CLAIMS

1. An anti-CD200R1 antibody comprising (i) a first light chain hypervariable region (HVR-L1), a second light chain hypervariable region (HVR-L2), and a third light chain hypervariable region (HVR-L3), and/or (ii) a first heavy chain hypervariable region (HVR-H1), a second heavy chain hypervariable region (HVR-H2), and a third heavy chain hypervariable region (HVR-H3), wherein:

(a) HVR-L1 comprises an amino acid sequence selected from RASESVDYSGNSFMH (SEQ ID NO: 11), SASSSVSYMY (SEQ ID NO: 19), RASKSISKYLA (SEQ ID NO: 27), RASKSISKYLA (SEQ ID NO: 35), QASHTINLN (SEQ ID NO: 43), QASHTINLN (SEQ ID NO: 51), RASKSVSTSGYSYMH (SEQ ID NO: 59), and RASESVDYSGNSFMH (SEQ ID NO: 77);

(b) HVR-L2 comprises an amino acid sequence selected from RASNLES (SEQ ID NO: 12), LTSKLAS (SEQ ID NO: 20), SGSTLQS (SEQ ID NO: 28), SGSTLQS (SEQ ID NO: 36), GTSNLED (SEQ ID NO: 44), GTSNLED (SEQ ID NO: 52), LASNLES (SEQ ID NO: 60), and RASNLES (SEQ ID NO: 78);

(c) HVR-L3 comprises an amino acid sequence selected from HQSNEDPPT (SEQ ID NO: 13), QQWSSYPLT (SEQ ID NO: 21), QQYNEYPWT (SEQ ID NO: 29), QQYNEYPWT (SEQ ID NO: 37), LQHTYLPWT (SEQ ID NO: 45), LQHTYLPWT (SEQ ID NO: 53), QHNRELLT (SEQ ID NO: 61), and HQSNWDPPT (SEQ ID NO: 79);

(d) HVR-H1 comprises an amino acid sequence selected from TNYAVS (SEQ ID NO: 15), KDDYMH (SEQ ID NO: 23), KDDYMH (SEQ ID NO: 31), KDDYIH (SEQ ID NO: 39), KDDYIH (SEQ ID NO: 47), TSYWMH (SEQ ID NO: 55), TSYVMF (SEQ ID NO: 63), TNYRVS (SEQ ID NO: 81), and TNYWVS (SEQ ID NO: 85);

(e) HVR-H2 comprises an amino acid sequence selected from VMWAGGGTNYNS (SEQ ID NO: 16), RIDPANDNTKYAP (SEQ ID NO: 24), RIDPENGNTKYGP (SEQ ID NO: 32), RIDPANGNTKYAP (SEQ ID NO: 40), RIDPANGNTKYAP (SEQ ID NO: 48), AIYPGNSDTNYNQ (SEQ ID NO: 56), YINPYNDDTKYNE (SEQ ID NO: 64), VMYAGGGTNYNS (SEQ ID NO: 82), and TMWAGGGTNYNS (SEQ ID NO: 86);

(f) HVR-H3 comprises an amino acid sequence selected from ARERPLTGVMDY (SEQ ID NO: 17), TRVEGRTGTYFDY (SEQ ID NO: 25), TRQLGLRRVWYALDY (SEQ ID NO: 33), ARQLGLRRTWYSLDY (SEQ ID NO: 41), TRQLGLRRTWYAMDY (SEQ ID NO: 49), TTAVGSY (SEQ ID NO: 57), AREDYYGSRFVYW (SEQ ID NO: 65), ARERPLTGVMDN (SEQ ID NO: 83), and ARERPLTGPMDY (SEQ ID NO: 87).

2. The antibody of claim 1 comprising:

(a) HVR-L1 of SEQ ID NO: 11, HVR-L2 of SEQ ID NO: 12, and HVR-L3 of SEQ ID NO: 13; and/or HVR-H1 of SEQ ID NO: 15, HVR-H2 of SEQ ID NO: 16, and HVR-H3 of SEQ ID NO: 17;

(b) HVR-L1 of SEQ ID NO: 19, HVR-L2 of SEQ ID NO: 20, and HVR-L3 of SEQ ID NO: 21; and/or HVR-H1 of SEQ ID NO: 23, HVR-H2 of SEQ ID NO: 24, and HVR-H3 of SEQ ID NO: 25;

(c) HVR-L1 of SEQ ID NO: 27, HVR-L2 of SEQ ID NO: 28, and HVR-L3 of SEQ ID NO: 29; and/or HVR-H1 of SEQ ID NO: 31, HVR-H2 of SEQ ID NO: 32, and HVR-H3 of SEQ ID NO: 33;

