

cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express CD33, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza. The methods provided herein also find use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. The methods provided herein find further use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cell in an individual in need thereof.

[0020] Certain parts of the present disclosure are based, at least in part, on the identification of anti-CD33 antibodies that are capable of decreasing cell surface levels of CD33 on human primary immune cells and CD33-expressing cell lines, and/or that are capable of inhibiting the binding of CD33 ligands on red blood cells to CD33 (*see, e.g., Examples 1-5*). Advantageously, the anti-CD33 antibodies decrease cellular levels of CD33 with a half-maximal effective concentration (EC_{50}) that ranges from 65 pM to 20 pM, decrease cellular levels of CD33 *in vivo* with a half-maximal effective concentration (EC_{50}) that ranges from 8.0 mg/kg to 2.0 mg/kg, bind to human cells, such as human dendritic cells with an EC_{50} that ranges from 200 pM to 10 pM, and have a dissociation constant (K_D) for human CD33 that ranges from 300 pM to 10 pM.

[0021] Accordingly, certain 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, or inhibits interaction between CD33 and one or more CD33 ligands, or both. In some examples, 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. 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] In one aspect, the present invention provides 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

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.. 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 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 EC₅₀ 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. In some examples, the EC₅₀ for decreasing cellular levels of CD33 *in vivo* is determined using a mouse.

[0023] In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody decreases cell surface levels of CD33, decreases intracellular levels of CD33, decreases total levels of CD33, or any combination thereof. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody induces CD33 degradation, CD33 cleavage, CD33 internalization, CD33 shedding, downregulation of CD33 expression, or any combination thereof. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody decreases cellular levels of CD33 without inhibiting the interaction between CD33 and one or more CD33 ligands. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody decreases cellular levels of CD33 and inhibits the interaction between CD33 and one or more CD33 ligands. In some examples that may be combined with any of the preceding examples, the antibody decreases cellular levels of CD33 *in vivo*. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody decreases cellular levels of CD33 *in vivo* with an EC₅₀ that ranges from about 8.0 mg/kg to about 2.0 mg/kg, or less than 2.0 mg/kg. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody inhibits the interaction between CD33 and one or more CD33 ligands without decreasing cellular levels of CD33. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody inhibits cell surface clustering of CD33. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody inhibits one or more CD33 activities. In some examples that may be combined with any of the preceding examples, the one or more CD33 activities selected from the group consisting of: (a) CD33 binding to sialic acid-containing glycoproteins, sialic acid-containing glycolipids, or both; (b) CD33 binding to SHP1 or SHP2; (c) phosphorylation of Tyr-340, Tyr-358, or both, induced by one or more SRC family tyrosine kinases, optionally, wherein the one or more SRC family tyrosine kinases are selected from the group consisting of Syk, LCK, and FYM; (d) phosphorylation of Ser-307, Ser-342, or both, optionally wherein the phosphorylation is induced by protein kinase C; (e) 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-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, or IL-6; (f) modulated expression of one or more anti-inflammatory cytokines in one or more cells selected from

dendritic cells, immunosuppressor macrophages, myeloid derived suppressor cells, tumor-associated macrophages, immunosuppressor neutrophils, and regulatory T cells into tumors; (pp) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; (qq) enhancing tumor-promoting activity of myeloid-derived suppressor cells; (rr) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (ss) increasing tumor infiltration of tumor-promoting FoxP3+ regulatory T lymphocytes; (tt) enhancing tumor-promoting activity of myeloid-derived suppressor cells (MDSC); (uu) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (vv) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (ww) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (xx) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (yy) increasing tumor volume; (zz) increasing tumor growth rate; (aaa) increasing rate of tumor recurrence; (bbb) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; (ccc) inhibition of PLC γ /PKC/calcium mobilization; and (ddd) inhibition of PI3K/Akt, Ras/MAPK signaling. In some examples that may be combined with any of the preceding examples, the one or more CD33 activities are selected from the group consisting of: (a) CD33 binding to sialic acid-containing glycoproteins, 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-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, 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, osteoclasts, T cells, T helper cells, cytotoxic T cells, 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 IFN-a4, IFN-b, IL-1 β , TNF- α , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, CRP, IL-33, MCP-1, and MIP-1-beta; (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, osteoclasts, T cells, T helper cells, cytotoxic T cells, granulocytes, neutrophils, and microglial cells; (f) modulated expression of one or more proteins selected from the

T cells; (n) inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells; (o) promoting functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, non-tumorigenic myeloid-derived suppressor cells, tumor-associated macrophages, immunosuppressor neutrophils, and regulatory T cells; (p) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, myeloid derived suppressor cells, tumor-associated macrophages, immunosuppressor neutrophils, non-tumorigenic CD45⁺CD14⁺ myeloid cells, and regulatory T cells into tumors; (q) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells in a tumor, in peripheral blood, or other lymphoid organ; (r) enhancing tumor-promoting activity of non-tumorigenic myeloid-derived suppressor cells and/or non-tumorigenic CD45⁺CD14⁺ myeloid cells; (s) enhancing survival of non-tumorigenic myeloid-derived suppressor cells (MDSC) and/or non-tumorigenic CD45⁺CD14⁺ myeloid cells; (t) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (u) decreasing activation of CD45⁺CD3⁺ T lymphocytes with tumor killing potential; (v) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (w) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (x) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (y) decreasing infiltration of CD45⁺CD3⁺ T lymphocytes; (z) increasing tumor volume; (aa) increasing tumor growth rate; and (bb) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more chemotherapy agent and/or cancer vaccines. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody 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, 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); (q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); and (r) killing CD33-expressing immunosuppressor non-tumorigenic myeloid cells and/or non-tumorigenic CD14-expressing cells in solid tumors and associated blood vessels when conjugated to a chemical or radioactive toxin. 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.

