between CD200 and CD200R, wherein said altered Fc constant region exhibits decreased effector function relative to the effector function of the corresponding native Fc constant region, and wherein the anti-CD200 antibody comprises:

(I.)

(a) a light chain polypeptide comprising:

(i) a light chain variable domain comprising a light chain CDR1 having the amino acid sequence set forth in residues 44 to 51 of SEQ ID NO:47; a light chain CDR2 having the amino acid sequence set forth in residues 70 to 76 of SEQ ID NO:47; and a light chain CDR3 having the amino acid sequence set forth in residues 109 to 117 of SEQ ID NO:47;

(ii) a light chain variable domain having an amino acid sequence comprising residues 19 to 128 of SEQ ID NO:47; or

(iii) an amino acid sequence comprising residues 19 to 240 of SEQ ID NO:47; and

(b) a heavy chain polypeptide comprising:

(iv) a heavy chain variable domain comprising: a heavy chain CDR1 having the amino acid sequence set forth in residues 46 to 55 of SEQ ID NO:15; a heavy chain CDR2 having the amino acid sequence set forth in residues 70 to 86 of SEQ ID NO:15; and a heavy chain CDR3 having the amino acid sequence set forth in residues 119 to 126 of SEQ ID NO:15;

(v) a heavy chain variable domain having an amino acid sequence comprising residues 20 to 137 of SEQ ID NO:15; or

(vi) an amino acid sequence comprising residues 20 to 463 of SEQ ID NO:15;

(II.)

(a) a light chain polypeptide comprising:

(i) a light chain variable domain comprising: a light chain CDR1 having the amino acid sequence set forth in residues 44 to 54 of SEQ ID NO:32; a light chain CDR2 having the amino acid sequence set forth in residues 70 to 76 of SEQ ID NO:32; and a light chain CDR3 having the amino acid sequence set forth in residues 109 to 117 of SEQ ID NO:32;

(ii) a light chain variable domain having an amino acid sequence comprising residues 21 to 127 of SEQ ID NO:32; or

(iii) an amino acid sequence comprising residues 21 to 234 of SEQ ID NO:32; and

(b) a heavy chain polypeptide comprising:

(iv) a heavy chain CDR1 having the amino acid sequence set forth in residues 46 to 55 of SEQ ID NO:20; a heavy chain CDR2 having the amino acid sequence set forth in residues 70 to 86 of SEQ ID NO:20; and a heavy chain CDR3 having the amino acid sequence set forth in residues 119 to 131 of SEQ ID NO:20; or

(v) a heavy chain variable domain having an amino acid sequence comprising residues 21 to 142 of SEQ ID NO:20;

(III.)

(a) a light chain polypeptide comprising:

(i) a light chain variable domain having an amino acid sequence comprising residues 23 to 129 of SEQ ID NO:28; or

(ii) an amino acid sequence comprising residues 23 to 236 of SEQ ID NO:28; and

(b) a heavy chain polypeptide comprising:

(iii) a heavy chain variable domain having an amino acid sequence comprising residues 20 to 136 of SEQ ID NO:13; or

(iv) an amino acid sequence comprising residues 20 to 462 of SEQ ID NO:13.

19. The anti-CD200 antibody of claim 18, wherein the effector function comprises one or more of the following:

(a) antibody-dependent cell-mediated cytotoxicity (ADCC);

(b) complement dependent cytotoxicity (CDC); or

(c) binding to one or more Fc receptors.

20. The anti-CD200 antibody of claim 18, wherein the anti-CD200 antibody is a murine antibody, a chimeric antibody, a humanized antibody, a deimmunized antibody, or a human antibody.

21. The anti-CD200 antibody of claim 18, wherein the altered Fc constant region is an altered form of a native Fc constant region selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgA, IgD, and IgE.

22. The anti-CD200 antibody of claim 18, wherein the altered Fc constant region comprises at least one amino acid substitution, insertion, or deletion, relative to the corresponding native constant region.