(d) HVR-L1 of SEQ ID NO: 35, HVR-L2 of SEQ ID NO: 36, and HVR-L3 of SEQ ID NO: 37; and/or HVR-H1 of SEQ ID NO: 39, HVR-H2 of SEQ ID NO: 40, and HVR-H3 of SEQ ID NO: 41;

(e) HVR-L1 of SEQ ID NO: 43, HVR-L2 of SEQ ID NO: 44, and HVR-L3 of SEQ ID NO: 45; and/or HVR-H1 of SEQ ID NO: 47, HVR-H2 of SEQ ID NO: 48, and HVR-H3 of SEQ ID NO: 49;

(f) HVR-L1 of SEQ ID NO: 51, HVR-L2 of SEQ ID NO: 52, and HVR-L3 of SEQ ID NO: 53; and/or HVR-H1 of SEQ ID NO: 55, HVR-H2 of SEQ ID NO: 56, and HVR-H3 of SEQ ID NO: 57;}

(g) HVR-L1 of SEQ ID NO: 59, HVR-L2 of SEQ ID NO: 60, and HVR-L3 of SEQ ID NO: 61; and/or HVR-H1 of SEQ ID NO: 63, HVR-H2 of SEQ ID NO: 64, and HVR-H3 of SEQ ID NO: 65;

(h) HVR-L1 of SEQ ID NO: 77, HVR-L2 of SEQ ID NO: 78, and HVR-L3 of SEQ ID NO: 79; and/or HVR-H1 of SEQ ID NO: 81, HVR-H2 of SEQ ID NO: 82, and HVR-H3 of SEQ ID NO: 83; }

(i) HVR-L1 of SEQ ID NO: 11, HVR-L2 of SEQ ID NO: 12, and HVR-L3 of SEQ ID NO: 13; and/or HVR-H1 of SEQ ID NO: 85, HVR-H2 of SEQ ID NO: 86, and HVR-H3 of SEQ ID NO: 87;

(j) HVR-L1 of SEQ ID NO: 11, HVR-L2 of SEQ ID NO: 12, and HVR-L3 of SEQ ID NO: 13; and/or HVR-H1 of SEQ ID NO: 81, HVR-H2 of SEQ ID NO: 82, and HVR-H3 of SEQ ID NO: 83; or

(k) HVR-L1 of SEQ ID NO: 77, HVR-L2 of SEQ ID NO: 78, and HVR-L3 of SEQ ID NO: 79; and/or HVR-H1 of SEQ ID NO: 85, HVR-H2 of SEQ ID NO: 86, and HVR-H3 of SEQ ID NO: 87.

3. The antibody of any one of claims 1-2, wherein the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 10, 18, 26, 34, 42, 50, 58, 66, or 76; and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 14, 22, 30, 38, 46, 54, 62, 67, 80, or 84.

4. The antibody of any one of claims 1-3, wherein

(a) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 10, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 14;

(b) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 18, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 22;

(c) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 26, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 30;

(d) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 34, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 38;

(e) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 42, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 46;

(f) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 50, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 54;

(g) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 58, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 62;

(h) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 66, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 67;

(i) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 76, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 80;

(j) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 66, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 84;

(k) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 66, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 80; or

(l) the antibody comprises a light chain variable domain (VL) amino acid sequence having at least 90% identity to SEQ ID NO: 76, and/or a heavy chain variable domain (VH) amino acid sequence having at least 90% identity to SEQ ID NO: 84.

5. The antibody of any one of claims 1-4, wherein the antibody comprises: a light chain (LC) amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 68, 71, and 74;

and/or a heavy chain (HC) amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 69, 70, 72, 73, 75, 88, and 89.

6. The antibody of any one of claims 1-5, wherein:

(a) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 68; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 69;

(b) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 68; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 70;

(c) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 71; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 88;

(d) a light chain (LC) amino acid sequence having at least 90% identity to SEQ ID NO: 71; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 72;

(e) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 68; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 89;

(f) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 68; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 73;

(g) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 68; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 88;

(h) a light chain (LC) amino acid sequence having at least 90% identity SEQ ID NO: 71; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 89; or

(i) a light chain (LC) amino acid sequence having at least 90% identity to SEQ ID NO: 74; and/or a heavy chain (HC) amino acid sequence having at least 90% identity to SEQ ID NO: 75.

