

with improved survival rate from pediatric acute myeloid leukemia (AML). The 3-year overall survival rate from remission is 84%+/- 8% for those carrying the variant rs35112940^{GG}, which is in strong linkage disequilibrium with the rs3865444^{AA} variant, associated with lower full-length expression of CD33. The remission rate for the non-protective allele is 68%+/- 15%. Carriers of the protective allele also have a lower relapse risk and superior disease-free survival. 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.

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

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

SUMMARY

[008] 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.

[009] 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 (*e.g.*, relative to an anti-CD33 antibody with a heavy chain variable region comprising the sequence of SEQ ID NO: 103 and a light chain variable region comprising the sequence SEQ ID NO: 104), including, for example, improved and/or enhanced capabilities of decreasing cell surface levels of CD33 on human primary immune cells, and/or have improved and/or enhanced binding kinetics. In some examples, anti-CD33 antibodies of the present disclosure have a K_D for human CD33 that is at least 9-fold lower than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 34 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77. In some examples, anti-CD33 antibodies of the present disclosure have a K_D for human CD33 that is at least 3-fold lower

than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86. In some examples, anti-CD33 antibodies of the present disclosure have a K_D for human CD33 that is at least 3-fold lower than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 52 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86. In some examples, anti-CD33 antibodies of the present disclosure reduce cell surface levels of CD33 *in vitro* with an EC_{50} that is at least about 50% lower than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 34 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77. In some examples, anti-CD33 antibodies of the present disclosure reduce cell surface levels of CD33 *in vitro* with an EC_{50} that is at least about 10% lower than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86. In some examples, anti-CD33 antibodies of the present disclosure reduce cell surface levels of CD33 *in vitro* with an EC_{50} that is at least about 10% lower than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 52 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86. In some examples, anti-CD33 antibodies of the present disclosure reduce cell surface levels of CD33 *in vitro* with an EC_{50} that is at least about 10-fold lower than an anti-CD33 antibody having a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 103 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 104, as measured by flow cytometry. Advantageously, the anti-CD33 antibodies decrease cellular levels of CD33 *in vitro* with a half-maximal effective concentration (EC_{50}) that ranges from about 151.1 pM to about 4.1 pM, bind to human cells (such as human primary dendritic cells), and have a dissociation constant (K_D) for human CD33 that ranges from about 8.57 nM to about 202 pM.

[010] 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 a sequence according to Formula I: $GX_1X_2X_3TDYNX_4H$ (SEQ ID NO: 152), wherein X_1 is Y, A, or V, X_2 is T or A, X_3 is F, E, or H, and X_4 is L, F, Y, or N; an HVR-H2 comprising a sequence according to Formula II: $FIYPX_1NX_2IX_3G$ (SEQ ID NO: 153), wherein X_1 is S or A, X_2 is G, Q, R, or V, and X_3 is T or R; and an HVR-H3 comprising a sequence according to Formula III: $SX_1VDYFDX_2$ (SEQ ID NO: 154), wherein X_1 is T, D, F, or S, and X_2 is Y, D, or L; and wherein the antibody is not an antibody comprising a heavy chain variable region comprising an HVR-H1 comprising the sequence of GYTFTDYNLH (SEQ ID NO: 105),

an HVR-H2 comprising the sequence of FIYPSNGITG (SEQ ID NO: 115), and an HVR-H3 comprising the sequence of STVDYFDY (SEQ ID NO: 121).

[011] 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: an HVR-L1 comprising a sequence according to Formula IV: $X_1X_2SQX_3VX_4X_5STYSYMH$ (SEQ ID NO: 155), wherein X_1 is R or K, X_2 is A, G, or V, X_3 is S or D, X_4 is S, G, or H, and X_5 is T or A; an HVR-L2 comprising a sequence according to Formula V: $YX_1X_2X_3X_4X_5S$ (SEQ ID NO: 156), wherein X_1 is A, V, or E, X_2 is S, V, or F, X_3 is N, A, Y, or F, X_4 is L or V, and X_5 is E, G, or N; and an HVR-L3 comprising a sequence according to Formula VI: $X_1HSX_2X_3X_4PLX_5$ (SEQ ID NO: 157), wherein X_1 is Q or E, X_2 is W or E, X_3 is E or A, X_4 is I or L, and X_5 is T or E; and wherein the antibody is not an antibody comprising a light chain variable region comprising an HVR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the sequence of YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the sequence of QHSWEIPLT (SEQ ID NO: 146).

