

[045a] In another example, the present disclosure refers to an isolated antibody that binds to CD33 produced by the method as disclosed herein.

[046] 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.

[046a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

[047] 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, taupathy 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.

[047a] In another aspect, the present disclosure refers to use of a therapeutically effective amount of the antibody as disclosed herein in the manufacture of a medicament for preventing, reducing risk, or treating Alzheimer's disease in an individual in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[048] FIG. 1 depicts results from a flow cytometry assay measuring CD33 levels on the surface of primary human monocyte-derived dendritic cells after treatment with humanized CD33 antibodies.

[049] FIG. 2 depicts flow cytometry results measuring CD33 levels on the surface of primary human monocyte-derived dendritic cells after incubation with different concentrations of affinity matured CD33 antibodies.

CLAIMS

What is claimed is:

1. An antibody that binds to a CD33 protein, 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: 105, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 115, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 122, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 127, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 135, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 146;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 105, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 118, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 122, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 127, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 135, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 146;

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 105, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 119, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 122, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 127, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 135, and the HVR-L3 comprises the amino acid sequence SEQ ID NO: 146; or

the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 105, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 120, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 122, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 127, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 135, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 146.

2. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 58, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 61, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 62, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 63, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 64, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 67, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;

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: 86;

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: 86;

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: 86;

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: 86; or

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: 86.

3. The antibody of claim 1 or claim 2, wherein:

the HVR-H1 comprises the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), the HVR-H2 comprises the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), the HVR-H3 comprises the amino acid sequence SDVDYFDY (SEQ ID NO: 122), the HVR-L1 comprises the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), the HVR-L2 comprises the amino acid sequence YASNLES (SEQ ID NO: 135), and the HVR-L3 comprises the amino acid sequence QHSWEIPLT (SEQ ID NO: 146).

4. An antibody that binds to a human CD33 protein, 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: 105, the HVR-H2 comprises the amino acid sequence of

SEQ ID NO: 119, the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 122, the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 127, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 135, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 146.

5. An antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86.
6. The antibody of claim 2, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59, and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 86.
7. A monoclonal antibody that binds to a human CD33 protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 58, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 60, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 61, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 62, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 63, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 64, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 67, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86;
 - 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: 86;

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: 86;

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: 86;

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: 86; or

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: 86.

8. An antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 58 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86, a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86, a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86, a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86, a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 67 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86, 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: 86, or 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: 86.

9. The antibody of any one of claims 1-8, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

10. The antibody of claim 9, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

11. The antibody of claim 10, wherein the antibody has an IgG2 isotype.

12. The antibody of claim 10, 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.

13. The antibody of claim 10, 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 or Kabat numbering.

14. The antibody of claim 13, 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 P331S, 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, P331S, 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; or
- (n) the Fc region comprises an amino acid substitution at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.

15. An antibody that binds to a CD33 protein, wherein the antibody is of the IgG class, wherein the antibody comprises:

- (a) 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:105, the HVR-H2 comprises the amino acid sequence of SEQ ID NO:119, the HVR-H3 comprises the amino acid sequence of SEQ ID NO:122, the HVR-L1 comprises the amino acid sequence of SEQ ID NO:127, the HVR-L2 comprises the amino acid sequence of SEQ ID NO:135, and the HVR-L3 comprises the amino acid sequence of SEQ ID NO:146;
- (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:59 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:86;
- (c) a heavy chain comprising the amino acid sequence of SEQ ID NO:177, and a light chain comprising the amino acid sequence of SEQ ID NO:185;
- (d) a heavy chain comprising the amino acid sequence of SEQ ID NO:177 without the C-terminal lysine, and a light chain comprising the amino acid sequence of SEQ ID NO:185;
- (e) a heavy chain comprising the amino acid sequence of SEQ ID NO:180, and a light chain comprising the amino acid sequence of SEQ ID NO:185;
- (f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 180 without the C-terminal lysine, and a light chain comprising the amino acid sequence of SEQ ID NO:185;
- (g) a heavy chain comprising the amino acid sequence of SEQ ID NO:183, and a light chain comprising the amino acid sequence of SEQ ID NO:185; or
- (h) a heavy chain comprising the amino acid sequence of SEQ ID NO: 183 without the C-terminal lysine, and a light chain comprising the amino acid sequence of SEQ ID NO:185.