23. The anti-CD200 antibody of claim 18, wherein:

(a) the altered Fc constant region is a G2/G4 constant region; or

(b) relative to the native Fc constant region, said altered Fc constant region comprises:

(i) altered glycosylation;

(ii) an Ala-Ala mutation;

(iii) the CH1 and hinge regions of an IgG2 antibody; or (iv) the CH2 and CH3 regions of an IgG4 antibody.

24. An anti-CD200 antibody comprising an altered Fc constant region, wherein said anti-CD200 antibody inhibits the interaction between CD200 and CD200R, wherein said altered Fc constant region exhibits decreased effector function relative to the effector function of the corresponding native Fc constant region, wherein said altered Fc constant region is a G2/G4 constant region, and wherein said G2/G4 constant region comprises the amino acid sequence depicted in any one of SEQ ID NOs: 13, 15, or 22.

CLAIMS

1. An anti-CD200 antibody or antigen-binding fragment thereof comprising an altered constant region that has 0 to 20% of the effector function of the corresponding native constant region, wherein said altered constant region comprises one of more of the following characteristics:

a) altered glycosylation comprising at least one of: a decrease in the number of glycosylated residues, an increase in the number of glycosylated residues, a change in the pattern of glycosylated residues, and a change in the location of glycosylated residues;
b) an Ala-Ala mutation comprising at least one of: (i) a replacement of residue 234 with Ala and (ii) a replacement of residue 235 with Ala;
c) a replacement of the G1 domain with a G2/G4 construct;
d) the constant region of an IgG2; and
e) the constant region of an lgG4.

2. The antibody or antigen-binding fragment of claim 1, wherein decreased effector function comprises one or more of the following:
   a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC);
   b) decreased complement dependent cytotoxicity (CDC) compared to a non-variant anti-CD200 antibody.

3. The antibody or antigen-binding fragment of claim 1, wherein the antibody is a murine antibody, a chimeric antibody, a humanized antibody, a single chain antibody, or a human antibody.

4. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of IgGl, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgA, IgD, and IgE.

5. The antibody or antigen-binding fragment of claim 1, wherein the constant region has been engineered to comprise at least one amino acid substitution, insertion, or deletion.

6. The antibody or antigen-binding fragment of claim 1, comprising an amino acid sequence that is encoded by a nucleic acid selected from the group consisting of SEQ ID NOS: 12, 14, 16, 17, and 21, or to fragments thereof.

7. The antibody or antigen-binding fragment of claim 1, comprising an amino acid sequence that is at least 90% identical to an amino acid sequence of SEQ ID NOS: 13, 15, 18, or

22, or to fragments thereof.

8. The antibody or antigen-binding fragment of claim 1, wherein said G2/G4 construct is selected from SEQ ID NOS: 13, 15, 18, and 22.

9. The antibody of claim 1, wherein said antibody is expressed in a host cell selected from the group consisting of a mammalian cell, a bacterial cell, and a plant cell.

10. The antibody of claim 9, wherein the host cell is E. coli.

11. The antibody of claim 9, wherein the host cell is a rat-hybridoma cell.

12. The antibody of claim 9, wherein the host cell is a CHO cell.

13. The antibody or antigen-binding fragment of claim 1, comprising one or more of the following characteristics:
a) decreased binding to one or more Fc receptors;
b) decreased ADCC activity; and
c) decreased CDC activity
relative to a non-variant anti-CD200 antibody.

14. The antibody or antigen-binding fragment of any one of claims 1-13, wherein the antibody is a blocking anti-CD200 antibody.

15. The antibody or antigen-binding fragment of claim 14, wherein the antibody is a murine antibody, a chimeric antibody, a humanized antibody, a single chain antibody, or a human antibody.

16. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises one or more amino acid sequence(s) that is encoded by a nucleic acid selected from:
a) SEQ ID NOS: 14 and 27 or fragments thereof;
b) SEQ ID NO: 14 and 23 or fragments thereof;
c) SEQ ID NOS: 16 and 27 or fragments thereof;
d) SEQ ID NOS: 17 and 29 or fragments thereof; or
e) SEQ ID NOS: 21 and 33 or fragments thereof.

17. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises one or more amino acid sequence(s) that is at least 90% identical to an amino acid sequence selected from:

a) SEQ ID NO: 15, SEQ ID NO: 24, the fragment of SEQ ID NO: 15 beginning at amino acid 21, the fragment of SEQ ID NO: 24 beginning at amino acid 21, and other fragments of SEQ ID NOS: 15 and 24;

b) SEQ ID NO: 13, SEQ ID NO: 28, the fragment of SEQ ID NO: 13 beginning at amino acid 20, the fragment of SEQ ID NO: 28 beginning at amino acid 23, and other fragments of SEQ ID NOS: 13 and 28;

c) SEQ ID NO: 18, SEQ ID NO: 30, the fragment of SEQ ID NO: 18 beginning at amino acid 21, the fragment of SEQ ID NO: 30 beginning at amino acid 21, and other fragments of SEQ ID NOS: 18 and 30; or

d) SEQ ID NO: 22, SEQ ID NO: 34, the fragment of SEQ ID NO: 22 beginning at amino acid 20, the fragment of SEQ ID NO: 34 beginning at amino acid 20, and other fragments of SEQ ID NOS: 22 and 34.

18. The antigen-binding fragment of claim 16 or 17, wherein the antigen-binding fragment exhibits reduced effector function.

19. An antibody or antigen-binding fragment of any of claims 1, 16, or 17, wherein said antibody or antigen-binding fragment is conjugated to an agent.

20. The antibody or antigen-binding fragment of claim 19, wherein the agent is selected from the group consisting of a toxin, enzyme, therapeutic agent, diagnostic agent, and imaging agent.

21. An antigen-binding fragment of any of claims 1, 16, or 17, wherein the antigen-binding fragment is modified to exhibit increased half-life in a subject.

22. The antigen-binding fragment of claim 21, wherein the antigen-binding fragment comprises one or more of the following characteristics:
a) is PEGylated;
b) is fused to a second polypeptide; and
c) is linked to a small molecule.

23. The antigen-binding fragment of claim 22, wherein the second polypeptide binds serum proteins.

24. The antigen-binding fragment of claim 22, wherein the second polypeptide is albumin.

25. The antigen-binding fragment of claim 22, wherein the small molecule binds serum proteins.

26. The antigen-binding fragment of claim 21 or 22, wherein the antigen-binding fragment is a single-chain fragment.

27. Use of the antibody or antigen-binding fragment of any of claims 1, 16, or 17 in the preparation of a medicament for decreasing the number of CD200 positive cells in a patient.

28. The use according to claim 27, wherein said antibody or antigen-binding fragment inhibits the interaction of CD200 with its receptor.

29. The use according to claim 27, wherein said anti-CD200 antibody exhibits a reduced ability to kill T cells.

30. The use according to claim 27, wherein said anti-CD200 antibody is a blocking antibody.

31. Use of the antibody or antigen-binding fragment of any of claims 1, 16, or 17 in the preparation of a medicament for treating a patient with cancer.

32. The use according to claim 31, wherein said cancer is derived from a neural crest cell cancer.

33. The use according to claim 31, wherein said cancer is selected from the group consisting of a plasma cell cancer, ovarian cancer, skin cancer, lung cancer, renal cancer, breast cancer, prostate cancer, neuroblastoma, lymphoma, myeloma, and leukemia.

34. Use of the antibody or antigen-binding fragment of any one of claims 1, 16, and 17 in combination with a second agent in the preparation of a medicament for treating cancer.

35. The use according to claim 34, wherein the second agent comprises one or more of the following characteristics:
    a) chemotherapeutic activity;
    b) regulatory activity on T cells; and
    c) immunomodulatory activity.

36. The use according to claim 34, wherein said second agent is selected from the group consisting of chemotherapeutic agent, immunomodulatory agent, heteroclitic peptide, antibody, antigen-binding fragment, nucleic acid, small molecule, organometallic compound, polypeptide, aptamer, spiegelmer, chemical, inorganic compound, metal, prodrug, and peptidomimetic compound.

37. The use according to claim 31, wherein said medicament further comprises an agent that can restore the activity of compromised dendritic cells in a tumor environment.

