

[0129] In certain embodiments, the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL). In certain embodiments, the MPN is selected from polycythaemia vera, essential thrombocythemia (ET), and myelofibrosis. In certain embodiments, the non-Hodgkin lymphoma is selected from B-cell lymphoma and T-cell lymphoma. In certain embodiments, the lymphoma is selected from chronic lymphocytic leukemia (CLL), lymphoblastic lymphoma (LPL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), primary mediastinal large B-cell lymphoma (PMBL), follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, plasma cell myeloma (PCM) or multiple myeloma (MM), mature T/NK neoplasms, and histiocytic neoplasms.

[0130] These and other aspects and advantages of the invention are illustrated by the following figures, detailed description and claims.

DESCRIPTION OF DRAWINGS

[0131] The invention can be more completely understood with reference to the following drawings.

[0132] **FIG. 1** shows a structural representation of the extracellular domain of human CD33 extracellular domain (ECD). CD33 ECD contains two prominent domains: distal V domain and membrane proximal C domain. Ligand binding interface is located on the V domain. Function of the C domain is unknown. ECD of CD33 is heavily glycosylated, with 2 N-linked glycosylation sites located in the V domain and 3 N-linked glycosylation sites located in the C domain. ECD of human CD33 contains several SNPs, with most prominent mutation R69G that is found in 42% patients. SNP R69G is in the V domain.

[0133] **FIG. 2** shows an alignment of the primary sequences of full length human and cyno CD33. V domain is marked by solid, and underlined in blue, C domain is marked by dashed underline underlined in green. Difference in sequences are framed ~~in red~~.

[0134] **FIGs. 3A-3K** show SPR profiles of Fab fragments from CD33 monoclonal antibodies binding to human CD33 ECD measured by Biacore at 37 °C. Each Fab fragment includes a CD33-binding clone described herein. FIG. 3A is a Biacore profile of ADI-10159; FIG. 3B is a Biacore profile of ADI-10177; FIG. 3C is a Biacore profile of ADI-11776; FIG. 3D is a Biacore profile of ADI-11801; FIG. 3E is a Biacore profile of ADI-11807; FIG. 3F is a Biacore profile of ADI-11809; FIG. 3G is a Biacore profile of ADI-11815; FIG. 3H is a Biacore profile of ADI-11819; FIG. 3I is a Biacore profile of ADI-11830; FIG. 3J is a

mutations: Fab1 targeting antigen 1 contains kappa LC, while second Fab targeting antigen 2 contains lambda LC. FIG. 30A is an exemplary representation of one form of a $\kappa\lambda$ -Body; FIG. 30B is an exemplary representation of another $\kappa\lambda$ -Body.

[0162] FIG. 31 is an Oasc-Fab heterodimeric construct that includes Fab binding to target 1 and scFab binding to target 2 fused to Fc. Heterodimerization is ensured by mutations in the Fc.

[0163] FIG. 32 is a DuetMab, which is an heterodimeric construct containing two different Fabs binding to antigens 1 and 2, and Fc stabilized by heterodimerization mutations. Fab 1 and 2 contain differential S-S bridges that ensure correct light chain (LC) and heavy chain (HC) pairing.

[0164] FIG. 33 is a CrossmAb, which is an heterodimeric construct with two different Fabs binding to targets 1 and 2 fused to Fc stabilized by heterodimerization. CL and CH1 domains and VH and VL domains are switched, *e.g.*, CH1 is fused in-line with VL, while CL is fused in-line with VH.

[0165] FIG. 34 is a Fit-Ig, which is a homodimeric constructs where Fab binding to antigen 2 is fused to the N terminus of HC of Fab that binds to antigen 1. The construct contains wild-type Fc.

[0166] FIG. 35 is a graph showing binding of A49-F3'-TriNKET-I07 and I07-F405L mAb to cell surface human NKG2D expressed on EL4 cells.

[0167] FIGs. 36A-36B are graphs showing binding of A49-F3'-TriNKET-I07 and I07-F405L mAb to CD33⁺ human AML cell lines Mv4-11 (FIG. 36A) and Molm-13 (FIG. 36B).

[0168] FIGs. 37A-37B are graphs showing internalization of A49-F3'-TriNKET-I07 and I07-F405L mAb after incubation with EOL-1 cells (FIG. 37A) and Molm-13 cells (FIG. 37B).

[0169] FIGs. 38A-38D are graphs showing specific lysis of Molm-13 (FIG. 38A), EOL-1 (FIG. 38B), and THP-1 (FIGs. 38C and 38D) human AML cells by rested human NK cells in the presence of A49-F3'-TriNKET-I07 and anti-CD33 monoclonal antibodies.

