[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 disclosure refers to a pharmaceutical composition comprising:

(a) an isolated anti-CD33 antibody, wherein the anti-CD33 antibody:

(i) has a human IgG2 or human IgG4 isotype,

(ii) decreases cell surface levels of CD33 on monocytes with an EC50 that is lower than that of anti-CD33 antibody gemtuzumab and lintuzumab, as determined by a fluorescence-activated cell sorting (FACS) assay, and

(iii) is not conjugated to an agent; and

(b) 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 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 (Cytoxan®), 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 disclosure refers to 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.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

(a) an isolated anti-CD33 antibody, wherein the anti-CD33 antibody:

(i) has a human IgG2 or human IgG4 isotype,

(ii) decreases cell surface levels of CD33 on monocytes with an EC_{50} that is lower than that of anti-CD33 antibody gemtuzumab and lintuzumab, as determined by a fluorescence-activated cell sorting (FACS) assay, and

(iii) is not conjugated to an agent; and

(b) a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein the anti-CD33 antibody inhibits interaction between human CD33 and one or more CD33 ligands.

3. The pharmaceutical composition of claim 1 or claim 2, wherein the anti-CD33 antibody inhibits cell surface clustering of CD33.

4. The pharmaceutical composition of any one of claims 1-3, 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-1β, 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.

5. The pharmaceutical composition of any one of claims 1-4, 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.

6. The pharmaceutical composition of any one of claims 1-5, 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.

7. The pharmaceutical composition of any one of claims 1-6, 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.

8. The pharmaceutical composition of any one of claims 1-6, 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.

9. The pharmaceutical composition of any one of claims 1-6, 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.

10. The pharmaceutical composition of any one of claims 1-6, 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.

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

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

13. The pharmaceutical composition of claim 11 or claim 12, 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.

14. The pharmaceutical composition of any one of claims 1-13, 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.

15. The pharmaceutical composition of any one of claims 1-14, wherein the anti-CD33 antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, or a multivalent antibody.

16. The pharmaceutical composition of any one of claims 1-15, wherein the anti-CD33 antibody increases phagocytosis by microglia.

17. 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.