[012] 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: an HVR-H1 comprising a sequence according to Formula I: $GX_1X_2X_3TDYNX_4H$ (SEQ ID NO: 152), wherein X_1 is Y, A, or V, X_2 is T or A, X_3 is F, E, or H, and X_4 is L, F, Y, or N; an HVR-H2 comprising a sequence according to Formula II: $FIYPX_1NX_2IX_3G$ (SEQ ID NO: 153), wherein X_1 is S or A, X_2 is G, Q, R, or V, and X_3 is T or R; and an HVR-H3 comprising a sequence according to Formula III: $SX_1VDYFDX_2$ (SEQ ID NO: 154), wherein X_1 is T, D, F, or S, and X_2 is Y, D, or L; and the light chain variable region comprises: an HVR-L1 comprising a sequence according to Formula IV: $X_1X_2SQX_3VX_4X_5STYSYMH$ (SEQ ID NO: 155), wherein X_1 is R or K, X_2 is A, G, or V, X_3 is S or D, X_4 is S, G, or H, and X_5 is T or A; an HVR-L2 comprising a sequence according to Formula V: $YX_1X_2X_3X_4X_5S$ (SEQ ID NO: 156), wherein X_1 is A, V, or E, X_2 is S, V, or F, X_3 is N, A, Y, or F, X_4 is L or V, and X_5 is E, G, or N; and an HVR-L3 comprising a sequence according to Formula VI: $X_1HSX_2X_3X_4PLX_5$ (SEQ ID NO: 157), wherein X_1 is Q or E, X_2 is W or E, X_3 is E or A, X_4 is I or L, and X_5 is T or E; and wherein the antibody is not an antibody comprising a heavy chain variable region comprising an HVR-H1 comprising the sequence of GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the sequence of FIYPSNGITG (SEQ ID NO: 115), and an HVR-H3 comprising the sequence of STVDYFDY (SEQ ID NO: 121), and a light chain variable region comprising an HVR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the sequence of

YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the sequence of QHSWEIPLT (SEQ ID NO: 146).

[013] 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 AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 3A to 3C).

[014] 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 AB-14.3, AB-14.4, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, or AB-64.8 (as shown in Tables 4A to 4C).

[015] 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 AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 3A to 3C); and the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody AB-14.3, AB-14.4, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, or AB-64.8 (as shown in Tables 4A to 4C).

[016] 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 HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody AB-

14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 3A to 3C and 4A to 4C).

[016a] In one aspect, the present disclosure refers to 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 antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 9A to 9C and 10A to 10C).

[017] Other examples of the present disclosure relate 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 Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of DYNLH (SEQ ID NO: 190), a CDR-H2 comprising the sequence of FIYPSNGITGYAQKFQ (SEQ ID NO: 194); and a CDR-H3 comprising the sequence of YCARSDVD (SEQ ID NO: 191). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), a CDR-L2 comprising the sequence of LLIKYAS (SEQ ID NO: 192); and a CDR-L3 comprising the sequence of VYYCQHSWE (SEQ ID NO: 193). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of DYNLH (SEQ ID NO: 190), a CDR-H2 comprising the sequence of FIYPSNGITGYAQKFQ (SEQ ID NO: 194); and a CDR-H3 comprising the sequence of YCARSDVD (SEQ ID NO: 191); and the light chain variable region comprises a CDR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), a CDR-L2 comprising the sequence of LLIKYAS (SEQ ID NO: 192); and a CDR-L3 comprising the sequence of VYYCQHSWE (SEQ ID NO: 193).

