

functionality of CD33 may be beneficial in Alzheimer's disease and cancer. However, no data has been reported on the ability of anti-CD33 antibodies to downregulate CD33, or block CD33 ligand/receptor interactions, in physiologically relevant, primary immune cells.

[0016] Antibodies to CD33 have been described in, for example, US7,342,110, US7,557,189, US 8,119,787, US 8,337,855, US8,124,069, US5,730,982, US7,695,71, WO2012074097, WO2004043344, WO1993020848, WO2012045752, WO2007014743, WO2003093298, WO2011036183, WO1991009058, WO2008058021, WO2011038301, Hoyer et al., (2008) *Am. J. Clin. Pathol.* 129, 316–323, Rollins-Raval and Roth, (2012) *Histopathology* 60, 933–942, Pérez-Oliva et al., (2011) *Glycobiol.* 21, 757–770, Ferlazzo et al. (2000) *Eur J Immunol.* 30:827–833, Vitale et al., (2001) *Proc Natl Acad Sci USA.* 98:5764–5769, Jandus et al., (2011) *Biochem. Pharmacol.* 82, 323–332, O'Reilly and Paulson, (2009) *Trends Pharmacol. Sci.* 30, 240–248, Jurcic, (2012) *Curr Hematol Malig Rep* 7, 65–73, and Ricart, (2011) *Clin. Cancer Res.* 17, 6417–6427. However, these antibodies are used primarily to either detect CD33 on cells or target toxins, such as calicheamicin-gamma derivatives, in order to kill leukemia cells that express CD33. Moreover, no data has been reported showing the ability of anti-CD33 antibodies to treat solid tumor cells that do not express CD33, by enhancing anti-tumor immune responses.

[0017] Accordingly, there is a need for therapeutic antibodies for treating one or more diseases, disorders, and conditions associated with undesired CD33 activity.

[0018] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0019] The present disclosure is generally directed to CD33 agents, such as anti-CD33 antibodies, and methods of using such CD33 agents. The methods provided herein find use in preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomatous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, solid and blood

binds to human dendritic cells with an EC_{50} that ranges from 200 pM to 10 pM, wherein the EC_{50} is determined at a temperature of approximately 4°C; f. decreases cellular levels of CD33 with an EC_{50} that ranges from 65 pM to 20 pM; or g. decreases cellular levels of CD33 *in vivo* with an EC_{50} that ranges from 8.0 mg/kg to 2.0 mg/kg. In some examples, the dissociation constant (K_D) for human CD33 is less than 300 pM, wherein the K_D is determined at a temperature of approximately 25°C. In some example, the K_D is determined using a monovalent antibody. In some example, the K_D is determined using a full-length antibody in a monovalent form. In some examples, the anti-CD33 antibody binds to human dendritic cells with an EC_{50} that is less than 200 pM, wherein the EC_{50} is determined at a temperature of approximately 4°C. In some examples, the EC_{50} for decreasing cellular levels of CD33 *in vivo* is determined using a mouse. In some examples, the anti-CD33 antibody decreases cellular levels of CD33 with an EC_{50} that ranges from 65 pM to 22 pM, or less than 22 pM. In some examples, the anti-CD33 antibody decreases cellular levels of CD33 with an EC_{50} of 65 pM or less, 60 pM or less, 55 pM or less, 50 pM or less, 45 pM or less, 40 pM or less, 35 pM or less, 30 pM or less, 25 pM or less, 24 pM or less, 23 pM or less, 22 pM or less, 21 pM or less, 20 pM or less, 10 pM or less, 9 pM or less, 8 pM or less, 7 pM or less, 6 pM or less, or 5 pM or less.