7. The antibody of any one of claims 1-6, wherein the antibody is characterized by one or more of the following properties:

(a) binds to hu-CD200R1 with a binding affinity of 1×10^{-8} M or less, 1×10^{-9} M or less, 1×10^{-10} M or less, or 1×10^{-11} M or less; optionally, wherein the binding affinity is measured by equilibrium dissociation constant (K_D) to a hu-CD200R1 polypeptide of SEQ ID NO: 1, 2, 3, and/or 4;

(b) binds to hu-CD200R1-iso4 and hu-CD200R1-iso1 with a binding affinity of 1×10^{-8} M or less, 1×10^{-9} M or less, 1×10^{-10} M or less, or 1×10^{-11} M or less; optionally, wherein the binding affinity is measured by equilibrium dissociation constant (K_D) to a hu-CD200R1-iso4 polypeptide of SEQ ID NO: 1 and/or 2, and a hu-CD200R1-iso1 polypeptide of SEQ ID NO: 3 and/or 4;

(c) binds to hu-CD200R1-iso4-Alt and hu-CD200R1-iso4-Ref with a binding affinity of 1×10^{-8} M or less, 1×10^{-9} M or less, 1×10^{-10} M or less, or 1×10^{-11} M or less; optionally, wherein the binding affinity is measured by equilibrium dissociation constant (K_D) to a hu-CD200R1-iso4-Alt polypeptide of SEQ ID NO: 1, and a hu-CD200R1-iso4-Ref polypeptide of SEQ ID NO: 2;

(d) binds to hu-CD200R1-iso4-Alt, hu-CD200R1-iso4-Ref, hu-CD200R1-iso1-Alt, and hu-CD200R1-iso1-Ref with a binding affinity of 1×10^{-8} M or less, 1×10^{-9} M or less, 1×10^{-10} M or less, or 1×10^{-11} M or less; optionally, wherein the binding affinity is measured by equilibrium

dissociation constant (K_D) to a hu-CD200R1-iso4-Alt polypeptide of SEQ ID NO: 1, hu-CD200R1-iso4-Ref polypeptide of SEQ ID NO: 2, hu-CD200R1-iso1-Alt polypeptide of SEQ ID NO: 3, and a hu-CD200R1-iso1-Ref polypeptide of SEQ ID NO: 4;

(e) binds to cyno-CD200R1 with a binding affinity of 1 x 10^{-8} M or less, 1 x 10^{-9} M or less, 1 x 10^{-10} M or less, or 1 x 10^{-11} M or less; optionally, wherein the binding affinity is measured by equilibrium dissociation constant (K_D) to a cyno-CD200R1 polypeptide of SEQ ID NO: 5;

(f) binds to hu-CD200R1 and to cyno-CD200R1 with a binding affinity of 1 x 10^{-8} M or less, 1 x 10^{-9} M or less, 1 x 10^{-10} M or less, or 1 x 10^{-11} M or less; optionally, wherein the binding affinity is measured by equilibrium dissociation constant (K_D) to a hu-CD200R1 polypeptide of SEQ ID NO: 1, 2, 3, and/or 4, and a cyno-CD200R1 polypeptide of SEQ ID NO: 5;

(g) blocks hu-CD200-Fc binding to hu-CD200R1-iso4-Alt (SEQ ID NO: 1), hu-CD200R1-iso4-Ref (SEQ ID NO: 2), hu-CD200R1-iso1-Alt (SEQ ID NO: 3), and hu-CD200R1-iso1-Ref (SEQ ID NO: 4) measured by ELISA with an IC_{50} of 10 nM or less, 7 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less;

(h) blocks hu-CD200-Fc binding to hu-CD200R1 expressed on a cell with an IC_{50} of 2.5 nM or less, 1 nM or less, or 0.5 nM or less; optionally, wherein the cell is a U937 cell stably expressing hu-CD200R1;

(i) binds to human T-cells with an EC_{50} of 2.5 nM or less, 1 nM or less, or 0.5 nM or less; optionally, wherein the human T-cells are CD4+ T-cells or CD8+ T-cells;

(j) increases IFNγ production from human tumor cells by at least 1.2-fold, 1.5-fold, 2-fold, or more, with an antibody concentration of 100 nM or less, 50 nM or less, or 10 nM or less; optionally, wherein the tumor cell type is selected from colorectal, endometrial, lung, melanoma, ovarian, pancreatic, or prostate;

(k) increases IFNγ and/or IL-2 production from hu-CD200-Fc coated human T cells relative to IgG control by at least 1.2-fold, 1.5-fold, 2-fold, or more;

(l) increases activation of human CD4+ T-cells or human Cd8+ T-cells by at least 1.5-fold, at least 2-fold, at least 2.5-fold, at least 3-fold or more;

(m) does not agonize CD200R1 signaling;

(n) blocks induction of pDok2 activity in U937 monocytic cell lines treated with soluble hu-CD200-Fc; and/or

(o) blocks NFkβ transcription induced by hu-CD200 binding hu-CD200R1 expressing cell-lines; optionally, wherein the cell lines are a CD200R1-expressing K562 reporter cells and CD200-expressing 293T cells.