[0170] ~~FIG. 39~~FIGs.39A-39C ~~is~~are series of flow cytograms showing the expression levels of CD3, CD8(FIG.39A), NKG2D(FIG.39B), and CD16(FIG.39C) on isolated primary CD8⁺ T cells.

[0171] FIGs. 40A-40B are graphs showing specific lysis of Molm-13 cells by isolated primary CD8⁺ T cells in the presence of A49-F3'-TriNKET-I07, A49-F3'-TriNKET-H76, a non-target TriNKET, or I07-F405L mAb (denoted as I07 in the figures). The primary CD8⁺ T cells in FIG. 40A were isolated from PBMCs of donor 1, and the primary CD8⁺ T cells in

other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a Y349C substitution.

[0398] In certain embodiments of the present disclosure, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by Y349C substitution and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by S354C substitution.

[0399] In certain embodiments of the present disclosure, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by K360E and K409W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by Q347R, D399V and F405T substitutions.

[0400] In certain embodiments of the present disclosure, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a ~~Q347R~~Q347R, D399V and F405T substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by K360E and K409W substitutions.

[0401] In certain embodiments of the present disclosure, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T366W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T366S, T368A and Y407V substitutions.

[0402] In certain embodiments of the present disclosure, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T366S, T368A and Y407V substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a T366W substitution.

[0403] In certain embodiments of the present disclosure, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, L351Y, F405A and Y407V substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, T366L, K392L and T394W substitutions.

[0632] THP-1 cells express FcγRI, which can bind to IgG1 Fc at high affinity. The competition for Fc binding by target cells can further reduce NK cell killing. Therefore, as shown in FIGs. 38C and 38D, when THP-1 cells were incubated with CD16^{F/F} NK cells in the presence of I07-F405L or lintuzumab-GA mAb, no specific lysis of THP-1 cells was observed. Even I07-DE, an ADCC-enhancing variant of I07, failed to elicit NK cell cytotoxicity. Among the monoclonal antibodies tested, only 280-31-01(mut)-DE, an ADCC-enhancing variant of antibody clone 280-31-01 (mut) disclosed in WO2012045752, exhibited cell killing activity at high concentrations. Remarkably, A49-F3'-TriNKET-I07 mediated more potent NK cell killing with a higher specific lysis of THP-1 cells, likely due to its additional ability to engage NK cells by NKG2D binding.

Example 12: Activation of primary CD8⁺ T cells by TriNKET

[0633] NKG2D is expressed on NK cells and many T cells, including CD8⁺ T cells. The ability of A49-F3'-TriNKET-I07 to elicit cytotoxicity of primary CD8⁺ T cells against human AML cells was assessed using the DELFIA cytotoxicity assay.

[0634] Briefly, human peripheral blood mononuclear cells (PBMCs) were isolated from human peripheral blood buffy coats using density gradient centrifugation. The isolated PBMCs were stimulated with 1 μg/mL Concanavalin A (ConA) at 37 °C for 18 hours. Then ConA was removed, and the PBMCs were cultured with 25 unit/mL IL-2 at 37 °C for 4 days. CD8⁺ T cells were purified using a negative selection technique with magnetic beads, then cultured in media containing 10 ng/mL IL-15 at 37 °C for 7-13 days.

[0635] The primary human effector CD8⁺ T cells generated above were characterized for cell markers. The cells were stained with fluorophore-conjugated antibodies against CD3, CD8, NKG2D, and CD16, and analyzed by flow cytometry. As shown in ~~FIG. 39~~FIGs. 39A-39C, the isolated CD8⁺ T cells had high purity, as more than 99% of them were positive of CD3, CD8(FIG.39A), and NKG2D expression(FIG.39B), and were negative of CD16 expression (FIG.39C).

[0636] To assess the ability of A49-F3'-TriNKET-I07 to elicit cytotoxicity of primary CD8⁺ T cells, Molm-13 cells were harvested from culture, washed, and resuspended in growth media at 10⁶ cells/mL. The cells were labeled with BATDA reagent (Perkin Elmer AD0116) following manufacturer instructions. After labeling, the cells were washed three times with HBS, and were resuspended at 0.5×10⁵ cells/mL in culture media. 100 μl of BATDA labeled cells were added to each well of a 96-well plate. 50 μl of serially diluted monoclonal antibody or TriNKET was added to each well.