[0021a] Disclosed is an isolated anti-CD33 antibody, wherein the anti-CD33 antibody decreases cellular levels of CD33, or inhibits interaction between CD33 and one or more CD33 ligands, or both, and wherein the anti-CD33 antibody exhibits one or more of the following properties: a. has a dissociation constant (K_D) for human CD33 that is lower than that of anti-CD33 antibody gemtuzumab; b. binds to human dendritic cells with an EC_{50} that is lower than that of anti-CD33 antibody gemtuzumab or lintuzumab; c. decreases cellular levels of CD33 with an EC_{50} that is lower than that of anti-CD33 antibody gemtuzumab or lintuzumab; d. has a dissociation constant (K_D) for human CD33 that ranges from 300 pM to 10 pM, wherein the K_D is determined at a temperature of approximately 25°C; e. binds to human dendritic cells with an EC_{50} that ranges from 200 pM to 10 pM, wherein the EC_{50} is determined at a temperature of approximately 4°C; f. decreases cellular levels of CD33 with an EC_{50} that ranges from 65 pM to 20 pM; or g. decreases cellular levels of CD33 *in vivo* with an EC_{50} that ranges from 8.0 mg/kg to 2.0 mg/kg.

[0022] Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both, and wherein the anti-CD33 antibody exhibits one or more of the following properties: a. has a dissociation constant (K_D) for human CD33 that is lower than that of anti-CD33 antibody gemtuzumab; b. binds to human dendritic cells with an EC_{50} that is lower than that of anti-CD33 antibody gemtuzumab or lintuzumab; c. decreases cellular levels of CD33 with an EC_{50} that is lower than that of anti-CD33 antibody

homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 26-29, and 187.

[0030a] Disclosed is an isolated anti-CD33 antibody which binds essentially the same CD33 epitope as an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2.

[0030b] Disclosed is an isolated anti-CD33 antibody, wherein the anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises: (a) an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-11, 67, 68, 184, and 228, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-11, 67, 68, 184, and 228; (b) an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12-14, 69-71, 185, and 229, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 12-14, 69-71, 185, and 229; and (c) an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15-17, 72-74, and 230, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15-17, 72-74, and 230; and wherein the heavy chain variable domain comprises: (a) an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18-21, 75, 231, and 232, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 18-21, 75, 231, and 232; (b) an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 22-25, 76, 77, 186, and 233, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 22-25, 76, 77, 186, and 233; and (c) an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 26-29, and 187, or an amino acid sequence with at least about 90% homology to an amino acid sequence selected from the group consisting of SEQ ID NOs: 26-29, and 187.

[0031] In some examples that may be combined with any of the preceding examples, the antibody is of the IgG class the IgM class, or the IgA class. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody has an IgG1, IgG2, IgG3, or IgG4 isotype. In some examples that may be combined with any of the preceding examples, the antibody binds an inhibitory Fc receptor. In some examples that may be combined with any of the preceding examples, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some examples that may be combined with any of the preceding examples:

repeat-expansion RNA, and any combination thereof. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody has a dissociation constant (K_D) for human CD33 and mouse CD33 that ranges from about 100 nM to about 100 pM, or less than 100 pM, and wherein the K_D is determined at a temperature of 25°C. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody has a dissociation constant (K_D) for human CD33 that ranges from about 10 nM to about 500 pM, or less than 500 pM, and wherein the K_D is determined at a temperature of 25°C. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody has a dissociation constant (K_D) for human CD33 that ranges from about 100 nM to about 100 pM, or less than 100 pM, and wherein the K_D is determined at a temperature of 25°C. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody has a dissociation constant (K_D) for mouse CD33 that ranges from about 100 nM to about 100 pM, or less than 100 pM, and wherein the K_D is determined at a temperature of 25°C. In some examples that may be combined with any of the previous examples, the K_D is determined using a monovalent antibody. In some examples that may be combined with any of the previous examples, the K_D is determined using a full-length antibody in a monovalent form. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is not conjugated to an agent, optionally wherein the agent is drug, toxin, chemotherapeutic, or radioisotope.

[0032] Other parts of the present disclosure relate to an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-CD33 antibody of any of the preceding examples. Other parts of the present disclosure relate to a vector comprising the nucleic acid any of the preceding examples. Other parts of the present disclosure relate to a host cell comprising the vector of any of the preceding examples. Other parts of the present disclosure relate to a method of producing an anti-CD33 antibody, comprising culturing the host cell of any of the preceding examples so that the anti-CD33 antibody is produced. In some examples, the method further comprises recovering the anti-CD33 antibody produced by the host cell. Other parts of the present disclosure relate to an isolated anti-CD33 antibody produced by the method of any of the preceding examples. Other parts of the present disclosure relate to a pharmaceutical composition comprising the anti-CD33 antibody of any of the preceding examples, and a pharmaceutically acceptable carrier.