[0024] In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds a discontinuous CD33 epitope. In some examples that may be combined with any of the preceding examples, the discontinuous CD33 epitope comprises two or more peptides, three or more peptides, four or more peptides, five or more peptides, six or more peptides, seven or more peptide, eight or more peptides, nine or more peptides, or 10 or more peptides. In some examples that may be combined with any of the preceding examples, each of the peptides comprise five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues of the amino acid sequence of SEQ ID NO: 1; or five or more, six or more, seven or more, eight or more, nine or more, 10 or more, 11 or more, 12 or more, 13 or more 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, or 20 or more amino acid residues on a mammalian CD33 protein corresponding to the amino acid sequence

of SEQ ID NO: 1. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to a conformational epitope of CD33. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to one 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. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 39-51 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51 of SEQ ID NO:1; ii. amino acid residues 48-54 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 48-54 of SEQ ID NO:1; iii. amino acid residues 88-98 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 88-98 of SEQ ID NO:1; iv. amino acid residues 110-120 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 110-120 of SEQ ID NO:1; v. amino acid residues 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 112-122 of SEQ ID NO:1; vi. amino acid residues 39-51, 88-98, and 110-120 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, and 110-120 of SEQ ID NO:1; vii. amino acid residues 39-51, 88-98, and 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, and 112-122 of SEQ ID NO:1; and viii. amino acid residues 39-51, 88-98, 110-120, and 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, 110-120, and 112-122 of SEQ ID NO:1. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to one 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 one 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. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to one or more amino acid residues selected from the group consisting of Y49, Y50, and K52 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian CD33 protein corresponding to an amino acid residue selected from the group consisting of Y49, Y50, and K52 of SEQ ID NO: 1. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to amino acid residues Y49 and K52 of SEQ ID NO: 1, or to amino acid residues on a mammalian CD33 protein corresponding to an amino acid residues Y49 and K52 of SEQ ID NO: 1. In some examples that

may be combined with any of the preceding examples, the anti-CD33 antibody binds to amino acid residues Y49, Y50, and K52 of SEQ ID NO: 1, or to amino acid residues on a mammalian CD33 protein corresponding to an amino acid residues Y49, Y50, and K52 of SEQ ID NO: 1. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody competes with one or more antibodies selected from the group consisting of 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.2, and any combination thereof for binding to CD33. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody 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 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2. In some examples that may be combined with any of the preceding examples, the cellular levels of CD33 are measured on primary cells selected from the group consisting of dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, T cells, and macrophages, or on cell lines, and wherein the cellular levels of CD33 are measured utilizing an *in vitro* cell assay. In some examples that may be combined with any of the preceding examples, the one or more CD33 ligands are selected from the group consisting of CD33 ligands expressed on red blood cells, CD33 ligands expressed on bacterial cells, CD33 ligands expressed on apoptotic cells, CD33 ligands expressed on tumor cells, CD33 ligands expressed on viruses, CD33 ligands expressed on dendritic cells, CD33 ligands expressed on nerve cells, CD33 ligands expressed on glial cells, CD33 ligands expressed on microglial cells, CD33 ligands expressed on astrocytes, CD33 ligands on beta amyloid plaques, CD33 ligands on Tau tangles, CD33 ligands on disease-causing proteins, CD33 ligands on disease-causing peptides, CD33 ligands expressed on macrophages, CD33 ligands expressed on natural killer cells, CD33 ligands expressed on T cells, CD33 ligands expressed on T helper cells, CD33 ligands expressed on cytotoxic T cells, CD33 ligands expressed on B cells, CD33 ligands expressed on tumor-imbedded immunosuppressor dendritic cells, CD33 ligands expressed on tumor-imbedded immunosuppressor macrophages, CD33 ligands expressed on non-tumorigenic myeloid-derived suppressor cells, CD33 ligands expressed on regulatory T cells, secreted mucins, sialic acid, sialic acid-containing glycolipids, sialic acid-containing glycoproteins, alpha-2,6-linked sialic acid-containing glycolipids, alpha-2,6-linked sialic acid-containing glycoproteins, alpha-2,3-linked sialic acid-containing glycolipids, alpha-2,3-linked sialic acid-containing glycoproteins, alpha-1-acid glycoprotein (AGP), CD24 protein, and gangliosides.

[0025] In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain, the heavy chain variable domain, or both comprise at least

one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2. In some examples that may be combined with any of the preceding examples: (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:12, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:15, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:18, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:22, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:26; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:13, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:16, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:19, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:23, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:27; (c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:69, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:72, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:19, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:23, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:27; (d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:11, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:14, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:17, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:20, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:24, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:28; (e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:68, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:71, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:74, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:75, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:77, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:28; (f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:67, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:70, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:73, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:25, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:67, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:70, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:73, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:76, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (h) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2

comprises the amino acid sequence of SEQ ID NO:25, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (i) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:76, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:184, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:185, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:17, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:75, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:186, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:187; (k) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:13, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:72, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:231, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:23, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:27; or (l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:228, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:229, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:230, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:232, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:233, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29. In some examples that may be combined with any of the preceding examples, 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. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 is the HVR-H3 of an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 comprises 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. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 30-48, 112-153, 192-202, and 241-243; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 49-66, 154-183, 203-213, and 244-246. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody comprises a light chain variable domain of an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2; and/or a heavy chain variable domain of an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2.