[018] Other examples of the present disclosure relate 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 Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of DYNLH (SEQ ID NO: 190), a CDR-H2 comprising the sequence of FIYPSNRITGYAQKFQ (SEQ ID NO: 195); and a CDR-H3 comprising the sequence of YCARSDVD (SEQ ID NO: 191). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), a CDR-L2 comprising the sequence of LLIKYAS (SEQ ID NO: 192); and a CDR-L3 comprising the sequence of VYYCQHSWE (SEQ ID NO: 193). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of DYNLH (SEQ ID NO: 190), a CDR-H2 comprising the sequence of FIYPSNRITGYAQKFQ (SEQ ID NO: 195); and a CDR-H3 comprising the sequence of YCARSDVD

(SEQ ID NO: 191); and the light chain variable region comprises a CDR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), a CDR-L2 comprising the sequence of LLIKYAS (SEQ ID NO: 192); and a CDR-L3 comprising the sequence of VYYCQHSWE (SEQ ID NO: 193).

[019] Other examples of the present disclosure relate 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 Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of DYNLH (SEQ ID NO: 190), a CDR-H2 comprising the sequence of FIYPSNQITGYAQKFQ (SEQ ID NO: 196); and a CDR-H3 comprising the sequence of YCARSDVD (SEQ ID NO: 191). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), a CDR-L2 comprising the sequence of LLIKYAS (SEQ ID NO: 192); and a CDR-L3 comprising the sequence of VYYCQHSWE (SEQ ID NO: 193). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of DYNLH (SEQ ID NO: 190), a CDR-H2 comprising the sequence of FIYPSNQITGYAQKFQ (SEQ ID NO: 196); and a CDR-H3 comprising the sequence of YCARSDVD (SEQ ID NO: 191); and the light chain variable region comprises a CDR-L1 comprising the sequence of RASQSVSTSTYSYMH (SEQ ID NO: 127), a CDR-L2 comprising the sequence of LLIKYAS (SEQ ID NO: 192); and a CDR-L3 comprising the sequence of VYYCQHSWE (SEQ ID NO: 193).

[020] 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 according to Formula VII: QVQLVQSGAEVKKPGX₁SVKX₂SCKAS (SEQ ID NO: 158), wherein X₁ is A or S, and X₂ is V or I; VH FR2 comprises the sequence of SEQ ID NO: 5; VH FR3 comprises a sequence according to Formula VIII: X₁AX₂X₃X₄X₅X₆RX₇TX₈TVDX₉X₁₀X₁₁STX₁₂YMELSSLRSEDTAVYYCAR (SEQ ID NO: 159), wherein X₁ is Y or S, X₂ is Q or E, X₃ is K or D, X₄ is F or D, X₅ is Q, F, E, or T, X₆ is G, D, or H, X₇ is V or A, X₈ is M or L, X₉ is T, N, or Q, X₁₀ is S or P, X₁₁ is T or A, and X₁₂ is V or A; and VH FR4 comprises a sequence according to Formula IX: WGQGTLX₁TVSS (SEQ ID NO: 160), wherein X₁ is V or L; and/or the light chain 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 according to Formula X: X₁IX₂X₃TQSPX₄SLX₅X₆SX₇GX₈RX₉TIX₁₀C (SEQ ID NO: 161), wherein X₁ is D or G, X₂ is Q or V, X₃ is M or L, X₄ is S or D, X₅ is S, P, or A, X₆ is A or V, X₇ is V or L, X₈ is D or E, X₉ is V or A, and X₁₀ is T, N, or D; VL FR2 comprises a sequence according to Formula XI: WYQQKPGX₁X₂PKLLIK (SEQ ID NO: 162), wherein X₁ is K or Q, and X₂ is A or P; VL FR3 comprises a sequence according to Formula

XII: GVPX₁RFSGSGSGTDFLTISLQX₂EDX₃AX₄YYC (SEQ ID NO: 163), wherein X₁ is S or D, X₂ is P or A, X₃ is F, L, or V, and X₄ is T or V; and VL FR4 comprises a sequence according to Formula XIII: FGQGTKLEIX₁ (SEQ ID NO: 164), wherein X₁ is K or E. 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: 2-4; VH FR2 comprises the sequence of SEQ ID NO: 5; VH FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 6-19; and VH FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 20-21; and/or the light chain 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: 22-26; VL FR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 27-28; VL FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 29-31; and VL FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 32-33.