[0032a] Disclosed is an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-CD33 antibody as described herein.

- [0032b] Disclosed is a vector comprising the nucleic acid as described herein.
- [0032c] Disclosed is an isolated host cell comprising the vector as described herein.
- [0032d] Disclosed is a method of producing an anti-CD33 antibody, comprising culturing the host cell as described herein so that the anti-CD33 antibody is produced.
- [0032e] Disclosed is an isolated anti-CD33 antibody produced by the method as described herein.
- [0032f] In one aspect, the present invention provides a pharmaceutical composition comprising an isolated anti-CD33 antibody, wherein the anti-CD33 antibody has a human IgG2 or human IgG4 isotype, decreases cell surface levels of CD33 with an EC50 that is lower than that of anti-CD33 antibody gemtuzumab and lintuzumab, is not conjugated to an agent, and optionally inhibits interaction between human CD33 and one or more CD33 ligands; and a pharmaceutically acceptable carrier.
- [0033] Other parts of the present disclosure relate to a method of preventing, reducing risk, or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, lupus, acute and chronic colitis,

be combined with any of the preceding examples, the agent exhibits one or more activities selected from the group consisting of: (a) increasing the number of tumor infiltrating CD3⁺ T cells; (b) decreasing cellular levels of CD33 in non-tumorigenic CD14⁺ myeloid cells, optionally wherein the non-tumorigenic CD14⁺ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic CD14⁺ myeloid cells are present in blood; (c) reducing the number of non-tumorigenic CD14⁺ myeloid cells, optionally wherein the non-tumorigenic CD14⁺ myeloid cells are tumor infiltrating cells or optionally wherein the non-tumorigenic CD14⁺ myeloid cells are present in blood; (d) reducing PD-L1 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (e) reducing PD-L2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (f) reducing B7-H2 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (g) reducing B7-H3 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (h) reducing CD200R levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (i) reducing CD163 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (j) reducing CD206 levels in one or more cells, optionally wherein the one or more cells are non-tumorigenic myeloid-derived suppressor cells (MDSC); (k) decreasing tumor growth rate of solid tumors; (l) reducing tumor volume; (m) increasing efficacy of one or more PD-1 inhibitors; (n) increasing efficacy of one or more checkpoint inhibitor therapies and/or immune-modulating therapies, optionally wherein the one or more checkpoint inhibitor therapies and/or immune-modulating therapies target one or more of CTL4, the adenosine pathway, PD-L1, PD-L2, OX40, TIM3, LAG3, or any combination thereof; (o) increasing efficacy of one or more chemotherapy agents, optionally wherein the one or more of the chemotherapy agents are gemcitabine, capecitabine, anthracyclines, doxorubicin (Adriamycin[®]), epirubicin (Ellence[®]), taxanes, paclitaxel (Taxol[®]), docetaxel (Taxotere[®]), 5-fluorouracil (5-FU), cyclophosphamide (Cytosan[®]), carboplatin (Paraplatin[®]), and any combination thereof; (p) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC); and (q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); and (r) killing CD33-expressing immunosuppressor myeloid cells and/or CD14-expressing cells in solid tumors and associated blood vessels when conjugated to a chemical or radioactive toxin.

[0033a] In yet another aspect, the present invention provides use of a therapeutically effective amount of an agent that decreases cellular levels of CD33 and optionally inhibits interaction between human CD33 and one or more CD33 ligands in the manufacture of a medicament for the treatment of a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, and tauopathy disease.