16. The antibody of any one of claims 1-15, wherein the CD33 protein is a mammalian protein or a human protein.

17. The antibody of any one of claims 1-16, wherein the CD33 protein is a wild-type protein.
18. The antibody of any one of claims 1-16, wherein the CD33 protein is a naturally occurring variant.
19. The 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 antibody of any one of claims 1-19, wherein the antibody binds specifically to a human CD33 protein.
21. The antibody of any one of claims 1-20, wherein the antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human CD33 or a mammalian CD33 protein.
22. The antibody of any one of claims 1-20, 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.
23. The antibody of claim 21 or claim 22, 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.
24. The antibody of any one of claims 21-23, wherein the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.
25. The antibody of any one of claims 1-24, wherein the antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.
26. The antibody of any one of claims 1-25, wherein the antibody is a monoclonal antibody.
27. The antibody of any one of claims 1-25, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.
28. The antibody of claim 27, 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.

29. The antibody of any one of claims 1-28, 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.

30. The antibody of any one of claims 1-29, wherein the antibody has a dissociation constant (K_D) for human CD33 that ranges from 2 nM to 200 pM, or less than 200 pM, and wherein the K_D is determined by BioLayer Interferometry.

31. The antibody of any one of claims 1-30, wherein the antibody reduces cell surface levels of CD33.

32. The antibody of claim 31, wherein the CD33 is expressed on the surface of human dendritic cells.

33. The antibody of claim 31 or claim 32, wherein the antibody reduces cell surface levels of CD33 *in vitro*.

34. The antibody of any one of claims 31-33, wherein the antibody reduces cell surface levels of CD33 *in vitro* with a half maximal effective concentration (EC_{50}) that is less than 150 pM, as measured by flow cytometry.

35. An antibody that binds to a CD33 protein, wherein the antibody comprises

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 176 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 176 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
- (c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 177 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
- (d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 177 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
- (e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 178 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
- (f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 178 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;

- (g) a heavy chain comprising the amino acid sequence of SEQ ID NO: 179 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (h) a heavy chain comprising the amino acid sequence of SEQ ID NO: 179 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 180 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (j) a heavy chain comprising the amino acid sequence of SEQ ID NO: 180 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (k) a heavy chain comprising the amino acid sequence of SEQ ID NO: 181 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (l) a heavy chain comprising the amino acid sequence of SEQ ID NO: 181 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (m) a heavy chain comprising the amino acid sequence of SEQ ID NO: 182 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (n) a heavy chain comprising the amino acid sequence of SEQ ID NO: 182 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (o) a heavy chain comprising the amino acid sequence of SEQ ID NO: 183 and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (p) a heavy chain comprising the amino acid sequence of SEQ ID NO: 183 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185;
 - (q) a heavy chain comprising the amino acid sequence of SEQ ID NO: 184 and a light chain comprising the amino acid sequence of SEQ ID NO: 185; or
 - (r) a heavy chain comprising the amino acid sequence of SEQ ID NO: 184 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185.
36. An antibody that binds to a human CD33 protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 180 and a light chain comprising the amino acid sequence of SEQ ID NO: 185.
37. An antibody that binds to a human CD33 protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 180 without the C-terminal lysine and a light chain comprising the amino acid sequence of SEQ ID NO: 185.
38. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-37.
39. A vector comprising the nucleic acid of claim 38.

- 40. An isolated host cell comprising the vector of claim 39.
- 41. A method of producing an antibody that binds to CD33, comprising culturing the cell of claim 40 so that the antibody is produced.
- 42. The method of claim 41, further comprising recovering the antibody produced by the cell.
- 43. A pharmaceutical composition comprising the antibody of any one of claims 1-37 and a pharmaceutically acceptable carrier.
- 44. Use of a therapeutically effective amount of the antibody of any one of claims 1-37 in the manufacture of a medicament for preventing, reducing risk, or treating Alzheimer's disease in an individual in need thereof.