WHAT IS CLAIMED IS:

1. An antigen-binding site comprising:

- (i) a heavy chain variable domain (VH) complementarity-determining region 1 (CDR1) sequence identical to the amino acid sequence of SEQ ID NO:45 or SEQ ID NO:181, a VH complementarity-determining region 2 (CDR2) sequence identical to the amino acid sequence of SEQ ID NO:46, a VH complementarity-determining region 3 (CDR3) sequence identical to the amino acid sequence of SEQ ID NO:47 or SEQ ID NO:182, a light chain variable domain (VL) CDR1 sequence identical to the amino acid sequence of SEQ ID NO:48, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:49, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:50;
- (ii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:21 or SEQ ID NO:434, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:22, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:23 or SEQ ID NO:435, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:24, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:25, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:26;
- (iii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:27 or SEQ ID NO:181, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:28, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:29 or SEQ ID NO:436, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:30, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:31, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:32;
- (iv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:33 or SEQ ID NO:183, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:34, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:35, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:36, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:37, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:38;
- (v) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:39 or SEQ ID NO:437, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:40, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:438; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:42, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:43, and a VL CDR3

sequence identical to the amino acid sequence of SEQ ID NO:44;

(vi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:51 or SEQ ID NO:181, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:52, and a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:53 or SEQ ID NO:439, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:54, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:55, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:56;

(vii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:63 or SEQ ID NO:442, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:64, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:65 or SEQ ID NO:443, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:66, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:67, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:68;

(viii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:69 or SEQ ID NO:181, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:70, and a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:71 or SEQ ID NO:444, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:72, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:73, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:74;

(ix) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:75 or SEQ ID NO:445, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:76, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:77 or SEQ ID NO:446; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:78, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:79, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:80;

(x) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:528 or SEQ ID NO:304, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:305, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:529 or SEQ ID NO:306; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:307, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:308, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:309;

(xi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:530 or SEQ ID NO:310, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:311, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:531 or

SEQ ID NO:312; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:313, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:314, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:315;

(xii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:532 or SEQ ID NO:316, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:317, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:533 or SEQ ID NO:318, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:319, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:320, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:321;

(xiii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:534 or SEQ ID NO:322, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:323, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:535 or SEQ ID NO:324, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:325, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:326, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:327;

(xiv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:536 or SEQ ID NO:328, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:329, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:537 or SEQ ID NO:330, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:331, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:332, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:333;

(xv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:538 or SEQ ID NO:334, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:335, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:539 or SEQ ID NO:336, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:337, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:338, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:339;

(xvi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:542 or SEQ ID NO:346, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:347, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:543 or SEQ ID NO:348, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:349, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:350, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:351;

(xvii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:364 or

SEQ ID NO:548, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:365, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:366 or SEQ ID NO:549, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:367, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:368, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:369;

(xviii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:552 or SEQ ID NO:376, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:377, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:553 or SEQ ID NO:378, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:379, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:380, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:381;

(xix) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:554 or SEQ ID NO:382, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:383, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:555 or SEQ ID NO:384, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:385, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:386, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:387;

(xx) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:556 or SEQ ID NO:388, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:389, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:557 or SEQ ID NO:390, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:391, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:392, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:393;

(xxi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:558 or SEQ ID NO:394, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:395, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:559 or SEQ ID NO:396, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:397, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:398, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:399;

(xxii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:560 or SEQ ID NO:400, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:401, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:561 or SEQ ID NO:402, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:403, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:404, and

a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:405;
 (xxiii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:562 or SEQ ID NO:406, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:407, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:563 or SEQ ID NO:408, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:409, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:410, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:411; or
 (xxiv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:564 or SEQ ID NO:412, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:413, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:565 or SEQ ID NO:414, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:415, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:416, and a VLCDR3 sequence identical to the amino acid sequence of SEQ ID NO:417.

~~42. An antibody~~ The antigen-binding site according to claim 1, wherein the heavy chain variable domain comprising comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:9, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:266, SEQ ID NO:268, SEQ ID NO:270, SEQ ID NO:272, SEQ ID NO:274, SEQ ID NO:276, SEQ ID NO:278, SEQ ID NO:280, SEQ ID NO:282, SEQ ID NO:284, SEQ ID NO:286, SEQ ID NO:288, SEQ ID NO:290, SEQ ID NO:292, SEQ ID NO:294, SEQ ID NO:296, SEQ ID NO:298, SEQ ID NO:300, or SEQ ID NO:302.

