

Likewise, patients homozygous for the minor variant allele (TT) of rs12459419, which is associated with over 46% lower expression of the full-length CD33, are more likely to have favorable disease outcome than carriers of the variants CC and CT (52% vs. 31%) and have significantly lower diagnostic blast CD33 expression than other genotypes. This is the case even in patients undergoing treatment with anti-CD33 antibody and a toxic calicheamicin-gamma derivative (Mortland et al., (2013) Clin Cancer Res; 1–8). Carriers of the 2459419^{TT} allele, as well as carriers of the rs12459419^{CT} allele, which show over 25% reduction in expression of full-length CD33, also display reduced Alzheimer's disease risk (Malik M. et al. (2015) Human Molecular Genetics, 1–14). This suggests that reduced expression or functionality of CD33 may be beneficial in Alzheimer's disease and cancer.

[0006] Antibodies to CD33 have been described in, for example, US7,342,110, US7,557,189, US8,119,787, US8,337,855, US8,124, 069, US5,730, 982, WO2012/074097, WO2004/043344, WO1993/020848, WO2012/045752, WO2007/014743, WO2003/093298, WO2011/036183, WO1991/009058, WO2008/058021, WO2011/038301, WO2016/201389, WO2016/201388, Hoyer et al (2008) Am J Clin Pathol, 129:316-323, Rollins-Ravel and Roth (2012) Histopathology 60:933-942, Perez-Olivaria et al (2011) Glycobiol 21:757-770, Ferlasso et al (2000) Eur J Immunol 30:827-833, Vitale et al (2001) Proc Natl Acad Sci USA 98:5764-5769, Jandus et al (2011) Biochem Pharmacol 82:323-332, O'Reilly and Paulson (2009) Trends Pharmacol Sci 30:240-248, Jurcic (2012) Curr Hematol Malig Rep 7:65-73, and Ricart (2011) Clin Cancer Res 17:6417-6427.

[0007] Accordingly, there is a need for therapeutic anti-CD33 antibodies to treat diseases, disorders, and conditions associated with undesired CD33 activity.

[0008] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0009] The present disclosure is generally directed to compositions that include antibodies, e.g., monoclonal, chimeric, humanized antibodies, antibody fragments, etc., that specifically bind human CD33, and to methods of using such compositions.

[0010] Certain examples of the present disclosure are based, at least in part, on the identification of anti-CD33 antibodies with improved and/or enhanced functional characteristics. In some examples, anti-CD33 antibodies of the present disclosure comprise one or more improved and/or enhanced functional characteristics relative to a reference antibody (e.g., an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4). In some examples, anti-CD33 antibodies of the present disclosure have an affinity for CD33 (e.g., human CD33) that is higher than that of a reference anti-CD33 antibody (e.g., an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4). In some examples, anti-CD33 antibodies of the present disclosure bind to human cells, such as human

primary dendritic cells, with a half-maximal effective concentration (EC_{50}) that is lower than that of a reference antibody (*e.g.*, an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4). In some examples, anti-CD33 antibodies of the present disclosure decrease cellular levels (*e.g.*, decrease or reduce cell surface levels) of CD33 with a half-maximal effective concentration (EC_{50}) that is lower than that of a reference antibody (*e.g.*, an anti-CD33 antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO: 3 and a light chain variable region comprising the sequence of SEQ ID NO: 4).

[0011] Accordingly, in one example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs:8-30, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:33, an HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs:39-40, an HVR-L1 comprising the amino acid sequence of SEQ ID NO:47, an HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs:53-55, and an HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 58-62.

[0011a] In one aspect, the present disclosure refers to an isolated antibody that binds to CD33, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2

[0012] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54.

[0013] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54.

[0014] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27,

6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54; and the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54.

[0015] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises the heavy chain variable region of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54; and the antibody comprises the light chain variable region of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54.