[0026] Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody binds to one 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. In some examples, the anti-CD33 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 39-51 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51 of SEQ ID NO:1; ii. amino acid residues 48-54 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 48-54 of SEQ ID

NO:1; iii. amino acid residues 88-98 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 88-98 of SEQ ID NO:1; iv. amino acid residues 110-120 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 110-120 of SEQ ID NO:1; v. amino acid residues 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 112-122 of SEQ ID NO:1; vi. amino acid residues 39-51, 88-98, and 110-120 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, and 110-120 of SEQ ID NO:1; vii. amino acid residues 39-51, 88-98, and 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, and 112-122 of SEQ ID NO:1; and viii. amino acid residues 39-51, 88-98, 110-120, and 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, 110-120, and 112-122 of SEQ ID NO:1.

[0027] Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody binds to one or more amino acids within amino acid residues 19-228 of SEQ ID NO:1; or within amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 19-228 of SEQ ID NO:1. In some examples, the anti-CD33 antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 39-51 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51 of SEQ ID NO:1; ii. amino acid residues 48-54 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 48-54 of SEQ ID NO:1; iii. amino acid residues 88-98 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 88-98 of SEQ ID NO:1; iv. amino acid residues 110-120 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 110-120 of SEQ ID NO:1; v. amino acid residues 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 112-122 of SEQ ID NO:1; vi. amino acid residues 39-51, 88-98, and 110-120 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, and 110-120 of SEQ ID NO:1; vii. amino acid residues 39-51, 88-98, and 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, and 112-122 of SEQ ID NO:1; and viii. amino acid residues 39-51, 88-98, 110-120, and 112-122 of SEQ ID NO:1, or amino acid residues on a mammalian CD33 protein corresponding to amino acid residues 39-51, 88-98, 110-120, and 112-122 of SEQ ID NO:1.

[0028] Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody binds to one 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 one 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. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to one or more amino acid residues selected from the group consisting of Y49, Y50, and K52 of SEQ ID NO: 1, or one or more amino acid residues on a mammalian CD33 protein corresponding to an amino acid residue selected from the group consisting of Y49, Y50, and K52 of SEQ ID NO: 1. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to amino acid residues Y49 and K52 of SEQ ID NO: 1, or to amino acid residues on a mammalian CD33 protein corresponding to an amino acid residues Y49 and K52 of SEQ ID NO: 1. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds to amino acid residues Y49, Y50, and K52 of SEQ ID NO: 1, or to amino acid residues on a mammalian CD33 protein corresponding to an amino acid residues Y49, Y50, and K52 of SEQ ID NO: 1.

[0029] Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain, the light chain variable domain, or both comprises at least one, two, three, four, five, or six HVRs selected from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3 of an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.21A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.2, and any combination thereof. In some examples: (a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:9, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:12, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:15, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:18, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:22, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:26; (b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:13, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:16, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:19, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:23, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:27; (c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:69, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:72, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:19, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:23, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:27; (d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:11, the HVR-L2 comprises the amino acid

sequence of SEQ ID NO:14, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:17, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:20, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:24, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:28; (e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:68, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:71, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:74, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:75, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:77, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:28; (f) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:67, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:70, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:73, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:25, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (g) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:67, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:70, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:73, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:76, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (h) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:25, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (i) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:21, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:76, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29; (j) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:184, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:185, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:17, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:75, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:186, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:187; (k) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:10, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:13, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:72, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:231, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:23, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:27; or (l) the HVR-L1 comprises the amino acid sequence of SEQ ID NO:228, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:229, the HVR-L3 comprises the amino acid sequence of SEQ ID NO:230, the HVR-H1 comprises the amino acid sequence of SEQ ID NO:232, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:233, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO:29. In some examples that may be combined with any of the preceding examples, 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: 226-29, and 187.

[0030] Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 30-48, 112-153, 192-202, and 241-243; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 49-66, 154-183, 203-213, and 244-246. Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody comprises a light chain variable domain of 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; and/or a heavy chain variable domain of 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. Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein the anti-CD33 antibody competes with one or more antibodies selected from the group consisting of 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.2. 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.2 and any combination thereof for binding to CD33. Other parts of the present disclosure relate to an isolated (e.g., monoclonal) 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 6C7.2.1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2.

Other parts of the present disclosure relate to an isolated (e.g., monoclonal) 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; or 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. Other parts of the present disclosure relate to an isolated (e.g., monoclonal) 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 HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 is the HVR-H3 of an antibody selected from the group consisting of: 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2.1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, and 6C7.2. Other parts of the present disclosure relate to an isolated (e.g., monoclonal) anti-CD33 antibody, wherein anti-CD33 antibody comprises a light chain variable domain and a heavy chain variable domain, wherein the light chain variable domain comprises HVR-L1, HVR-L2, HVR-L3, the heavy chain variable domain comprises HVR-H1, HVR-H2, and HVR-H3, and wherein the HVR-H3 comprises 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.