8. An anti-CD200R1 antibody that specifically binds to the same epitope as the antibody of any one of claims 1-7; optionally, wherein the antibody binds to the same epitope as an antibody selected from 10F6, h10F6, 22.1, or h22.1.

9. An isolated polynucleotide or vector encoding the antibody of any one of claims 1-8.

10. An isolated host cell comprising the oligonucleotide or vector of claim 9; optionally, wherein the host cell is selected from a Chinese hamster ovary (CHO) cell, a myeloma cell (e.g.,Y0, NS0, Sp2/0), a monkey kidney cell (COS-7), a human embryonic kidney line (293), a baby hamster kidney cell (BHK), a mouse Sertoli cell (e.g., TM4), an African green monkey kidney cell (VERO-76), a human cervical carcinoma cell (HELA), a canine kidney cell, a human lung cell (W138), a human liver cell (Hep G2), a mouse mammary tumor cell, a TR1 cell, a Medical Research Council 5 (MRC 5) cell, and a FS4 cell.

11. A method of producing an antibody comprising culturing the host cell of claim 10 so that an antibody is produced.

12. A pharmaceutical composition comprising an anti-CD200 antibody of any one of claims 1-8 and a pharmaceutically acceptable carrier; optionally, wherein the composition further comprises a chemotherapeutic agent or an antibody comprising a specificity for an immune checkpoint molecule; or optionally, wherein the anti-CD200R1 antibody is the sole active agent of the composition.

13. Use of a therapeutically effective amount of an antibody of any one of claims 1-8, or a therapeutically effective amount of a pharmaceutical composition of claim 12, in the manufacture of a medicament for the treatment of a CD200R1 mediated disease.

14. The use of claim 13, wherein the therapeutically effective amount is at least about 1 mg/kg, at least about 2 mg/kg, at least about 10 mg/kg, at least about 20 mg/kg.

15. The use of claim 13, wherein the therapeutically effective amount is at least about 0.3 mg, at least about 1.0 mg, at least about 3.0 mg, at least about 10 mg, at least about 30 mg, at least about 100 mg, at least about 300 mg, or at least about 900 mg.

16. The use of claim 13, wherein the therapeutically effective amount is at least about 10 mg/kg, at least about 20 mg/kg, or at least about 100 mg/kg.

17. The use of any one of claims 13-16, wherein there are no significant off-target effects of the antibody of any one of claims 1-8 at the therapeutically effective amount.

18. The use of any one of claims 13-16, wherein there are no significant off-target effects of the antibody of any one of claims 1-8 at a dose of not more than 10 mg/kg.

19. The use of any one of claims 13-16, wherein there are no significant off-target effects of the antibody of any one of claims 1-8 at a dose of not more than 20 mg/kg.

20. The use of claim 13, wherein the disease is a cancer; optionally, wherein the cancer is selected from the cancer is selected from adrenal gland cancer, bladder cancer, sarcomas, microsatellite instability-high (MSI-H) cancer (including solid MSI-cancer), TMB (tumor mutational burden)-high tumor, mismatch repair deficient (dMMR) cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer,

EGJ adenocarcinoma, esophageal cancer, gall bladder cancer, gastric cancer (e.g. gastrointestinal carcinoid (GI carcinoid)), head and neck cancer, heart cancer, hepatocellular carcinoma, kidney cancer, liver cancer, melanoma, mesothelioma (e.g. pleural mesothelioma), non-small cell lung cancer, ovarian cancer, epithelial ovarian cancer, endometrial cancer, pediatric solid cancers, pancreatic cancer, prostate cancer, spleen cancer, small cell lung cancer, testicular cancer, thyroid cancer (e.g. medullary thyroid cancer or follicular thyroid cancer), blood cancers (e.g. diffuse large B cell lymphoma (DLBCL), leukemias, lymphomas, myelomas), renal cell carcinoma, clear cell renal carcinoma, neuroendocrine tumors (e.g. malignant pheochromocytoma and paraganglioma), and uterine cancer.

21. A therapeutically effective amount of an antibody of any one of claims 1-8, or a therapeutically effective amount of a pharmaceutical composition of claim 12, for use in therapy.