[0016] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region comprising an amino acid sequence selected from SEQ ID NOs:68-93; and/or a light chain variable region comprising an amino acid sequence selected from SEQ ID NOs:97-103.

[0017] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises the heavy chain variable region of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54; and the antibody comprises the light chain variable region of antibody 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, or 6C7H54.

[0018] In another aspect, the present disclosure relates to an isolated antibody that binds to CD33, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:33, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 39; and wherein the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:47, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 53, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 61.

[0019] In another aspect, the present disclosure relates to an isolated antibody that binds to CD33, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102.

[0020] In another aspect, the present disclosure relates to an isolated antibody that binds to CD33, wherein the antibody comprises:

(a) a heavy chain comprising the amino acid sequence of SEQ ID. NO: 120 and a light chain comprising the amino acid sequence of SEQ ID NO: 122; or

(b) a heavy chain comprising the amino acid sequence of SEQ ID. NO: 121 and a light chain comprising the amino acid sequence of SEQ ID NO: 122.

[0020a] In another aspect, the present disclosure refers to a monoclonal antibody that binds to human CD33, wherein the antibody comprises

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 99;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 70, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102.

[0021] In some examples that may be combined with any of the preceding examples, the heavy chain variable region comprises one, two, three, or four framework regions selected from VH FR1, VH FR2, VH FR3, and VH FR4, wherein: VH FR1 comprises a sequence selected from the group consisting of SEQ ID NOs:5-6; VH FR2 comprises a sequence selected from the group consisting of SEQ ID NOs:31-32; VH FR3 comprises a sequence selected from the group consisting of SEQ ID NOs:34-36; and VH FR4 comprises the sequence of SEQ ID NO:41; and the light chain variable region comprises one, two, three, or four framework regions selected from VL FR1, VL FR2, VL FR3, and VL FR4, wherein: VL FR1 comprises a sequence selected from the group consisting of SEQ ID NOs:42-46; VL FR2 comprises a sequence selected from the group consisting of SEQ ID NOs:48-51; VL FR3 comprises a sequence selected from the group consisting of SEQ ID NOs:56-57; and VL FR4 comprises a sequence selected from the group consisting of SEQ ID NOs:63-64.

[0022] 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, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In some examples, the antibody has an IgG4 isotype, and wherein the antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering. In some examples, the antibody comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: C127S, L234A, L234F, L235A,

L235E, S267E, K322A, L328F, A330S, P331S, E345R, E430G, S440Y, and any combination thereof, wherein the numbering of the residues is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at position E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions L234A, L235A, and P331A, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions L234A, L235A, P331A, and E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions K322A and E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions P331S and E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions A330S, P331S, and E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions K322A, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions K322A, P331S, and E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at position E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions A330S, P331S, and E430G, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at positions S267E and L328F, wherein the numbering of the residue position is according to EU numbering; the Fc region comprises an amino acid substitution at position C127S, wherein the numbering of the residue position is according to EU numbering; or the Fc region comprises an amino acid substitution at positions E345R, E430G, and S440Y, wherein the numbering of the residue position is according to EU numbering.

[0023] 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, the CD33 protein is a wildtype protein. In some 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.

[0024] In some examples that may be combined with any of the preceding examples, the antibody binds specifically to a human CD33 protein. In some examples, the antibody binds to a human CD33 protein and does not cross-react with a CD33 ortholog or homolog from another species. In some examples that may be combined with any of the preceding examples, the 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 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, 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, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.