[0030a] In another aspect, the present invention provides 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] In yet another aspect, the present invention provides 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:

(a) the anti-CD33 antibody has a human IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, D265A, D270A, L234A, L235A, G237A, P238D, L328E, E233D, G237D, H268D, P271G, A330R, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, N297Q, P238S, P238A, A327Q, A327G, P329A, K322A, T394D,, and any combination thereof, wherein the numbering of the residues is according to EU numbering, or comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236; (b) the anti-CD33 antibody has a human IgG1 isotype and comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region, optionally wherein the IgG2 isotype CH1 and hinge region comprises the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPKPS NTKVDKTVERKCCVECPCP (SEQ ID NO:214), and optionally wherein the antibody Fc region comprises a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues is according to EU numbering; (c) 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; (d) 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 (e) the anti-CD33 antibody has a hybrid 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 numbering. In some examples that may be combined with any of the preceding examples: (a) the anti-CD33 antibody has a human IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, N297Q, D270A, D265A, L234A, L235A, C226S, C229S, P238S, E233P, L234V, P238A, A327Q, A327G, P329A, K322A, L234F, L235E, P331S, T394D, A330L, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; (b) 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, H268E, V309L, N297A, N297Q, A330S, P331S, C232S, C233S, M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or (c) 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: E233P, F234V, L234A/F234A, L235A, G237A, E318A, S228P, L236E, S241P, L248E, T394D, M252Y, S254T, T256E, N297A, N297Q, and any combination thereof, wherein the numbering of the residues is according to EU numbering. In some examples that may be combined with any of the preceding examples: (a) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of A330L, L234F; L235E, P331S, and any combination thereof, wherein the numbering of the residues is according to EU numbering; (b) the Fc region further comprises one or more additional amino acid substitutions at a position selected from the group consisting of M252Y, S254T, T256E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or (c) the Fc region further comprises a S228P amino acid substitution according to EU numbering. In some examples that may be combined with any of the preceding examples, the CD33 protein is a mammalian protein or a human protein. In some examples that may be combined with any of the preceding examples, the CD33 protein is a wild-type protein. In some examples that may be combined with any of the preceding examples, the CD33 protein is a naturally occurring variant. In some examples that may be combined with any of the preceding examples, the CD33 protein is expressed on one or more cells selected from the group consisting of human dendritic cells, human macrophages, human monocytes, human osteoclasts, human neutrophils, human T cells, human T helper cell, human cytotoxic T cells, human granulocytes, and human microglia. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds specifically to a mammalian CD33 protein, human CD33 protein, or both. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds specifically to human CD33, mouse CD33, or both. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds CD33 in a pH

dependent manner. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody binds CD33 at a pH that ranges from 5.5 to 8.0. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody dissociates from CD33 at a pH of less than 5.0. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human CD33 or a mammalian CD33 protein. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human CD33, a naturally occurring variant of human CD33, and a disease variant of human CD33. In some examples that may be combined with any of the preceding examples, the antibody fragment is cross-linked to a second antibody fragment that binds to one or more human proteins selected from the group consisting of human CD33, a naturally occurring variant of human CD33, and a disease variant of human CD33. In some examples that may be combined with any of the preceding examples, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is a murine antibody. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is a bispecific antibody recognizing a first antigen and a second antigen. In some examples that may be combined with any of the preceding examples, the first antigen is CD33 and the second antigen is: (a) an antigen facilitating transport across the blood-brain-barrier; (b) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopep peptide, and ANG1005; (c) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins and disease-causing nucleic acids, wherein the disease-causing peptides or 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 the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA; (d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, and phosphatidylserine; and (e) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is a conjugated antibody. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is conjugated to a detectable marker, a toxin, or a therapeutic agent. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is conjugated to a toxin selected from the group consisting of ricin, ricin A-chain, doxorubicin, daunorubicin, a maytansinoid, taxol, ethidium bromide, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, *Saponaria officinalis* inhibitor, glucocorticoid, auristatin, auromycin, yttrium, bismuth, combrestatin, duocarmycins, dolastatin, cc1065, and a cisplatin. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is used in combination with one or more antibodies that specifically bind a disease-causing agent selected from the group consisting of disease-causing peptides, disease-causing proteins, 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), 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 any combination thereof; or with one or more antibodies that bind an immunomodulatory protein selected from the group consisting of: CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, TREM1, TREM2, Siglec-5, Siglec-7, Siglec-9, Siglec-11, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4)

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] In yet another aspect, the present invention provides an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-CD33 antibody as described herein.

[0032b] In yet another aspect, the present invention provides a vector comprising the nucleic acid as described herein.

[0032c] In yet another aspect, the present invention provides an isolated host cell comprising the vector as described herein.

[0032d] In yet another aspect, the present invention provides 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] In yet another aspect, the present invention provides an isolated anti-CD33 antibody produced by the method as described herein.

[0032f] In yet another aspect, the present invention provides a pharmaceutical composition comprising the anti-CD33 antibody as described herein, 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,

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, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myeloid sclerosis, myeloid-derived tumors, tumors that express CD33, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both. Other parts of the present disclosure relate to an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both for use in 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, 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, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer,

renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express CD33, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, *Cruzi* infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza. Other parts of the present disclosure relate to use of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both in the manufacture of a medicament for 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, 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, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express CD33, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, *Cruzi* infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza. In some examples, the agent is selected from the group consisting of an antibody, a soluble CD33 receptor, a CD33-Fc fusion protein, a CD33 immunoadhesin, a soluble Siglec receptor that binds one or more CD33 ligands, a Siglec-Fc fusion protein, a Siglec

immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some examples, the agent is an isolated anti-CD33 antibody. In some examples, the anti-CD33 antibody is the anti-CD33 antibody of any of the preceding examples. In some examples that may be combined with any of the preceding examples, the disease, disorder, or injury is cancer. In some examples that may be combined with any of the preceding examples, the agent inhibits one or more CD33 activities selected from the group consisting of: (a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, , non-tumorigenic CD14⁺ myeloid cells, and regulatory T cells; (b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, and regulatory T cells into tumors; (c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells and/or non-tumorigenic CD14⁺ myeloid cells in a tumor, in peripheral blood, or other lymphoid organ; (d) enhancing tumor-promoting activity of non-tumorigenic myeloid-derived suppressor cells and/or non-tumorigenic CD14⁺ myeloid cells; (e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (f) increasing tumor infiltration of tumor-promoting FoxP3⁺ regulatory T lymphocytes; (g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (i) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (j) decreasing tumor killing potential of NK cells; (k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (l) increasing tumor volume; (m) increasing tumor growth rate; (n) increasing metastasis; (o) increasing rate of tumor recurrence; (p) increasing expression of one or more PD-1 ligands; (q) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; (r) inhibition of PLCγ/PKC/calcium mobilization; (s) inhibition of PI3K/Akt, Ras/MAPK signaling; and (t) decreasing 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. In some examples that may