[0034] Other parts of the present disclosure relate to a method of preventing, reducing risk, or treating a disease, disorder, or injury selected from the group consisting of d dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, tauopathy disease,

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising an isolated anti-CD33 antibody, wherein the anti-CD33 antibody has a human IgG2 or human IgG4 isotype, decreases cell surface levels of CD33 with an EC₅₀ that is lower than that of anti-CD33 antibody gemtuzumab and lintuzumab, is not conjugated to an agent, and optionally inhibits interaction between human CD33 and one or more CD33 ligands; and a pharmaceutically acceptable carrier.
2. The pharmaceutical composition of claim 1, wherein the anti-CD33 antibody inhibits cell surface clustering of CD33.
3. The pharmaceutical composition of claim 1 or claim 2, wherein the anti-CD33 antibody inhibits one or more CD33 activities, wherein the one or more CD33 activities are selected from the group consisting of:
 - (a) CD33 binding to sialic acid-containing glycoproteins, or sialic acid-containing glycolipids, or both;
 - (b) modulated expression of one or more anti-inflammatory cytokines, optionally wherein the one or more anti-inflammatory cytokines are selected from a group consisting of IL-10, TGF-beta, or IL-6;
 - (c) modulated expression of one or more anti-inflammatory cytokines in one or more cells selected from the group consisting of macrophages, dendritic cells, bone marrow-derived dendritic cells, monocytes, granulocytes, neutrophils, and microglial cells;
 - (d) modulated expression of one or more pro-inflammatory cytokines, optionally wherein the one or more pro-inflammatory cytokines are selected from the group consisting of IL-1 β , TNF- α , IL-6, IL-8, IL-12, and MCP-1;
 - (e) modulated expression of one or more pro-inflammatory cytokines in one or more cells selected from the group consisting of macrophages, dendritic cells, bone marrow-derived dendritic cells, monocytes, granulocytes, neutrophils, and microglial cells;
 - (f) modulated expression of one or more proteins selected from the group consisting of C1qa, C1qB, C1qC, C1s, C1R, C4, C2, C3, ITGB2, HMOX1, LAT2, CASP1, CSTA, VSIG4, MS4A4A, C3AR1, GPX1, TyroBP,

ALOX5AP, ITGAM, SLC7A7, CD4, ITGAX, PYCARD, CD14, CD16, HLA-DR, and CCR2;

- (g) reducing T cell proliferation induced by one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, M2 microglia, macrophages, M1 macrophages, activated M1 macrophages, and M2 macrophages;
- (h) decreasing proliferation of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia;
- (i) decreasing one or more functions of one or more cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, granulocytes, neutrophils, microglia, M1 microglia, activated M1 microglia, and M2 microglia;
- (j) inhibition of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, dysfunctional synapses, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, and disease-causing nucleic acids; optionally wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP)

- repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides and
- (k) binding to CD33 ligand on cells selected from the group consisting of neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, and macrophages.
4. The pharmaceutical composition of any one of claims 1-3, wherein the anti-CD33 antibody binds to two or more amino acids within amino acid residues 19-259, 19-135, 145-228, or 229-259 of SEQ ID NO:1; or within amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 19-259, 19-135, 145-228, or 229-259 of SEQ ID NO:1.
5. The pharmaceutical composition of any one of claims 1-4, wherein the anti-CD33 antibody binds to two or more amino acid residues selected from the group consisting of D18, P19, N20, F21, F44, P46, Y49, Y50, K52, and N53 of SEQ ID NO: 1, or two or more amino acid residues on a mammalian CD33 protein corresponding to an amino acid residue selected from the group consisting of D18, P19, N20, F21, F44, P46, Y49, Y50, K52, and N53 of SEQ ID NO: 1.
6. The pharmaceutical composition of any one of claims 1-5, wherein the anti-CD33 antibody competes with one or more antibodies selected from the group consisting of:
- (a) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 16, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 19, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27;
- (b) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 72, and wherein the heavy chain variable domain comprises an HVR-H1

- comprising an amino acid sequence of SEQ ID NO: 231, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27;
- (c) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 69, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 72, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 19, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27;
 - (d) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 11, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 14, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 17, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 20, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 24, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 28;
 - (e) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 68, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 71, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 74, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 75, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 77, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 28;
 - (f) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising an amino acid

sequence of SEQ ID NO: 76, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29;

- (g) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 25, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29; and
- (h) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 228, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 229, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 230, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 232, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 233, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29;

and any combination thereof for binding to CD33.