[0025] In some examples that may be combined with any of the preceding examples, the antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody. In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is a bispecific antibody recognizing a first antigen and a second antigen. In some examples, the first antigen is CD33 and the second antigen is: an antigen facilitating transport across the blood-brain-barrier; 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; 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; 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, LIGHT, BTLA, CD38, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR5, CD39, CD70, CD73, TREM1, TREM2, Siglec-5, Siglec-7, Siglec-9, Siglec-11, SirpA, CD47, CSF1-receptor, and phosphatidylserine; and a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

[0026] In some examples that may be combined with any of the preceding examples, the 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, LIGHT, BTLA, CD38, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR3, DR5, CD39, CD70, CD73, LAG3, TREM1, TREM2, Siglec-5, Siglec-7, Siglec-9, Siglec-11, SirpA, CD47, CSF1-receptor, phosphatidylserine, disease-causing nucleic acids, antisense GGCCC (G2C4) repeat-expansion RNA, and any combination thereof.

[0027] In some examples that may be combined with any of the preceding examples, the antibody has a dissociation constant (K_D) for human CD33 that is at least 1.8-fold lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4, wherein the K_D is determined by BioLayer Interferometry.

[0028] In some examples that may be combined with any of the preceding examples, the antibody has a dissociation constant (K_D) for human CD33 that ranges from about 2 nM to about 200 pM, or less than about 200 pM, and wherein the K_D is determined by BioLayer Interferometry.

[0029] In some examples that may be combined with any of the preceding examples, the antibody reduces cell surface levels of CD33. In some examples, the CD33 is expressed on the surface of human dendritic cells. In some examples, the antibody reduces cell surface levels of CD33 *in vitro*. In some examples, the antibody reduces cell surface levels of CD33 *in vitro* with a half maximal effective concentration (EC_{50}) that is less than 40 pM, as measured by flow cytometry.

[0030] In some examples that may be combined with any of the preceding examples, the antibody increases expression of one or more disease-associated microglia (DAM) markers.

In some examples, the one or more DAM markers is ApoE3, Tyrobp, B2m, Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, or any combination thereof.

[0031] In some examples that may be combined with any of the preceding examples, the antibody competes with one or more antibodies selected from the group consisting of 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, and 6C7H54, and any combination thereof for binding to human CD33.

[0032] In some examples that may be combined with any of the preceding examples, the antibody binds essentially the same or overlapping CD33 epitope as an antibody selected from the group consisting of 6C7H8, 6C7H9, 6C7H10, 6C7H11, 6C7H12, 6C7H13, 6C7H14, 6C7H15, 6C7H16, 6C7H17, 6C7H18, 6C7H19, 6C7H20, 6C7H21, 6C7H22, 6C7H23, 6C7H24, 6C7H25, 6C7H26, 6C7H27, 6C7H28, 6C7H29, 6C7H30, 6C7H31, 6C7H32, 6C7H33, 6C7H34, 6C7H35, 6C7H36, 6C7H37, 6C7H38, 6C7H39, 6C7H40, 6C7H41, 6C7H42, 6C7H43, 6C7H44, 6C7H45, 6C7H46, 6C7H47, 6C7H48, 6C7H49, 6C7H50, 6C7H51, 6C7H52, 6C7H53, and 6C7H54.

[0033] In some examples that may be combined with any of the preceding examples, the antibody has an Fc region comprising the amino acid sequence of SEQ ID NO: 118.

[0034] In some examples that may be combined with any of the preceding examples, anti-CD33 antibodies of the present disclosure comprise a heavy chain variable domain and a light chain variable domain, wherein (a) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:8, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:38, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:47, HVR-L2 comprises the amino acid sequence of SEQ ID NO:52, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO:58; (b) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:8, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO:58; (c) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:54, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO:58; (d) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO:58; (e) the HVR-H1 comprises the amino acid sequence of SEQ ID NO:9, the HVR-H2 comprises the

the amino acid sequence of SEQ ID NO:28, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO:61.

[0035] In some examples that may be combined with any of the preceding examples, anti-CD33 antibodies of the present disclosure comprise a light chain variable region comprising an amino acid sequence selected from any of SEQ ID NOs:94-103; and/or a heavy chain variable domain comprising an amino acid sequence selected from any of SEQ ID NOs:65-93. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 94; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 65. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 94; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 66. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 95; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 65. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 95; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 67. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 95; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 66. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 96; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 65. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 96; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 67. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 97; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 68. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 98; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 69. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 97; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 69. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 94; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 65. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 99; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 69. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 97; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 70. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 97; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 71. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 97; and the heavy

SEQ ID NO: 100; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 93. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 102; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 93. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 100; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 83. In some examples, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 102; and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 83.