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 the anti-CD33 antibody of any one of claims 1-21 in the manufacture of a medicament for 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, taupathy disease, infections, and cancer, wherein the antibody is to be administered to an individual in need thereof

[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, taupathy disease,

infections, and cancer, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both. Other parts of the present disclosure relate to an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both for use in 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, taupathy disease, infections, and cancer. Other parts of the present disclosure relate to use of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both in the manufacture of a medicament for 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, taupathy disease, infections, and cancer. In some examples, the agent is selected from the group consisting of an antibody, a soluble CD33 receptor, a CD33-Fc fusion protein, a CD33 immunoadhesin, a soluble Siglec receptor that binds one or more CD33 ligands, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some examples, the agent is an isolated anti-CD33 antibody. In some examples, the anti-CD33 antibody is the anti-CD33 antibody of any of the preceding examples. In some examples that may be combined with any of the preceding examples, the disease, disorder, or injury is cancer. In some examples that may be combined with any of the preceding examples, the cancer expresses CD33. In some examples that may be combined with any of the preceding examples, the cancer is selected from the group consisting of bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and multiple myeloma. In some examples that may be combined with any of the preceding examples, the agent inhibits one or more CD33 activities selected from the group consisting of: (a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, , non-tumorigenic CD14⁺ myeloid cells, and regulatory T cells; (b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, and regulatory T cells into tumors; (c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells and/or non-tumorigenic CD14⁺ myeloid cells in a

tumor, in peripheral blood, or other lymphoid organ; (d) enhancing tumor-promoting activity of non-tumorigenic myeloid-derived suppressor cells and/or non-tumorigenic CD14⁺ myeloid cells; (e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (f) increasing tumor infiltration of tumor-promoting FoxP3⁺ regulatory T lymphocytes; (g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (i) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (j) decreasing tumor killing potential of NK cells; (k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (l) increasing tumor volume; (m) increasing tumor growth rate; (n) increasing metastasis; (o) increasing rate of tumor recurrence; (p) increasing expression of one or more PD-1 ligands; (q) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more cancer vaccines; (r) inhibition of PLCγ/PKC/calcium mobilization; (s) inhibition of PI3K/Akt, Ras/MAPK signaling; and (t) decreasing 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. In some examples that may 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. In some examples that may be combined with any of the preceding examples, the disease, disorder, or injury is an infection. In some examples that may be combined with any of the preceding examples, the infection is selected from the group consisting of CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza.

[0035] Other parts of the present disclosure relate to a method of preventing, reducing risk, or treating cancer, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both. Other parts of the present disclosure relate to an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both for use in preventing, reducing risk, or treating cancer in an individual in need thereof. Other parts of the present disclosure relate to use of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both in the manufacture of a medicament for preventing, reducing risk, or treating cancer in an individual in need thereof. In some examples, the agent is selected from the group consisting of an antibody, a soluble CD33 receptor, a CD33-Fc fusion protein, a CD33 immunoadhesin, a soluble Siglec receptor that binds one

or more CD33 ligands, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some examples, the agent is an isolated anti-CD33 antibody. In some examples, the anti-CD33 antibody is the anti-CD33 antibody of any of the preceding examples. In some examples, the cancer is selected from the group consisting of bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and multiple myeloma. In some examples, the cancer is a CD33-expressing cancer. In some examples, the cancer comprises tumors that express CD33. In some examples that may be combined with any of the preceding examples, the agent inhibits one or more CD33 activities selected from the group consisting of: (a) promoting proliferation, maturation, migration, differentiation, and/or functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, , non-tumorigenic CD14⁺ myeloid cells, and regulatory T cells; (b) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, immunosuppressor neutrophils, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, and regulatory T cells into tumors; (c) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells and/or non-tumorigenic CD14⁺ myeloid cells in a tumor, in peripheral blood, or other lymphoid organ; (d) enhancing tumor-promoting activity of non-tumorigenic myeloid-derived suppressor cells and/or non-tumorigenic CD14⁺ myeloid cells; (e) increasing expression of tumor-promoting cytokines in a tumor or in peripheral blood, optionally wherein the tumor-promoting cytokines are TGF-beta or IL-10; (f) increasing tumor infiltration of tumor-promoting FoxP3⁺ regulatory T lymphocytes; (g) decreasing activation of tumor-specific T lymphocytes with tumor killing potential; (h) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential; (i) decreasing infiltration of tumor-specific NK cells with tumor killing potential; (j) decreasing tumor killing potential of NK cells; (k) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response; (l) increasing tumor volume; (m) increasing tumor growth rate; (n) increasing metastasis; (o) increasing rate of tumor recurrence; (p) increasing expression of one or more PD-1 ligands; (q) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any

combination thereof, or of one or more cancer vaccines; (r) inhibition of PLC γ /PKC/calcium mobilization; (s) inhibition of PI3K/Akt, Ras/MAPK signaling; and (t) decreasing 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. In some examples that may 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 (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.