[021] In some examples that may be combined with any of the preceding examples, the antibody comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-72; and/or a light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 77-101. In some examples, the antibody comprises the heavy chain variable region of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Table 7); and/or the antibody comprises the light chain variable region of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Table 8). In some examples that may be combined with any of the preceding examples, 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); or the HVR-H1 comprises the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), the HVR-H2 comprises the amino acid sequence FIYPSNQITG (SEQ ID NO: 118), 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).

[022] 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 an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146); or the heavy chain comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNQITG (SEQ ID NO: 118), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146).

[022a] In another aspect, the present disclosure refers 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: (a) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146);

(b) the heavy chain comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNQITG (SEQ ID NO: 118), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146); or

(c) the heavy chain comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 108), an HVR-H2 comprising the amino acid sequence FIYPSNGITG (SEQ ID NO: 115), and an HVR-H3 comprising the amino acid sequence STVDYFDY (SEQ ID NO: 121), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146).

[023] 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 the group consisting of SEQ ID NOs: 34-72; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 77-101. In some examples, the antibody comprises the heavy chain variable region of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-

64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Table 7); and/or the antibody comprises the light chain variable region of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Table 8). In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 86; or the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 65, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 86.

[023a] In another aspect, the present disclosure refers to 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: 34, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 35, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 36, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 37, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 81;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 82;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 83;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 84;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85;

[illegible]

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.

[024] 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 the group consisting of SEQ ID NOs: 34, 40, 42, 52, 53, and 73-76; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 77, 86, and 102. In some examples, the antibody comprises the heavy chain variable region of AB-H2, AB-H9, AB-H14, AB-H15, AB-H63, AB-H64, AB-H65, or AB-H66 (as shown in Table 7); and/or the antibody comprises the light chain variable region of antibody AB-H2, AB-H9, AB-H14, AB-H15, AB-H63, AB-H64, AB-H65, or AB-H66 (as shown in Table 8).

[024a] In another aspect, the present disclosure refers to 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: 34, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40, 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: 42, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 42, 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: 42, 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: 52, 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: 53, 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: 73, 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: 73, 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: 74, 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: 74, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 75, 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: 76, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86.

[025] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody competes with one or more antibodies selected from the group consisting of AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, AB-64.1.15, AB-H2, AB-H9, AB-H14, AB-H15, AB-H63, AB-H64, AB-H65, AB-H66, and any combination thereof for binding to CD33.

[026] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody binds essentially the same CD33 epitope as an antibody selected from the group consisting of AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11,

AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, AB-64.1.15, AB-H2, AB-H9, AB-H14, AB-H15, AB-H63, AB-H64, AB-H65, and AB-H66.

[027] 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: an HVR-H1 comprising a sequence according to Formula I: $GX_1X_2X_3TDYNX_4H$ (SEQ ID NO: 186), wherein X_1 is Y or V, X_2 is T or A, X_3 is F, E, or H, and X_4 is L, F, Y, or N; an HVR-H2 comprising a sequence according to Formula II: $FIYPX_1NX_2IX_3G$ (SEQ ID NO: 153), wherein X_1 is S or A, X_2 is G, Q, R, or V, and X_3 is T or R; and an HVR-H3 comprising a sequence according to Formula III: $SX_1VDYFDX_2$ (SEQ ID NO: 187), wherein X_1 is T, D, or F, and X_2 is Y, D, or L; and wherein the light chain variable region comprises: an HVR-L1 comprising a sequence according to Formula IV: $X_1X_2SQX_3VX_4X_5STYSYMH$ (SEQ ID NO: 188), wherein X_1 is R or K, X_2 is A, G, or V, X_3 is S or D, X_4 is S, G, or H, and X_5 is T; an HVR-L2 comprising a sequence according to Formula V: $YX_1X_2X_3X_4X_5S$ (SEQ ID NO: 189), wherein X_1 is A or E, X_2 is S or F, X_3 is N, Y, or F, X_4 is L or V, and X_5 is E or N; and an HVR-L3 comprising a sequence according to Formula VI: $X_1HSX_2X_3X_4PLX_5$ (SEQ ID NO: 157), wherein X_1 is Q or E, X_2 is W or E, X_3 is E or A, X_4 is I or L, and X_5 is T or E.

[028] 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: an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 105 and 108-114; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 115-120; and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 121-123 and 125-126; and the light chain variable region comprises: an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 127-128 and 130-134; an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 135 and 140-145; and an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 146-151.