[0036] In another example, the present disclosure relates to isolated nucleic acids comprising a nucleic acid sequence encoding any of the antibodies described herein.

[0036a] In another aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody as disclosed herein.

[0037] In another example, the present disclosure relates to vectors comprising any of the nucleic acids described herein. In some examples, the vector is an expression vector and/or a display vector.

[0037a] In another aspect, the present disclosure refers to a vector comprising the nucleic acid disclosed herein.

[0038] In another example, the present disclosure relates to isolated host cells comprising any of the nucleic acids or vectors described herein.

[0038a] In another aspect, the present disclosure refers to an isolated host cell comprising the vector disclosed herein.

[0039] In another example, the present disclosure relates to a method of producing an antibody that binds to CD33 comprising culturing any of the host cells described herein so that the antibody is produced. In some examples, the method further comprises recovering the antibody produced by the cell.

[0039a] In another aspect, the present disclosure refers to a method of producing an antibody that binds to CD33, comprising culturing the cell disclosed herein so that the antibody is produced.

[0040] In another example, the present disclosure relates to an antibody produced by any of the methods described herein.

[0040a] In another aspect, the present disclosure refers to an isolated antibody that binds to CD33 produced by the method disclosed herein.

[0041] In another example, the present disclosure relates to pharmaceutical compositions comprising any of the antibodies described herein and a pharmaceutically acceptable carrier. In some examples, the present disclosure relates to the use of any of the antibodies described herein for the preparation of a medicament.

[0041a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

[0042] In another example, the present disclosure relates 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, tauopathy disease, infections, and cancer, comprising administering to an individual in need thereof a therapeutically effective amount of any of the antibodies described herein. In some examples, the disease, disorder, or injury is cancer. 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 present disclosure relates to the use of any of the antibodies described herein for the preparation of a medicament useful 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 disease, disorder, or injury is cancer. 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.

[0042a] In another aspect, the present disclosure refers to the use of the antibody as disclosed herein 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.

[0043] It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure. These and other examples of the disclosure will become apparent to one of skill in the art. These and other examples of the disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **FIG. 1** sets forth data showing anti-CD33 antibodies of the present disclosure bind to primary human dendritic cells.

[0045] **FIG. 2** sets forth data showing anti-CD33 antibodies of the present disclosure down-regulate CD33 cell surface levels in human dendritic cells.

[0046] **FIG. 3** sets forth data showing anti-CD33 antibodies of the present disclosure bind to primary human dendritic cells.

[0047] **FIG. 4** sets forth data showing anti-CD33 antibodies of the present disclosure bind to human CD33 and cyno CD33 protein.

[0048] **FIG. 5** sets forth data showing anti-CD33 antibodies of the present disclosure down-regulate cell surface levels of CD33 in human dendritic cells.

[0049] **FIG. 6A and FIG. 6B** set forth data showing anti-CD33 antibodies of the present disclosure bind recombinant human CD33.

[0050] **FIG. 7** sets forth data showing anti-CD33 antibodies of the present disclosure bind primary human dendritic cells.

[0051] **FIG. 8A and FIG. 8B** set forth data comparing the reduction of cell surface levels of CD33 in dendritic cells by various anti-CD33 antibodies of the present disclosure.

[0052] **FIG. 9** sets forth data showing anti-CD33 antibody variants of the present disclosure binding to primary human dendritic cells.

[0053] **FIG. 10A and FIG. 10B** set forth data showing anti-CD33 antibody variants of the present disclosure bind to human CD33 and cyno CD33 protein, respectively.