[0036] Other parts of the present disclosure relate to a method of inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both. Other parts of the present disclosure relate to an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both for use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. Other parts of the present disclosure relate to use of an agent that decreases cellular levels of CD33, inhibits interaction between CD33 and one or more CD33 ligands, or both in the manufacture of a medicament for inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. In some examples, the agent is selected from the group consisting of an antibody, a soluble CD33 receptor, a CD33-Fc fusion protein, a CD33 immunoadhesin, a soluble Siglec receptor that binds one or more CD33 ligands, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some examples, the agent is an isolated anti-CD33 antibody. In some examples, the anti-CD33 antibody is the anti-CD33 antibody of any of the preceding examples. In some examples, the one or more immune cells are selected from the group consisting of dendritic cells, macrophages, microglia, neutrophils, T cells, T helper cells, cytotoxic T cells, and any combination thereof.

[0037] Other parts of the present disclosure relate to a method of decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, non-tumorigenic myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an agent that binds or interacts with CD33. Other parts of the present disclosure relate to an agent that binds or interacts with CD33 for use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, non-tumorigenic myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof. Other parts of the present disclosure relate to use of

an agent that binds or interacts with CD33 in the manufacture of a medicament for decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, non-tumorigenic myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cells in an individual in need thereof. In some examples, the agent is selected from the group consisting of an antibody, an antagonist antibody, an inert antibody, an agonist antibody, a CD33 ligand, a CD33 ligand agonist fragment, a CD33 immunoadhesin, a CD33 ligand mimetic, a soluble CD33 receptor, a CD33-Fc fusion protein, a soluble Siglec receptor that binds one or more CD33 ligands, a Siglec-Fc fusion protein that binds one or more CD33 ligands, and a small molecule compound. In some examples, the agent is an isolated anti-CD33 antibody or anti-CD33 antibody conjugate. In some examples, the anti-CD33 antibody conjugate comprises an anti-CD33 antibody conjugated to a detectable marker, a toxin, or a therapeutic agent. In some examples, the anti-CD33 antibody conjugate comprises an anti-CD33 antibody conjugated to a toxin selected from the group consisting of ricin, ricin A-chain, doxorubicin, daunorubicin, a maytansinoid, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, *Saponaria officinalis* inhibitor, glucocorticoid, auristatin, auromycin, yttrium, bismuth, combrestatin, duocarmycins, dolastatin, cc1065, and a cisplatin. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is an anti-CD33 antibody of any of the preceding examples that does not significantly decrease cell surface levels of CD33 and/or does not inhibit interaction between CD33 and one or more CD33 ligands.

[0038] Other parts of the present disclosure relate to a method of decreasing cellular levels of CD33, inhibiting interaction between CD33 and one or more CD33 ligands, or both on one or more cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated anti-CD33 antibody. Other parts of the present disclosure relate to an isolated anti-CD33 antibody for use in decreasing cellular levels of CD33, inhibiting interaction between CD33 and one or more CD33 ligands, or both on one or more cells in an individual in need thereof. Other parts of the present disclosure relate to use of an isolated anti-CD33 antibody in the manufacture of a medicament for decreasing cellular levels of CD33, inhibiting interaction between CD33 and one or more CD33 ligands, or both on one or more cells in an individual in need thereof. In some examples, the one or more cells are selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, T cells, and macrophages; and/or cell lines. In some examples, the anti-CD33 antibody decreases cellular levels of CD33 *in vivo*. In some

examples that may be combined with any of the preceding examples, the anti-CD33 antibody decreases cellular levels of CD33 with an EC_{50} that ranges from 65 pM to 20 pM. In some examples that may be combined with any of the preceding 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. In some examples that may be combined with any of the preceding 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 that may be combined with any of the preceding examples, the anti-CD33 antibody decreases cellular levels of CD33 *in vivo* with an EC_{50} that ranges from about 8.0 mg/kg to about 2.0 mg/kg. 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 300 pM to 10 pM, wherein the K_D is determined at a temperature of approximately 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 is less than 300 pM, wherein the K_D is determined at a temperature of approximately 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 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. In some examples that may be combined with any of the preceding 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 anti-CD33 antibody is selected from the group consisting of an antagonist anti-CD33 antibody, an inert anti-CD33 antibody, and an agonist anti-CD33 antibody. In some examples, the anti-CD33 antibody is the anti-CD33 antibody of any of the preceding examples.

[0039] In some examples that may be combined with any of the preceding examples, the individual comprises a variant of CD33. In some examples that may be combined with any of the preceding examples, the variant comprises one or more polymorphisms selected from the group consisting of: (a) SNP *rs3865444*^{AC}; (b) SNP *rs3865444*^{CC}; (c) SNP *rs35112940*^{GG, AA, AG}; (d) SNP *rs12459419*^{CC, CT or TT}; and any combinations thereof. In some examples that may be combined with any of the preceding examples, the method further comprising administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or

one or more standard or investigational anti-cancer therapies. In some examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the anti-CD33 antibody. In some examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from the group consisting of an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti-B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-TNF α antibody, an anti-Siglec-5 antibody, an anti-Siglec-7 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an antagonistic anti-TREM2 antibody, and any combination thereof. In some examples that may be combined with any of the preceding examples, the one or more standard or investigational anti-cancer therapies are selected from the group consisting of radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy. In some examples that may be combined with any of the preceding examples, the method further comprising administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the anti-CD33 antibody. In some examples that may be combined with any of the preceding examples, the at least one antibody that specifically binds to an inhibitory cytokine is selected from the group consisting of an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof. In some examples that may be combined with any of the preceding examples, the method further comprising administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some examples that may be combined with any of the preceding examples, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the anti-CD33 antibody. In some examples that may be combined with any of the preceding examples, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from the group consisting of an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and

any combination thereof. In some examples that may be combined with any of the preceding examples, the method further comprising administering to the individual at least one stimulatory cytokine. In some examples that may be combined with any of the preceding examples, the at least one stimulatory cytokine is administered in combination with the anti-CD33 antibody. In some examples that may be combined with any of the preceding examples, the at least one stimulatory cytokine is selected from the group consisting of IFN-a4, IFN-b, IL-1 β , TNF- α , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, CRP, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