[028a] In another aspect, the present disclosure refers to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, an HVR-H2, and an HVR-H3 and a light chain variable region comprising an HVR-L1, an HVR-L2, and an HVR-L3, wherein:

HVR-L3 of amino acid sequence SEQ ID NO: 149;

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 113, the HVR-H2 of amino acid sequence SEQ ID NO: 116, the HVR-H3 of amino acid sequence SEQ ID NO: 122, the HVR-L1 of amino acid sequence SEQ ID NO: 130, the HVR-L2 of amino acid sequence SEQ ID NO: 135, and the HVR-L3 of amino acid sequence SEQ ID NO: 146;

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 113, the HVR-H2 of amino acid sequence SEQ ID NO: 115, the HVR-H3 of amino acid sequence SEQ ID NO: 125, the HVR-L1 of amino acid sequence SEQ ID NO: 130, the HVR-L2 of amino acid sequence SEQ ID NO: 142, and the HVR-L3 of amino acid sequence SEQ ID NO: 150; or

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 114, the HVR-H2 of amino acid sequence SEQ ID NO: 115, the HVR-H3 of amino acid sequence SEQ ID NO: 122, the HVR-L1 of amino acid sequence SEQ ID NO: 127, the HVR-L2 of amino acid sequence SEQ ID NO: 143, and the HVR-L3 of amino acid sequence SEQ ID NO: 146.

[029] 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 according to Formula VII:

QVQLVQSGAEVKKPGX₁SVKX₂SCKAS (SEQ ID NO: 158), wherein X₁ is A or S, and X₂ is V or I;

VH FR2 comprises the sequence of SEQ ID NO: 5; VH FR3 comprises a sequence according to Formula VIII: $X_1AX_2X_3X_4X_5X_6RX_7TX_8TVDX_9X_{10}X_{11}STX_{12}YMELSSLRSED TAVYYCAR$ (SEQ ID NO: 159), wherein X_1 is Y or S, X_2 is Q or E, X_3 is K or D, X_4 is F or D, X_5 is Q, F, E, or T, X_6 is G, D, or H, X_7 is V or A, X_8 is M or L, X_9 is T, N, or Q, X_{10} is S or P, X_{11} is T or A, and X_{12} is V or A; and VH FR4 comprises a sequence according to Formula IX: $WGQGTLX_1TVSS$ (SEQ ID NO: 160), wherein X_1 is V or L; and/or the light chain 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 according to Formula X: $X_1IX_2X_3TQSPX_4SLX_5X_6SX_7GX_8RX_9TIX_{10}C$ (SEQ ID NO: 161), wherein X_1 is D or G, X_2 is Q or V, X_3 is M or L, X_4 is S or D, X_5 is S, P, or A, X_6 is A or V, X_7 is V or L, X_8 is D or E, X_9 is V or A, and X_{10} is T, N, or D; VL FR2 comprises a sequence according to Formula XI: $WYQQKPGX_1X_2PKLLIK$ (SEQ ID NO: 162), wherein X_1 is K or Q, and X_2 is A or P; VL FR3 comprises a sequence according to Formula XII: $GVPX_1RFGSGSGTDFLTISLQX_2EDX_3AX_4YYC$ (SEQ ID NO: 163), wherein X_1 is S or D, X_2 is P or A, X_3 is F, L, or V, and X_4 is T or V; and VL FR4 comprises a sequence according to Formula XIII: $FGQGTLKLEIX_1$ (SEQ ID NO: 164), wherein X_1 is K or E.

[030] 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: 2-4; VH FR2 comprises the sequence of SEQ ID NO: 5; VH FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 6-19; and VH FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 20-21; and/or the light chain 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: 22-26; VL FR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 27-28; VL FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 29-31; and VL FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 32-33. In some examples that may be combined with any of the preceding examples, the heavy chain variable region comprises a VH FR3 comprising a sequence selected from the group consisting of SEQ ID NOs: 12-15.

[031] 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 the group consisting of SEQ ID NOs: 38 and 40-72; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 86-101.

[031a] In another aspect, the present disclosure refers to a monoclonal 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: 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.

[032] In another aspect, the present disclosure refers to 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.