~~2. An antibody heavy chain variable domain comprising:~~

- ~~(i) a complementarity determining region 1 (CDR1) sequence identical to the amino acid sequence of SEQ ID NO:45; a complementarity determining region 2 (CDR2) sequence identical to the amino acid sequence of SEQ ID NO:46; and a complementarity determining region 3 (CDR3) sequence identical to the amino acid sequence of SEQ ID NO:47;~~
- ~~(ii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:21; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:22; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:23;~~
- ~~(iii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:27; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:28; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:29;~~

- (iv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:33; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:34; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:35;
- (v) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:39; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:40; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:41;
- (vi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:51; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:52; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:53;
- (vii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:57; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:58; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:59;
- (viii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:63; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:64; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:65;
- (ix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:69; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:70; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:71;
- (x) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:75; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:76; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:77;
- (xi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:528; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:305; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:529;
- (xii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:530; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:311; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:531;
- (xiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:532; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:317; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:533;
- (xiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:534; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:323; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:535;
- (xv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:536; a CDR2

sequence identical to the amino acid sequence of SEQ ID NO:329; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:537;

(xvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:538; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:335; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:539;

(xvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:540; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:341; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:541;

(xviii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:542; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:347; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:543;

(xix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:544; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:353; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:545;

(xx) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:546; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:359; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:547;

(xxi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:548; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:365; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:549;

(xxii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:550; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:371; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:551;

(xxiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:552; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:377; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:553;

(xxiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:554; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:383; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:555;

(xxv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:556; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:389; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:557;

(xxvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:558; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:395; and a CDR3 sequence

identical to the amino acid sequence of SEQ ID NO:559;
 (xxvii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:560; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:401; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:561;
 (xxviii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:562; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:407; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:563; or
 (xxix) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:564; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:413; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:565.

3. ~~An~~ The antigen-binding site ~~comprising the antibody heavy chain variable domain according to claim 1 or 2, and an antibody wherein the light chain variable domain comprising~~ comprises an amino acid sequence at least 90% identical to SEQ ID NO:10, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:267, SEQ ID NO:269, SEQ ID NO:271, SEQ ID NO:273, SEQ ID NO:275, SEQ ID NO:277, SEQ ID NO:279, SEQ ID NO:281, SEQ ID NO:283, SEQ ID NO:285, SEQ ID NO:287, SEQ ID NO:289, SEQ ID NO:291, SEQ ID NO:293, SEQ ID NO:295, SEQ ID NO:297, SEQ ID NO:299, SEQ ID NO:301, or SEQ ID NO:303.

4. ~~An antigen-binding site comprising the antibody heavy chain variable domain according to claim 1 or 2, and an antibody light chain variable domain comprising:~~

- (i) ~~— a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:48, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:49, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:50;~~
- (ii) ~~— a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:24, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:25, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:26;~~
- (iii) ~~— a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:30, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:31, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:32;~~
- (iv) ~~— a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:36, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:37, and a CDR3 sequence~~

identical to the amino acid sequence of SEQ ID NO:38;

(v) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:42, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:43, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:44;

(vi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:54, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:55, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:56;

(vii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:60, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:61, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:62;

(viii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:66, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:67, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:68;

(ix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:72, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:73, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:74;

(x) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:78, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:79, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:80;

(xi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:307, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:308, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:309;

(xii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:313, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:314, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:315;

(xiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:319, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:320, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:321;

(xiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:325, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:326, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:327;

(xv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:331, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:332, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:333;

(xvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:337, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:338, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:339;

(xvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:343, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:344, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:345;

(xviii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:349, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:350, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:351;

(xix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:355, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:356, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:357;

(xx) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:361, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:362, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:363;

(xxi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:367, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:368, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:369;

(xxii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:373, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:374, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:375;

(xxiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:379, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:380, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:381;

(xxiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:385, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:386, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:387;

(xxv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:391, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:392, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:393;

(xxvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:397, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:398, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:399;

(xxvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:403, a CDR2

~~sequence identical to the amino acid sequence of SEQ ID NO:404, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:405;~~

~~(xxviii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:409, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:410, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:411; or~~

~~(xxix) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:415, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:416, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:417.~~

54. A protein comprising the antigen-binding site according to ~~claim 3 or 4~~ any one of claims 1 to 3, wherein the antigen-binding site binds to human CD33.

65. ~~A protein comprising an antigen-binding site that binds to human CD33, wherein the antigen-binding site comprises the antibody heavy chain variable domain according to claim 1 or 2~~ The protein according to claim 5, and wherein the protein further comprises a second antigen binding site the same or different from the antigen-binding site that binds to human CD33.