[0040] Other parts of the present disclosure relate to a method of selecting a subject in need thereof for treatment with an agent that binds or interacts with CD33, the method comprising: a. obtaining a sample from the subject; b. detecting the CD33 alleles present in the subject; and c. selecting the subject for treatment with the agent that binds or interacts with CD33 is the subject has one or more CD33 alleles, wherein the one or more CD33 alleles are selected from the group consisting of *rs3865444^{AC}*, and *rs3865444^{CC}*. Other parts of the present disclosure relate to a method of assessing responsiveness of a subject in need thereof to an agent that binds or interacts with CD33, the method comprising: a. measuring the expression levels of CD45⁺ and CD14⁺ on non-tumorigenic myeloid cells in a blood sample obtained from the subject prior to administering to the subject an anti-CD33 antibody; b. administering to the subject a therapeutically effective amount of the agent; and c. measuring the expression levels of CD45⁺ and CD14⁺ on non-tumorigenic myeloid cells in a blood sample obtained from the subject after administration of the anti-CD33 antibody, wherein a reduction in the levels of CD45⁺ CD14⁺ on non-tumorigenic myeloid cells after administration of the anti-CD33 antibody indicates the subject is responsive to the agent. In some examples, the method of assessing responsiveness further comprises administering one or more additional therapeutically effective amounts of the agent. In some examples that may be combined with any of the preceding examples, the agent is selected from the group consisting of an antibody, a soluble CD33 receptor, a CD33-Fc fusion protein, a CD33 immunoadhesin, a soluble Siglec receptor, a Siglec-Fc fusion protein, a Siglec immunoadhesin, an antisense molecule, an siRNA, a small molecule inhibitor, a protein, and a peptide. In some examples that may be combined with any of the preceding examples, the agent is an isolated anti-CD33 antibody or anti-CD33 antibody conjugate. In some examples that may be combined with any of the preceding examples, the anti-CD33 antibody is the anti-CD33 antibody of any of the preceding examples.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] **FIG. 1** shows the structure of CD33, and a scheme depicting the domain structure of CD33 as well as individual amino acids that have been implicated in phosphorylation or

CLAIMS

What is claimed is:

1. 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.
2. The anti-CD33 antibody of claim 1, wherein the anti-CD33 antibody decreases cell surface levels of CD33, decreases intracellular levels of CD33, decreases total levels of CD33, or any combination thereof.
3. The anti-CD33 antibody of any one of claims 1-2, wherein
 - (a) the anti-CD33 antibody decreases cellular levels of CD33 without inhibiting the interaction between CD33 and one or more CD33 ligands; or
 - (b) the anti-CD33 antibody decreases cellular levels of CD33 and inhibits the interaction between CD33 and one or more CD33 ligands.
4. The anti-CD33 antibody of claim 1, wherein the anti-CD33 antibody inhibits the interaction between CD33 and one or more CD33 ligands without decreasing cellular levels of CD33.
5. The anti-CD33 antibody of any one of claims 1-4, wherein the anti-CD33 antibody inhibits cell surface clustering of CD33.

6. The anti-CD33 antibody of any one of claims 1-5, 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-4, IL-10, IL-13, IL-35, IL-16, TGF-beta, IL-1Ra, G-CSF, and soluble receptors for TNF, IFN-beta1a, IFN-beta1b, 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, osteoclasts, T cells, T helper cells, cytotoxic T cells, 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 IFN-a4, IFN-b, IL-1 β , TNF- α , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN-gamma, OSM, CNTF, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, IL-33, CRP, IL-33, MCP-1, and MIP-1-beta;
- (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, osteoclasts, T cells, T helper cells, cytotoxic T cells, 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, osteoclasts, T cells, T helper cells, cytotoxic T cells, 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, osteoclasts, T cells, T helper cells, cytotoxic T cells, 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, disease-causing nucleic acids, or tumor cells; 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 the tumor cells are from a cancer selected from the group consisting of bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, or thyroid cancer;
- (k) binding to CD33 ligand on tumor cells;
- (l) binding to CD33 ligand on cells selected from the group consisting of neutrophils, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, and macrophages;
- (m) inhibition of tumor cell killing by one or more of microglia, macrophages, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells;