[033] 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 or Kabat 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 L243A, 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 L243A, 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; or the Fc region comprises an amino acid substitution at positions L243A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.

[034] In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises 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. In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises 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. In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises 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. In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises 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. In another example, the present disclosure relates to an antibody that binds to a 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. In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises 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. In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises 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. In another example, the present disclosure relates to an antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 183 and a light chain comprising the amino acid

[034a] In another aspect, the present disclosure refers to 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: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;
- (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:52 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:176, 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:197, 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:179, 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:200, 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:182, 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:203, and a light chain comprising the amino acid sequence of SEQ ID NO:185.

[034b] In another aspect, the present disclosure refers to 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:198, 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:201, 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:204, and a light chain comprising the amino acid sequence of SEQ ID NO:185.

[034c] In another aspect, the present disclosure refers to 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: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;

(b) 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;

(c) 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;

(d) a heavy chain comprising the amino acid sequence of SEQ ID NO:199, 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:181, 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:202, 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:184, 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:205, and a light chain comprising the amino acid sequence of SEQ ID NO:185.

[034d] In another aspect, the present disclosure refers to 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: 197 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: 198 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: 199 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: 200 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: 201 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: 202 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: 203 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: 204 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: 205 and a light chain comprising the amino acid sequence of SEQ ID NO: 185.

[035] 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 wild-type 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.

[036] 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.

[037] 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.

[038] 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 GGCCCC (G2C4) repeat-expansion RNA, and any combination thereof.

[039] 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 4-fold lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 34 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77; at least 1-fold lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40 and a light chain variable region comprising the amino acid sequence of

SEQ ID NO: 86; or at least 1-fold lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 52 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86, wherein the K_D is determined by surface plasmon resonance. 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.

[040] 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 150 pM, as measured by flow cytometry. In some examples, the antibody reduces cell surface levels of CD33 *in vitro* with an EC_{50} that is at least 50% lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 34 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77; at least 10% lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86; at least 10% lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 52 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86; or at least 10-fold lower than an anti-CD33 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 103 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 104, as measured by flow cytometry.

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

[041a] In another aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody as disclosed herein.

[042] 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.

[042a] In another aspect, the present disclosure refers to a vector comprising the nucleic acid as disclosed herein.

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

[043a] In another aspect, the present disclosure refers to an isolated host cell comprising the vector as disclosed herein.

[044] 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.

[044a] In another aspect, the present disclosure refers to a method of producing an antibody that binds to CD33, comprising culturing the cell as disclosed herein so that the antibody is produced.

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

[045a] In another aspect, 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 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 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 antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 9A to 9C and 10A to 10C).
2. The antibody of claim 1, wherein 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: 2-4;
 - VH FR2 comprises the sequence of SEQ ID NO: 5;
 - VH FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 6-19; and
 - VH FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 20-21; and/orthe light chain 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: 22-26;
 - VL FR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 27-28;
 - VL FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 29-31; and
 - VL FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 32-33.
3. The antibody of claim 1 or claim 2, wherein the antibody comprises
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 34, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 35, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 36, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 37, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;

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.

4. The antibody of claim 3, wherein the antibody comprises the heavy chain variable region and the light chain variable region of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 13 and 14).

5. The antibody of any one of claims 1-4, wherein:

- (a) 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);
- (b) the HVR-H1 comprises the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), the HVR-H2 comprises the amino acid sequence FIYPSNQITG (SEQ ID NO: 118), 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);
or
- (c) the HVR-H1 comprises the amino acid sequence GYTFTDYNLH (SEQ ID NO: 108), the HVR-H2 comprises the amino acid sequence FIYPSNGITG (SEQ ID NO: 115), the HVR-H3 comprises the amino acid sequence STVDYFDY (SEQ ID NO: 121), 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).