76. A protein capable of specifically binding to CD33, wherein the protein comprises an antigen-binding site comprising

(i) a heavy chain variable domain (VH) complementarity-determining region 1 (CDR1) sequence identical to the amino acid sequence of SEQ ID NO:45 or SEQ ID NO:181, a VH complementarity-determining region 2 (CDR2) sequence identical to the amino acid sequence of SEQ ID NO:46, a VH complementarity-determining region 3 (CDR3) sequence identical to the amino acid sequence of SEQ ID NO:47 or SEQ ID NO:182, a light chain variable domain (VL) CDR1 sequence identical to the amino acid sequence of SEQ ID NO:48, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:49, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:50;

(ii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:21 or SEQ ID NO:434, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:22, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:23 or SEQ ID NO:435, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:24, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:25, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:26;

(iii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:27 or

SEQ ID NO:181, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:28, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:29 or SEQ ID NO:436, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:30, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:31, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:32;

(iv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:33 or SEQ ID NO:183, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:34, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:35, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:36, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:37, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:38;

(v) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:39 or SEQ ID NO:437, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:40, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:438; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:42, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:43, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:44;

(vi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:51 or SEQ ID NO:181, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:52, and a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:53 or SEQ ID NO:439, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:54, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:55, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:56;

(vii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:63 or SEQ ID NO:442, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:64, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:65 or SEQ ID NO:443, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:66, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:67, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:68;

(viii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:69 or SEQ ID NO:181, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:70, and a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:71 or SEQ ID NO:444, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:72, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:73, and a

VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:74;

(ix) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:75 or SEQ ID NO:445, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:76, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:77 or SEQ ID NO:446; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:78, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:79, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:80;

(x) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:528 or SEQ ID NO:304, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:305, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:529 or SEQ ID NO:306; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:307, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:308, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:309;

(xi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:530 or SEQ ID NO:310, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:311, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:531 or SEQ ID NO:312; a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:313, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:314, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:315;

(xii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:532 or SEQ ID NO:316, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:317, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:533 or SEQ ID NO:318, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:319, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:320, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:321;

(xiii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:534 or SEQ ID NO:322, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:323, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:535 or SEQ ID NO:324, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:325, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:326, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:327;

(xiv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:536 or SEQ ID NO:328, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:329, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:537 or

SEQ ID NO:330, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:331, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:332, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:333;

(xv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:538 or SEQ ID NO:334, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:335, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:539 or SEQ ID NO:336, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:337, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:338, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:339;

(xvi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:542 or SEQ ID NO:346, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:347, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:543 or SEQ ID NO:348, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:349, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:350, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:351;

(xvii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:364 or SEQ ID NO:548, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:365, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:366 or SEQ ID NO:549, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:367, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:368, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:369;

(xviii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:552 or SEQ ID NO:376, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:377, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:553 or SEQ ID NO:378, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:379, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:380, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:381;

(xix) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:554 or SEQ ID NO:382, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:383, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:555 or SEQ ID NO:384, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:385, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:386, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:387;

(xx) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:556 or

SEQ ID NO:388, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:389, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:557 or SEQ ID NO:390, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:391, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:392, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:393;

(xxi) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:558 or SEQ ID NO:394, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:395, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:559 or SEQ ID NO:396, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:397, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:398, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:399;

(xxii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:560 or SEQ ID NO:400, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:401, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:561 or SEQ ID NO:402, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:403, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:404, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:405;

(xxiii) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:562 or SEQ ID NO:406, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:407, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:563 or SEQ ID NO:408, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:409, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:410, and a VL CDR3 sequence identical to the amino acid sequence of SEQ ID NO:411; or

(xxiv) a VH CDR1 sequence identical to the amino acid sequence of SEQ ID NO:564 or SEQ ID NO:412, a VH CDR2 sequence identical to the amino acid sequence of SEQ ID NO:413, a VH CDR3 sequence identical to the amino acid sequence of SEQ ID NO:565 or SEQ ID NO:414, a VL CDR1 sequence identical to the amino acid sequence of SEQ ID NO:415, a VL CDR2 sequence identical to the amino acid sequence of SEQ ID NO:416, and a VLCDR3 sequence identical to the amino acid sequence of SEQ ID NO:417

~~an antibody heavy chain variable domain and an antibody light chain variable domain, wherein the antibody heavy chain viable domain comprises~~

~~(i) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:45; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:46; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:47;~~

- (ii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:21; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:22; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:23;
- (iii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:27; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:28; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:29;
- (iv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:33; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:34; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:35;
- (v) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:39; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:40; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:41;
- (vi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:51; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:52; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:53;
- (vii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:57; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:58; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:59;
- (viii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:63; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:64; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:65;
- (ix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:69; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:70; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:71;
- (x) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:75; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:76; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:77;
- (xi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:528; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:305; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:529;
- (xii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:530; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:311; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:531;
- (xiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:532; a CDR2

sequence identical to the amino acid sequence of SEQ ID NO:317; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:533;

(xiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:534; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:323; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:535;

(xv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:536; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:329; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:537;

(xvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:538; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:335; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:539;

(xvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:540; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:341; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:541;

(xviii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:542; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:347; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:543;

(xix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:544; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:353; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:545;

(xx) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:546; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:359; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:547;

(xxi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:548; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:365; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:549;

(xxii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:550; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:371; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:551;

(xxiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:552; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:377; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:553;

(xxiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:554; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:383; and a CDR3 sequence

identical to the amino acid sequence of SEQ ID NO:555;

(xxv) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:556; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:389; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:557;~~

(xxvi) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:558; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:395; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:559;~~

(xxvii) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:560; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:401; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:561;~~

(xxviii) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:562; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:407; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:563; or~~

(xxix) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:564; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:413; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:565, and~~

wherein the antibody light chain variable domain comprises:

(i) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:48, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:49, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:50;~~

(ii) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:24, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:25, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:26;~~

(iii) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:30, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:31, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:32;~~

(iv) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:36, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:37, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:38;~~

(v) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:42, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:43, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:44;~~

(vi) ~~a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:54, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:55, and a CDR3 sequence~~

identical to the amino acid sequence of SEQ ID NO:56;

(vii)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:60, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:61, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:62;

(viii)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:66, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:67, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:68;

(ix)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:72, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:73, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:74;

(x)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:78, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:79, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:80;

(xi)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:307, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:308, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:309;

(xii)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:313, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:314, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:315;

(xiii)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:319, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:320, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:321;

(xiv)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:325, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:326, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:327;

(xv)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:331, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:332, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:333;

(xvi)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:337, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:338, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:339;

(xvii)——a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:343, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:344, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:345;

(xviii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:349, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:350, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:351;

(xix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:355, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:356, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:357;

(xx) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:361, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:362, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:363;

(xxi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:367, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:368, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:369;

(xxii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:373, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:374, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:375;

(xxiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:379, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:380, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:381;

(xxiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:385, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:386, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:387;

(xxv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:391, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:392, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:393;

(xxvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:397, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:398, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:399;

(xxvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:403, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:404, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:405;

(xxviii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:409, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:410, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:411; or

(xxix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:415, a CDR2

sequence identical to the amino acid sequence of SEQ ID NO:416, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:417.

8. —A protein capable of specifically binding to CD33, wherein the protein comprises an antigen-binding site comprising an antibody heavy chain variable domain and an antibody light chain variable domain, wherein the antibody heavy chain viable domain comprises
- (i) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:181; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:46; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:182;
 - (ii) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:434; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:22; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:435;
 - (iii) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:181; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:28; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:436;
 - (iv) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:183; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:34; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:184;
 - (v) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:437; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:40; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:438;
 - (vi) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:181; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:52; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:439;
 - (vii) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:440; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:58; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:441;
 - (viii) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:442; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:64; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:443;
 - (ix) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:181; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:70; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:444;
 - (x) —a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:445; a CDR2

sequence identical to the amino acid sequence of SEQ ID NO:76; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:446;

(xi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:304; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:305; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:306;

(xii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:310; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:311; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:312;

(xiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:316; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:317; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:318;

(xiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:322; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:323; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:324;

(xv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:328; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:329; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:330;

(xvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:334; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:335; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:336;

(xvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:340; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:341; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:342;

(xviii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:346; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:347; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:348;

(xix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:352; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:353; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:354;

(xx) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:358; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:359; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:360;

(xxi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:364; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:365; and a CDR3 sequence

identical to the amino acid sequence of SEQ ID NO:366;

~~(xxii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:370; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:371; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:372;~~

~~(xxiii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:376; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:377; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:378;~~

~~(xxiv) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:382; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:383; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:384;~~

~~(xxv) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:388; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:389; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:390;~~

~~(xxvi) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:394; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:395; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:396;~~

~~(xxvii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:400; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:401; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:402;~~

~~(xxviii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:406; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:407; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:408; or~~

~~(xxix) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:412; a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:413; and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:414, and~~

wherein the antibody light chain variable domain comprises:

~~(i) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:48, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:49, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:50;~~

~~(ii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:24, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:25, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:26;~~

~~(iii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:30, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:31, and a CDR3 sequence~~

identical to the amino acid sequence of SEQ ID NO:32;

(iv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:36, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:37, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:38;

(v) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:42, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:43, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:44;

(vi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:54, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:55, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:56;

(vii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:60, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:61, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:62;

(viii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:66, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:67, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:68;