38. The use according to claim 37, wherein said agent is a MAP kinase inhibitor.

39. The use according to claim 31, wherein said medicament further comprises a chemotherapeutic agent.

40. The use according to claim 39, wherein said chemotherapeutic agent is selected from the group consisting of aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bicalutamide, bleomycin, buserelin, busulfan, camptothecin, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, and vinorelbine.

41. The use according to claim 39, wherein said medicament further comprises an anti-angiogenic agent.

42. The use according to claim 39, wherein said chemotherapeutic agent is an anti-metabolite.

43. The use according to claim 42, wherein said anti-metabolite is a pyrimidine analog.

44. The use according to claim 43, wherein said pyrimidine analog is selected from the group consisting of 5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine.

45. The use according to claim 42, wherein said anti-metabolite is a purine analog.

46. The use according to claim 45, wherein said purine analog is selected from the group consisting of mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine.

47. The use according to claim 39, wherein said medicament further comprises an antimitotic agent, microtubule disruptors, DNA damaging agents, antibiotics, antiplatelet agents, DNA alkylating agents, anticoagulants, fibrinolytic agents, antimigratory agents, antisecretory agents, immunosuppressives, immunomodulatory agents, growth factor inhibitors, topoisomerase inhibitors, corticosteroids and chromatin disruptors.

48. The use according to claim 47, wherein said immunosuppressive agent is selected from the group consisting of cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, and mycophenolate mofetil.

49. The use according to claim 47, wherein said immunomodulatory agent is selected from the group consisting of thalidomide and analogs thereof.

50. The use according to claim 47, wherein said immunomodulatory agent is selected from the group consisting of lenalidomide, Actimid, and cyclophosphamide.

51. The use according to claim 47, wherein said immunomodulatory agent is selected from the group consisting of heteroclitic peptides and cancer vaccines.

52. Use of the antibody or antigen-binding fragment of any of claims 1, 16, or 17 in the preparation of a medicament for treating a viral infection in a patient.

53. The use according to claim 52, wherein said antibody or antigen-binding fragment thereof is blocking.

54. The use according to claim 27, wherein the CD-200 positive cells are selected from B-cells and T-cells.

55. The use according to claim 27, wherein said patient has an autoimmune disease.

56. The use according to claim 55, wherein said autoimmune disease is selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, pernicious anemia, Addison's disease, type I diabetes, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, and Grave's disease.

57. The use according to claim 27, wherein said patient has received or will receive a transplant.

58. The use according to claim 57, wherein said patient has received or will receive an allograft.

59. The use according to claim 27, wherein said antibody or antigen-binding fragment is non-blocking.

60. The use according to claim 27, wherein said patient is a female.

61. The use according to claim 60, wherein said patient has been screened for pregnancy status.

62. The use according to claim 27, wherein cells or tissue samples from said patient have been tested for CD200 expression level.

63. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any of claims 1, 16, or 17.

64. The pharmaceutical composition of claim 63 that is substantially pyrogen-free.

65. The use of any of claims 27-62 wherein said patient has not received radiation therapy to the brain.

66. The use of any of claims 27-62 wherein said patient has not previously received brain surgery.

67. A de-immunized anti-CD200 antibody or antigen binding fragment thereof comprising an altered constant region that has 0 to 20% of the effector function of the corresponding native constant region, wherein said altered constant region comprises one of more of the following characteristics:

a) altered glycosylation comprising at least one of: a change in one or more sugar components, addition of one or more sugar components, and absence of sugar components;
b) an Ala-Ala mutation comprising at least one of: (i) a replacement of residue 234 with Ala and (ii) a replacement of residue 235 with Ala;
c) a replacement of the G1 domain with a G2/G4 construct;
d) the constant region of an IgG2; and
e) the constant region of an IgG4.

68. The de-immunized antibody or antigen-binding fragment of claim 67, wherein the de-immunized antibody or antigen binding fragment is a blocking anti-CD200 antibody or antigen-binding fragment thereof.

69. Use of the antibody or antigen-binding fragment of any of claims 1, 16, or 17 in the preparation of a medicament for treating cancer in a patient receiving a second therapy.

70. The use according to claim 69, wherein said second therapy is radiation therapy.