6. An antibody that binds to a CD33 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein:

- (a) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146);
 - (b) the heavy chain comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNQITG (SEQ ID NO: 118), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146); or
 - (c) the heavy chain comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 108), an HVR-H2 comprising the amino acid sequence FIYPSNGITG (SEQ ID NO: 115), and an HVR-H3 comprising the amino acid sequence STVDYFDY (SEQ ID NO: 121), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146).
7. 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: 34, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 35, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 36, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 37, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80;

8. The antibody of claim 7, wherein the antibody comprises the heavy chain variable region and the light chain variable region of antibody AB-14.1, AB-14.2, AB-14.3, AB-14.4, AB-14.5, AB-14.6, AB-14.7, AB-14.8, AB-14.9, AB-14.10, AB-14.11, AB-63.4, AB-63.5, AB-63.6, AB-63.7, AB-63.8, AB-63.9, AB-63.10, AB-63.11, AB-63.12, AB-63.13, AB-63.14, AB-63.15, AB-63.16, AB-63.17, AB-63.18, AB-64.1, AB-64.2, AB-64.3, AB-64.4, AB-64.5, AB-64.6, AB-64.7, AB-64.8, AB-64.1.1, AB-64.1.2, AB-64.1.3, AB-64.1.4, AB-64.1.5, AB-64.1.6, AB-64.1.7, AB-64.1.8, AB-64.1.9, AB-64.1.10, AB-64.1.11, AB-64.1.12, AB-64.1.13, AB-64.1.14, or AB-64.1.15 (as shown in Tables 13 and 14).
9. The antibody of claim 7 or claim 8, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 86.
10. The antibody of claim 7 or claim 8, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 65, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 86.
11. The antibody of claim 7 or claim 8, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 40, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 86.
12. 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: 34, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40, 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: 42, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;
 - a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 42, 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: 42, 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: 52, 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: 53, 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: 73, 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: 73, 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: 74, 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: 74, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 75, 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: 76, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86.

13. The antibody of claim 12, wherein the antibody comprises the heavy chain variable region and the light chain variable region of antibody AB-H2, AB-H9, AB-H14, AB-H15, AB-H63, AB-H64, AB-H65, or AB-H66 (as shown in Tables 13 and 14).

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

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 105, the HVR-H2 of amino acid sequence SEQ ID NO: 115, the HVR-H3 of amino acid sequence SEQ ID NO: 121, the HVR-L1 of amino acid sequence SEQ ID NO: 127, the HVR-L2 of amino acid sequence SEQ ID NO: 135, and the HVR-L3 of amino acid sequence SEQ ID NO: 146;

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 105, the HVR-H2 of amino acid sequence SEQ ID NO: 115, the HVR-H3 of amino acid sequence SEQ ID NO: 121, the HVR-L1 of amino acid sequence SEQ ID NO: 130, the HVR-L2 of amino acid sequence SEQ ID NO: 135, and the HVR-L3 of amino acid sequence SEQ ID NO: 146;

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 105, the HVR-H2 of amino acid sequence SEQ ID NO: 115, the HVR-H3 of amino acid sequence SEQ ID NO: 121, the HVR-L1 of amino acid sequence SEQ ID NO: 130, the HVR-L2 of amino acid sequence SEQ ID NO: 140, and the HVR-L3 of amino acid sequence SEQ ID NO: 147;

the antibody comprises the HVR-H1 of amino acid sequence SEQ ID NO: 105, the HVR-H2 of amino acid sequence SEQ ID NO: 117, the HVR-H3 of amino acid sequence SEQ ID NO: 122, the HVR-

L1 of amino acid sequence SEQ ID NO: 127, the HVR-L2 of amino acid sequence SEQ ID NO: 143, and the HVR-L3 of amino acid sequence SEQ ID NO: 146.

15. The antibody of claim 14, wherein 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: 2-4;

VH FR2 comprises the sequence of SEQ ID NO: 5;

VH FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 6-19; and

VH FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 20-21; and/or the light chain 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: 22-26;

VL FR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 27-28;

VL FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 29-31; and

VL FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 32-33.

16. A monoclonal 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: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 95;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40, 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: 41, 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: 42, 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: 42, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 87;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 42, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 88;

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 43, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 87;

17. 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.