(ix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:72, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:73, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:74;

(x) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:78, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:79, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:80;

(xi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:307, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:308, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:309;

(xii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:313, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:314, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:315;

(xiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:319, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:320, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:321;

(xiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:325, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:326, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:327;

- (xv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:331, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:332, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:333;
- (xvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:337, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:338, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:339;
- (xvii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:343, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:344, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:345;
- (xviii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:349, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:350, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:351;
- (xix) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:355, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:356, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:357;
- (xx) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:361, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:362, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:363;
- (xxi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:367, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:368, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:369;
- (xxii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:373, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:374, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:375;
- (xxiii) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:379, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:380, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:381;
- (xxiv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:385, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:386, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:387;
- (xxv) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:391, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:392, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:393;
- (xxvi) — a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:397, a CDR2

~~sequence identical to the amino acid sequence of SEQ ID NO:398, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:399;~~

~~(xxvii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:403, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:404, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:405;~~

~~(xxviii) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:409, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:410, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:411; or~~

~~(xxix) a CDR1 sequence identical to the amino acid sequence of SEQ ID NO:415, a CDR2 sequence identical to the amino acid sequence of SEQ ID NO:416, and a CDR3 sequence identical to the amino acid sequence of SEQ ID NO:417.~~

97. The protein of any one of claims 54 to 86, further comprising an antibody constant region, optionally wherein the antibody constant region is capable of binding to CD16 and comprises two polypeptide chains, each of which comprises a hinge, CH2 and CH3 domain.

108. The protein of claim 97, wherein each of the two polypeptide chains of the antibody constant region comprises amino acid sequence at least 90% identical to human IgG1 constant region, and optionally wherein the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, K392, T394, D399, S400, D401, F405, Y407, K409, T411 and K439; and the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Q347, Y349, L351, S354, E356, E357, S364, T366, L368, K370, N390, K392, T394, D399, D401, F405, Y407, K409, T411 and K439.

119. The protein of claim 97, wherein

(i) the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by an S354C substitution and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a Y349C substitution;

(ii) the amino acid sequence of one polypeptide chain of the antibody constant region

differs from the amino acid sequence of an IgG1 constant region by K360E and K409W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by Q347R, D399V and F405T substitutions;

(iii) the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a T366W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T366S, T368A, and Y407V substitutions; or

(iv) the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, L351Y, F405A, and Y407V substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, T366L, K392L, and T394W substitutions.

~~12. A protein comprising an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody comprising an antibody heavy chain variable domain and an antibody light chain variable domain having the amino acid sequences of SEQ ID NOs: 1 and 2; 3 and 4; 5 and 6; 7 and 8; 9 and 10; 11 and 12; 13 and 14; 15 and 16; 17 and 18; 19 and 20; 266 and 267; 268 and 269; 270 and 271; 272 and 273; 274 and 275; 276 and 277; 278 and 279; 280 and 281; 282 and 283; 284 and 285; 286 and 287; 288 and 289; 290 and 291; 292 and 293; 294 and 295; 296 and 297; 298 and 299; 300 and 301; or 302 and 303, respectively.~~

~~13~~10. A formulation comprising a protein of any one of claims ~~5-12~~4-9, and a pharmaceutically acceptable carrier.

~~14~~11. An isolated nucleic acid encoding a chimeric antigen receptor (CAR), wherein the nucleic acid comprises a nucleic acid sequence that encodes a CD33-binding scFv comprising a sequence at least 90%, at least 95%, or at least 99% identical to an amino acid sequence selected from SEQ ID NOs: 188, 198, ~~206-223, and 447-484~~206-215, 218-223, 447-458, 461-462, 467-468, and 471-484; a nucleic acid sequence encoding a transmembrane domain; and a nucleic acid sequence encoding an intracellular signaling domain.

~~15~~12. An expression vector comprising the isolated nucleic acid of claim ~~14~~11.

~~16~~13. A chimeric antigen receptor (CAR), wherein the CAR comprises a CD33-binding scFv comprising amino acid sequence at least 90% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, ~~206-223, and 447-484~~206-215, 218-223, 447-458, 461-462, 467-468, and 471-484; a transmembrane domain; and an intracellular signaling domain.

~~17~~14. An immune effector cell comprising the isolated nucleic acid of claim ~~14~~11.

~~18~~15. An immune effector cell expressing the CAR of claim ~~16~~13.

~~19~~16. A CD33/CD3-directed bispecific T-cell engager comprising a protein comprising a sequence at least 90%, at least 95%, or at least 99% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, ~~206-223, and 447-484~~206-215, 218-223, 447-458, 461-462, 467-468, and 471-484.