- (n) inhibiting anti-tumor cell proliferation activity of one or more of microglia, macrophages, dendritic cells, bone marrow-derived dendritic cells, neutrophils, T cells, T helper cells, or cytotoxic T cells;
- (o) promoting functionality of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, non-tumorigenic myeloid-derived suppressor cells, tumor-associated macrophages, immunosuppressor neutrophils, and regulatory T cells;
- (p) enhancing infiltration of one or more of immunosuppressor dendritic cells, immunosuppressor macrophages, non-tumorigenic myeloid derived suppressor cells, tumor-associated macrophages, immunosuppressor neutrophils, non-tumorigenic CD45⁺CD14⁺ myeloid cells, and regulatory T cells into tumors;
- (q) increasing number of tumor-promoting myeloid/granulocytic immune-suppressive cells and/or non-tumorigenic CD45⁺CD14⁺ myeloid cells in a tumor, in peripheral blood, or other lymphoid organ;
- (r) enhancing tumor-promoting activity of non-tumorigenic myeloid-derived suppressor cells (MDSC) and/or non-tumorigenic CD45⁺CD14⁺ myeloid cells;
- (s) enhancing survival of non-tumorigenic myeloid-derived suppressor cells (MDSC) and/or non-tumorigenic CD45⁺CD14⁺ myeloid cells;
- (t) decreasing activation of tumor-specific T lymphocytes with tumor killing potential;
- (u) decreasing activation of CD45⁺CD3⁺ T lymphocytes with tumor killing potential;
- (v) decreasing infiltration of tumor-specific NK cells with tumor killing potential;
- (w) decreasing infiltration of tumor-specific B lymphocytes with potential to enhance immune response;
- (x) decreasing infiltration of tumor-specific T lymphocytes with tumor killing potential;
- (y) decreasing infiltration of CD45⁺CD3⁺ T lymphocytes;
- (z) increasing tumor volume;
- (aa) increasing tumor growth rate; and
- (bb) decreasing efficacy of one or more immune-therapies that modulate anti-tumor T cell responses, optionally wherein the one or more immune-therapies are immune-therapies that target one or more proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG, DR-5, TREM1, TREM2, CSF-1 receptor, and any combination thereof, or of one or more chemotherapy agents and/or cancer vaccines.

7. The anti-CD33 antibody of any one of claims 1-6, wherein the anti-CD33 antibody 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 (Cytosan[®]), carboplatin (Paraplatin[®]), and any combination thereof;

- (p) increasing proliferation of T cells in the presence of non-tumorigenic myeloid-derived suppressor cells (MDSC);
- (q) inhibiting differentiation, survival, and/or one or more functions of non-tumorigenic myeloid-derived suppressor cells (MDSC); and
- (r) killing CD33-expressing immunosuppressor non-tumorigenic myeloid cells and/or non-tumorigenic CD14-expressing cells in solid tumors and associated blood vessels when conjugated to a chemical or radioactive toxin.

8. The anti-CD33 antibody of any one of claims 1-7, wherein the anti-CD33 antibody binds to one 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.

9. The anti-CD33 antibody of any one of claims 1-7, wherein the anti-CD33 antibody binds to one 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 one 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.

10. The anti-CD33 antibody of any one of claims 1-9, wherein the anti-CD33 antibody competes with one or more antibodies selected from the group consisting of 1A8, 2B4, 2E12, 2E12.1, 2F5, 2F5.1, 3A12a, 3A12b, 6A3a, 6A3b, 6C7a, 6C7b, 6C7.2, and any combination thereof for binding to CD33.

11. The anti-CD33 antibody of any one of claims 1-10, 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.

12. The anti-CD33 antibody of any one of claims 1-10, wherein the anti-CD33 antibody comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 30-48, 112-153, 192-202, and 241-243; and/or a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 49-66, 154-183, 203-213, and 244-246.

13. 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.

14. 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.

15. The anti-CD33 antibody of any one of claims 1-14, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

16. The anti-CD33 antibody of claim 15, wherein the anti-CD33 antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.

17. The anti-CD33 antibody of claim 16, wherein the antibody binds an inhibitory Fc receptor, optionally, wherein the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB).

18. The anti-CD33 antibody of claim 16 or claim 17, wherein:

- (a) the anti-CD33 antibody has a human IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, D265A, D270A, L234A, L235A, G237A, P238D, L328E, E233D, G237D, H268D, P271G, A330R, C226S, C229S, E233P, L234V, L234F,

- L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, N297Q, P238S, P238A, A327Q, A327G, P329A, K322A, T394D, and any combination thereof, wherein the numbering of the residues is according to EU numbering, or comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236;
- (b) the anti-CD33 antibody has a human IgG1 isotype and comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region, optionally wherein the IgG2 isotype CH1 and hinge region comprises the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVERKCCVECP (SEQ ID NO:214), and optionally wherein the antibody Fc region comprises a S267E amino acid substitution, or a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues is according to EU numbering;
- (c) 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;
- (d) 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
- (e) the anti-CD33 antibody has a hybrid 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.

19. The anti-CD33 antibody of any one of claims 1-18, 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 osteoclasts, human neutrophils, human T cells, human T helper cell, human cytotoxic T cells, human granulocytes, and human microglia.

20. The anti-CD33 antibody of any one of claims 1-19, wherein the antibody is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.

21. The anti-CD33 antibody of any one of claims 1-20, wherein the anti-CD33 antibody is a murine antibody, a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.
22. An isolated nucleic acid comprising a nucleic acid sequence encoding the anti-CD33 antibody of any one of the preceding claims.
23. A vector comprising the nucleic acid of claim 22.
24. An isolated host cell comprising the vector of claim 23.
25. A method of producing an anti-CD33 antibody, comprising culturing the host cell of claim 24 so that the anti-CD33 antibody is produced.
26. The method of claim 25, further comprising recovering the anti-CD33 antibody produced by the host cell.
27. An isolated anti-CD33 antibody produced by the method of claim 25 or claim 26.
28. A pharmaceutical composition comprising the anti-CD33 antibody of any one of claims 1-21, and a pharmaceutically acceptable carrier.
29. Use of a therapeutically effective amount of the anti-CD33 antibody of any one of claims 1-21 in the manufacture of a medicament for 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, tauopathy disease, infections, and cancer, wherein the antibody is to be administered to an individual in need thereof.
30. The use of claim 29, wherein the disease, disorder, or injury is cancer, wherein the cancer is selected from the group consisting of bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and multiple myeloma.