18. The antibody of any one of claims 1-17, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

19. The antibody of claim 18, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

20. The antibody of claim 19, wherein the antibody has an IgG2 isotype.

21. The antibody of claim 19, 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.

22. The antibody of claim 19, 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.

23. The antibody of claim 22, 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;

- (a) the Fc region comprises an amino acid substitution at positions L243A, L235A, and P331A, wherein the numbering of the residue position is according to EU numbering;
- (b) the Fc region comprises an amino acid substitution at positions L243A, L235A, P331A, and E430G, wherein the numbering of the residue position is according to EU numbering;
- (c) 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;
- (d) 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;
- (e) 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;
- (f) 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;
- (g) 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;
- (h) the Fc region comprises an amino acid substitution at position E430G, wherein the numbering of the residue position is according to EU numbering;
- (i) 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;
- (j) 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;
- (k) the Fc region comprises an amino acid substitution at position C127S, wherein the numbering of the residue position is according to EU numbering;

(l) 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

(m) the Fc region comprises an amino acid substitution at positions L243A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.

24. 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: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;
- (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:52 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:176, 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:197, 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:179, 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:200, 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:182, 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:203, and a light chain comprising the amino acid sequence of SEQ ID NO:185.

25. 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:198, 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:201, 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:204, and a light chain comprising the amino acid sequence of SEQ ID NO:185.
26. 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: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;
 - (b) 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;

- (c) 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;
 - (d) a heavy chain comprising the amino acid sequence of SEQ ID NO:199, 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:181, 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:202, 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:184, 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:205, and a light chain comprising the amino acid sequence of SEQ ID NO:185.
27. The antibody of any one of claims 1-26, wherein the CD33 protein is a mammalian protein or a human protein.
28. The antibody of any one of claims 1-27, wherein the CD33 protein is a wild-type protein.
29. The antibody of any one of claims 1-27, wherein the CD33 protein is a naturally occurring variant.
30. The antibody of any one of claims 1-29, 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.
31. The antibody of any one of claims 1-30, wherein the antibody binds specifically to a human CD33 protein.
32. The antibody of any one of claims 1-31, wherein the antibody is an antibody fragment that binds to an epitope comprising amino acid residues on human CD33 or a mammalian CD33 protein.
33. The antibody of any one of claims 1-31, 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.

34. The antibody of claim 32 or claim 33, 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.
35. The antibody of any one of claims 32-34, wherein the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv, or scFv fragment.
36. The antibody of any one of claims 1-35, wherein the antibody is a humanized antibody, a bispecific antibody, a monoclonal antibody, a multivalent antibody, a conjugated antibody, or a chimeric antibody.
37. The antibody of any one of claims 1-36, wherein the antibody is a monoclonal antibody.
38. The antibody of any one of claims 1-36, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.
39. The antibody of claim 38, 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.

40. The antibody of any one of claims 1-39, 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.

41. The antibody of any one of claims 1-40, 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.

42. The antibody of any one of claims 1-41, wherein the antibody reduces cell surface levels of CD33.

43. The antibody of claim 42, wherein the CD33 is expressed on the surface of human dendritic cells.
44. The antibody of claim 42 or claim 43, wherein the antibody reduces cell surface levels of CD33 *in vitro*.
45. The antibody of any one of claims 42-44, wherein the antibody reduces cell surface levels of CD33 *in vitro* with a half maximal effective concentration (EC₅₀) that is less than 150 pM, as measured by flow cytometry.
46. 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: 197 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: 198 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: 199 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: 200 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: 201 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: 202 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: 203 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: 204 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: 205 and a light chain comprising the amino acid sequence of SEQ ID NO: 185.
47. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-46.
 48. A vector comprising the nucleic acid of claim 47.
 49. An isolated host cell comprising the vector of claim 48.
 50. A method of producing an antibody that binds to CD33, comprising culturing the cell of claim 49 so that the antibody is produced.
 51. The method of claim 50, further comprising recovering the antibody produced by the cell.
 52. An isolated antibody that binds to CD33 produced by the method of claim 50 or claim 51.
 53. A pharmaceutical composition comprising the antibody of any one of claims 1-46 and a pharmaceutically acceptable carrier.
 54. Use of a therapeutically effective amount of the antibody of any one of claims 1-46 in the manufacture of a medicament for preventing, reducing risk, or treating a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, taupathy disease, infections, and cancer, in an individual in need thereof.
 55. The use of claim 54, wherein the disease, disorder, or injury is cancer.
 56. The use of claim 54 or claim 55, 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.