~~20~~17. An isolated nucleic acid encoding the CD33/CD3-directed bispecific T-cell engager of claim ~~19~~16.

~~21~~18. An antibody-drug conjugate comprising a protein comprising a sequence at least 90%, at least 95%, or at least 99% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, ~~206-223, and 447-484~~206-215, 218-223, 447-458, 461-462, 467-468, and 471-484.

~~22~~19. An immunocytokine comprising a sequence at least 90%, at least 95%, or at least 99% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, ~~206-223, and 447-484~~206-215, 218-223, 447-458, 461-462, 467-468, and 471-484 connected to a cytokine.

~~23~~20. An isolated nucleic acid encoding an immunocytokine of claim ~~22~~19.

~~24~~21. Use of the protein according to any one of claims ~~5-12~~4-9, the formulation according to claim ~~13~~10, the immune effector cell according to any one of claims ~~17-18~~14-15, the CD33/CD3-directed bispecific T-cell engager according to claim ~~19~~16, the antibody-drug conjugate according to claim ~~21~~18, or the immunocytokine according to claim ~~22~~19 in the manufacture of a medicament for treating a CD33-expressing cancer.

~~25~~22. The use of claim ~~24~~21, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic lymphocytic leukemia (CML), myeloid blast crisis of CML, acute lymphoblastic leukemia (ALL), acute

lymphoblastic lymphoma, myeloproliferative neoplasms (MPNs), lymphoma, non-Hodgkin lymphomas, and classical Hodgkin lymphoma.

~~26~~23. The use of claim ~~25~~22, wherein the AML is selected from undifferentiated acute myeloblastic leukemia, acute myeloblastic leukemia with minimal maturation, acute myeloblastic leukemia with maturation, acute promyelocytic leukemia (APL), acute myelomonocytic leukemia, acute myelomonocytic leukemia with eosinophilia, acute monocytic leukemia, acute erythroid leukemia, acute megakaryoblastic leukemia (AMKL), acute basophilic leukemia, acute panmyelosis with fibrosis, and blastic plasmacytoid dendritic cell neoplasm (BPDCN).

~~27~~24. The use of claim ~~25~~22 or ~~26~~23, wherein the AML is characterized by expression of CLL-1 on the AML leukemia stem cells (LSCs).

~~28~~25. The use of claim ~~27~~24, wherein the LSCs further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96.

~~29~~26. The use of any one of claims ~~25-28~~22-25, wherein the AML is a minimal residual disease (MRD).

~~30~~27. The use of claim ~~29~~26, wherein the MRD is characterized by the presence or absence of a mutation selected from FLT3-ITD ((Fms-like tyrosine kinase 3)-internal tandem duplications (ITD)), NPM1 (Nucleophosmin 1), DNMT3A (DNA methyltransferase gene DNMT3A), and IDH (Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2)).

~~34~~28. The use of claim ~~25~~22, wherein the MDS is selected from MDS with multilineage dysplasia (MDS-MLD), MDS with single lineage dysplasia (MDS-SLD), MDS with ring sideroblasts (MDS-RS), MDS with excess blasts (MDS-EB), MDS with isolated del(5q), and MDS, unclassified (MDS-U).

~~32~~29. The use of claim ~~25~~22 or ~~34~~28, wherein the MDS is a primary MDS or a secondary MDS.

~~33~~30. The ~~method~~ use of claim ~~25~~22, wherein the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL).

~~34~~31. The use of claim ~~25~~22, wherein the MPN is selected from polycythaemia vera,

essential thrombocythemia (ET), and myelofibrosis.

~~35~~32. The use of claim ~~25~~22, wherein the non-Hodgkin lymphoma is selected from B-cell lymphoma and T-cell lymphoma.

~~36~~33. The use of claim ~~25~~22, wherein the lymphoma is selected from chronic lymphocytic leukemia (CLL), lymphoblastic lymphoma (LPL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), primary mediastinal large B-cell lymphoma (PMBL), follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, plasma cell myeloma (PCM) or multiple myeloma (MM), mature T/NK neoplasms, and histiocytic neoplasms.

~~37~~34. The protein according to any one of claims ~~5-12~~4-9, the formulation according to claim ~~13~~11, the immune effector cell according to any one of claims ~~17-18~~14-15, the CD33/CD3-directed bispecific T-cell engager according to claim ~~19~~16, the antibody-drug conjugate according to claim ~~21~~18, or the immunocytokine according to claim ~~22~~in the manufacture of a medicament for treating a CD33-expressing cancer19 for use in therapy.