- 7. The pharmaceutical composition of any one of claims 1-5, wherein the anti-CD33 antibody binds essentially the same CD33 epitope as an antibody selected from the group consisting of:
 - (a) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 16, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 19, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27;
 - (b) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, an HVR-L3 comprising an amino acid sequence of SEQ

- ID NO: 72, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 231, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27;
- (c) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 69, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 72, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 19, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27;
 - (d) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 11, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 14, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 17, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 20, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 24, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 28;
 - (e) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 68, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 71, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 74, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 75, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 77, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 28;
 - (f) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising an amino acid

sequence of SEQ ID NO: 76, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29;

- (g) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 21, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 25, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29; and
- (h) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 228, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 229, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 230, and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 232, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 233, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29.

8. The pharmaceutical composition of any one of claims 1-5, wherein the anti-CD33 antibody is selected from the group consisting of:

- (a) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, or an amino acid sequence of SEQ ID NO: 10 having one or more conservative amino acid substitutions; an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, or an amino acid sequence of SEQ ID NO: 13 having one or more conservative amino acid substitutions; an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 16, or an amino acid sequence of SEQ ID NO: 16 having one or more conservative amino acid substitutions; and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 19, or an amino acid sequence of SEQ ID NO: 19 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, or an amino acid sequence of SEQ ID NO: 23 having one or more conservative amino acid substitutions; and an HVR-H3

- comprising an amino acid sequence of SEQ ID NO: 27, or an amino acid sequence of SEQ ID NO: 27 having one or more conservative amino acid substitutions;
- (b) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, or an amino acid sequence of SEQ ID NO: 10 having one or more conservative amino acid substitutions; an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, or an amino acid sequence of SEQ ID NO: 13 having one or more conservative amino acid substitutions; an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 72, or an amino acid sequence of SEQ ID NO: 72 having one or more conservative amino acid substitutions; and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 231, or an amino acid sequence of SEQ ID NO: 231 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, or an amino acid sequence of SEQ ID NO: 23 having one or more conservative amino acid substitutions; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27, or an amino acid sequence of SEQ ID NO: 27 having one or more conservative amino acid substitutions;
- (c) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, or an amino acid sequence of SEQ ID NO: 10 having one or more conservative amino acid substitutions; an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 69, or an amino acid sequence of SEQ ID NO: 69 having one or more conservative amino acid substitutions; an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 72, or an amino acid sequence of SEQ ID NO: 72 having one or more conservative amino acid substitutions; and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 19, or an amino acid sequence of SEQ ID NO: 19 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, or an amino acid sequence of SEQ ID NO: 23 having one or more conservative amino acid substitutions; and an HVR-H3

- comprising an amino acid sequence of SEQ ID NO: 27, or an amino acid sequence of SEQ ID NO: 27 having one or more conservative amino acid substitutions;
- (d) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 11, or an amino acid sequence of SEQ ID NO: 11 having one or more conservative amino acid substitutions; an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 14, or an amino acid sequence of SEQ ID NO: 14 having one or more conservative amino acid substitutions; an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 17, or an amino acid sequence of SEQ ID NO: 17 having one or more conservative amino acid substitutions; and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 20, or an amino acid sequence of SEQ ID NO: 20 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 24, or an amino acid sequence of SEQ ID NO: 24 having one or more conservative amino acid substitutions; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 28, or an amino acid sequence of SEQ ID NO: 28 having one or more conservative amino acid substitutions;
- (e) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 68, or an amino acid sequence of SEQ ID NO: 68 having one or more conservative amino acid substitutions; an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 71, or an amino acid sequence of SEQ ID NO: 71 having one or more conservative amino acid substitutions; an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 74, or an amino acid sequence of SEQ ID NO: 74 having one or more conservative amino acid substitutions; and wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 75, or an amino acid sequence of SEQ ID NO: 75 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 77, or an amino acid sequence of SEQ ID NO: 77 having one or more conservative amino acid substitutions; and an HVR-H3

comprising an amino acid sequence of SEQ ID NO: 28, or an amino acid sequence of SEQ ID NO: 28 having one or more conservative amino acid substitutions;