[0054] **FIG. 11** sets forth data showing anti-CD33 antibody variants of the present disclosure reduce cell surface levels of CD33 in primary human dendritic cells.

CLAIMS

What is claimed is:

1. An isolated antibody that binds to CD33, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 8, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 9, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 55, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 10, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 11, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 58;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 12, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 59;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 30, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 61;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 59;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 23, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 33, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 39, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 47, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 53, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 61.

2. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region comprising an amino acid sequence selected from SEQ ID NOs:68-93; and/or a light chain variable region comprising an amino acid sequence selected from SEQ ID NOs:97-103

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 99;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 70, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 92, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102.

3. An isolated antibody that binds to CD33, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:33, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 39; and wherein the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:47, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 53, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 61.

4. An isolated antibody that binds to CD33, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102.

5. An isolated antibody that binds to CD33, wherein the antibody comprises
(a) a heavy chain comprising the amino acid sequence of SEQ ID. NO: 120 and a light chain comprising the amino acid sequence of SEQ ID NO: 122; or
(b) a heavy chain comprising the amino acid sequence of SEQ ID. NO: 121 and a light chain comprising the amino acid sequence of SEQ ID NO: 122.

6. A monoclonal antibody that binds to human CD33, wherein the antibody comprises
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98;
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 99;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 92, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 92, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102.

7. The antibody of any one of claims 1-6, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

8. The antibody of claim 7, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

9. The antibody of claim 8, wherein the antibody comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: C127S, L234A, L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, E345R, E430G, S440Y, and any combination thereof, wherein the numbering of the residues is according to EU numbering.

10. The antibody of claim 8, wherein the antibody has an IgG4 isotype, and wherein the antibody comprises an S228P amino acid substitution at residue position 228, an F234A amino acid substitution at residue position 234, and an L235A amino acid substitution at residue position 235, wherein the numbering of the residue position is according to EU numbering.

11. The antibody of claim 10, wherein:

(a) the Fc region comprises an amino acid substitution at position E430G, wherein the numbering of the residue position is according to EU numbering;

(b) the Fc region comprises an amino acid substitution at positions L234A, L235A, and P331A, wherein the numbering of the residue position is according to EU numbering;

(c) the Fc region comprises an amino acid substitution at positions L234A, L235A, P331A, and E430G, wherein the numbering of the residue position is according to EU numbering;

(d) the Fc region comprises an amino acid substitution at positions K322A and E430G, wherein the numbering of the residue position is according to EU numbering;

- (e) the Fc region comprises an amino acid substitution at positions P331S and E430G, wherein the numbering of the residue position is according to EU numbering;
 - (f) the Fc region comprises an amino acid substitution at positions A330S, P331S, and E430G, wherein the numbering of the residue position is according to EU numbering;
 - (g) the Fc region comprises an amino acid substitution at positions K322A, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (h) the Fc region comprises an amino acid substitution at positions K322A, P331S, and E430G, wherein the numbering of the residue position is according to EU numbering;
 - (i) the Fc region comprises an amino acid substitution at position E430G, wherein the numbering of the residue position is according to EU numbering;
 - (j) the Fc region comprises an amino acid substitution at positions A330S, P331S, and E430G, wherein the numbering of the residue position is according to EU numbering;
 - (k) the Fc region comprises an amino acid substitution at positions S267E and L328F, wherein the numbering of the residue position is according to EU numbering;
 - (l) the Fc region comprises an amino acid substitution at position C127S, wherein the numbering of the residue position is according to EU numbering;
 - (m) the Fc region comprises an amino acid substitution at positions E345R, E430G and S440Y, wherein the numbering of the residue position is according to EU numbering;
 - (n) the Fc region comprises an amino acid substitution at position P331S, wherein the numbering of the residue position is according to EU numbering; or
 - (o) the Fc region comprises an amino acid substitution at positions L234A, L235A, P331S, wherein the numbering of the residue positions is according to EU numbering.
12. The antibody of any one of claims 1-11, wherein the CD33 protein is a mammalian protein or a human protein.
 13. The antibody of any one of claims 1-12, wherein the CD33 protein is a wild-type protein.
 14. The antibody of any one of claims 1-12, wherein the CD33 protein is a naturally occurring variant.
 15. The antibody of any one of claims 1-14, 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.
 16. The antibody of any one of claims 1-15, wherein the antibody binds specifically to a human CD33 protein.

17. The antibody of any one of claims 1-16, wherein the antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human CD33 or a mammalian CD33 protein.
18. The antibody of any one of claims 1-17, wherein the 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.
19. The antibody of claim 17 or claim 18, wherein 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.
20. The antibody of any one of claims 17-19, wherein the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.
21. The antibody of any one of claims 1-5 and 7-20, wherein the antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.
22. The antibody of any one of claims 1-5 and 7-21, wherein the antibody is a monoclonal antibody.
23. The antibody of any one of claims 1-21, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.
24. The antibody of claim 23, wherein 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, LIGHT, BTLA, CD38, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR5, CD39, CD70, CD73, TREM1, TREM2, Siglec-5, Siglec-7, Siglec-9, Siglec-11, SirpA, CD47, CSF1-receptor, and phosphatidylserine; and

(e) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

25. The antibody of any one of claims 1-24, wherein the 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, LIGHT, BTLA, CD38, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR3, DR5, CD39, CD70, CD73, LAG3, TREM1, TREM2, Siglec-5, Siglec-7, Siglec-9, Siglec-11, SirpA, CD47, CSF1-receptor, phosphatidylserine, disease-causing nucleic acids, antisense GGCCCC (G2C4) repeat-expansion RNA, and any combination thereof.

26. The antibody of any one of claims 1-25, wherein the antibody has an IgG2 isotype.

27. The antibody of any one of claims 1-26, wherein the antibody has a dissociation constant (K_D) for human CD33 that is at least 1.8-fold lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4, wherein the K_D is determined by BioLayer Interferometry.

28. The antibody of any one of claims 1-27, wherein the antibody has a dissociation constant (K_D) for human CD33 that ranges from about 2 nM to about 200 pM, or less than about 200 pM, and wherein the K_D is determined by BioLayer Interferometry.
29. The antibody of any one of claims 1-28, wherein the antibody reduces cell surface levels of CD33.
30. The antibody of claim 29, wherein the CD33 is expressed on the surface of human dendritic cells.
31. The antibody of claim 29 or claim 30, wherein the antibody reduces cell surface levels of CD33 *in vitro*.
32. The antibody of any one of claims 29-31, wherein the antibody reduces cell surface levels of CD33 *in vitro* with a half maximal effective concentration (EC_{50}) that is less than 40 pM, as measured by flow cytometry.
33. The antibody of any one of claims 1-32, wherein the antibody increases expression of one or more disease-associated microglia (DAM) markers.
34. The antibody of claim 33, wherein the one or more DAM markers is ApoE3, Tyrobp, B2m, Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, or any combination thereof.
35. The antibody of any one of claims 1-34, wherein the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 118.
36. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-35.
37. A vector comprising the nucleic acid of claim 36.
38. An isolated host cell comprising the vector of claim 37.
39. A method of producing an antibody that binds to CD33, comprising culturing the cell of claim 38 so that the antibody is produced.
40. The method of claim 39, further comprising recovering the antibody produced by the cell.
41. An isolated antibody that binds to CD33 produced by the method of claim 39 or 40.
42. A pharmaceutical composition comprising the antibody of any one of claims 1-35 and 41 and a pharmaceutically acceptable carrier.
43. Use of the antibody of any one of claims 1-35 and 41 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.

44. The use of claim 43, wherein the disease is Alzheimer's disease.
45. The use of claim 43, wherein the disease, disorder or injury is cancer.
46. The use of claim 45, 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.