- (f) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 21, or an amino acid sequence of SEQ ID NO: 21 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 76, or an amino acid sequence of SEQ ID NO: 76 having one or more conservative amino acid substitutions; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29, or an amino acid sequence of SEQ ID NO: 29 having one or more conservative amino acid substitutions;
- (g) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 21, or an amino acid sequence of SEQ ID NO: 21 having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 25, or an amino acid sequence of SEQ ID NO: 25 having one or more conservative amino acid substitutions; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29, or an amino acid sequence of SEQ ID NO: 29 having one or more conservative amino acid substitutions; and
- (h) an antibody comprising a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 228, or an amino acid sequence of SEQ ID NO: 228 having one or more conservative amino acid substitutions; an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 229, or an amino acid sequence of SEQ ID NO: 229 having one or more conservative amino acid substitutions; an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 230, or an amino acid sequence of SEQ ID NO: 230 having one or more conservative amino acid substitutions; and

wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 232, or an amino acid sequence of SEQ ID NO: 232

having one or more conservative amino acid substitutions; an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 233, or an amino acid sequence of SEQ ID NO: 233 having one or more conservative amino acid substitutions; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 29, or an amino acid sequence of SEQ ID NO: 29 having one or more conservative amino acid substitutions.

9. The pharmaceutical composition of any one of claims 1-5, wherein the anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises an HVR-L1 comprising an amino acid sequence of SEQ ID NO: 10, or an amino acid sequence of SEQ ID NO: 10 having one or more conservative amino acid substitutions, an HVR-L2 comprising an amino acid sequence of SEQ ID NO: 13, or an amino acid sequence of SEQ ID NO: 13 having one or more conservative amino acid substitutions, an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 72, or an amino acid sequence of SEQ ID NO: 72 having one or more conservative amino acid substitutions, and

wherein the heavy chain variable domain comprises an HVR-H1 comprising an amino acid sequence of SEQ ID NO: 231, or an amino acid sequence of SEQ ID NO: 231 having one or more conservative amino acid substitutions, an HVR-H2 comprising an amino acid sequence of SEQ ID NO: 23, or an amino acid sequence of SEQ ID NO: 23 having one or more conservative amino acid substitutions, and an HVR-H3 comprising an amino acid sequence of SEQ ID NO: 27, or an amino acid sequence of SEQ ID NO: 27 having one or more conservative amino acid substitutions.

10. The pharmaceutical composition of any one of claims 1-9, wherein the anti-CD33 antibody has a human IgG2 isotype.

11. The pharmaceutical composition of claim 10, wherein the antibody binds an inhibitory Fc receptor, optionally, wherein the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB).

12. The pharmaceutical composition of claim 10 or claim 11, wherein:

- (a) the anti-CD33 antibody has a human IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: P238S, V234A, G237A, H268A, H268Q, V309L, A330S, P331S, C214S, C232S, C233S, S267E, L328F, M252Y, S254T,

- T256E, H268E, N297A, N297Q, A330L, and any combination thereof, wherein the numbering of the residues is according to EU numbering;
- (b) the anti-CD33 antibody has a human IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, E233P, F234V, L234A/F234A, S228P, S241P, L248E, T394D, N297A, N297Q, L235E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or
- (c) the anti-CD33 antibody has a hybrid human IgG2/4 isotype, and optionally wherein the antibody comprises an amino acid sequence comprising amino acids 118 to 260 of human IgG2 and amino acids 261 to 447 of human IgG4, wherein the numbering of the residues is according to EU or Kabat numbering.
13. The pharmaceutical composition of any one of claims 1-12, wherein the CD33 protein is expressed on one or more cells selected from the group consisting of human dendritic cells, human macrophages, human monocytes, human neutrophils, human granulocytes, and human microglia.
14. The pharmaceutical composition of any one of claims 1-13, wherein the anti-CD33 antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, or a multivalent antibody.
15. The pharmaceutical composition of any one of claims 1-14, wherein the anti-CD33 antibody increases phagocytosis by microglia.
16. Use of a therapeutically effective amount of an agent that decreases cellular levels of CD33 and optionally inhibits interaction between human CD33 and one or more CD33 ligands in the manufacture of a medicament for the treatment of a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, and tauopathy disease.