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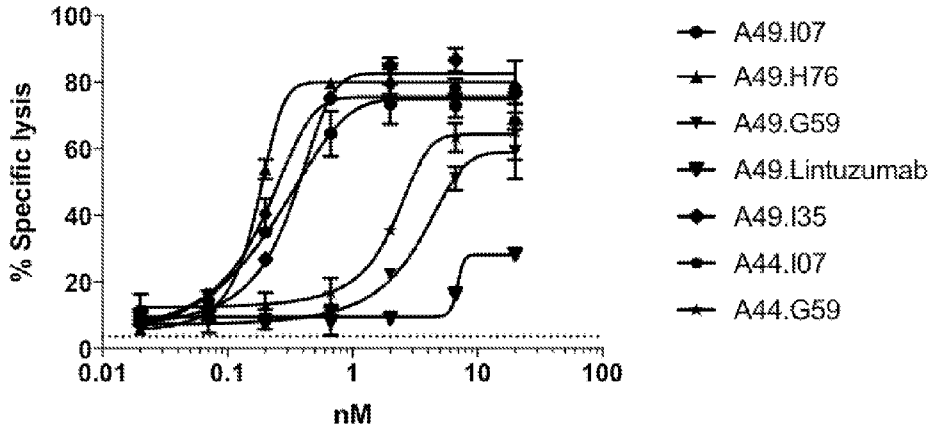
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(54) **Title:** MULTI-SPECIFIC BINDING PROTEINS THAT BIND CD33, NKG2D, AND CD16, AND METHODS OF USE

FIG. 15A



(57) **Abstract:** Multi-specific binding proteins that bind to and kill human cancer cells expressing CD33 (Siglec-3) are described, as well as pharmaceutical compositions and therapeutic methods useful for the treatment of CD33 expressing cancer. The invention relates to multi - specific binding proteins that bind to human cancer cells expressing CD33, and exhibit high potency and maximum lysis of target cells compared to anti-CD33 monoclonal antibodies.

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MULTI-SPECIFIC BINDING PROTEINS THAT BIND CD33, NKG2D, AND CD16, AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/632,756, filed February 20, 2018, the disclosure of which is hereby incorporated by reference in its entirety for all purposes; and U.S. Provisional Patent Application No. 62/677,137, filed May 28, 2018.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 20, 2019, is named DFY_070WO_SL25.txt and is 571,170 bytes in size.

FIELD OF THE INVENTION

[0003] The invention relates to multi-specific binding proteins that bind to CD33 (Siglec-3), and exhibit high potency and maximum lysis of target cells compared to anti-CD33 monoclonal antibodies.

BACKGROUND

[0004] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Some of the most frequently diagnosed cancers in adults include prostate cancer, breast cancer, and lung cancer. Hematological malignancies, though less frequent than solid cancers, have low survival rates. Current treatment options for these cancers are not effective for all patients and/or can have substantial adverse side effects. Other types of cancer also remain challenging to treat using existing therapeutic options.

[0005] Cancer immunotherapies are desirable because they are highly specific and can facilitate destruction of cancer cells using the patient's own immune system. Fusion proteins such as bi-specific T-cell engagers are cancer immunotherapies described in the literature that bind to tumor cells and T-cells to facilitate destruction of tumor cells. T cells are major effectors of the adaptive immune system that attack foreign cells as well as host cells that present mutant or mis-expressed peptides. Cells targeted by T cells may be virally-infected,

such that they express foreign proteins, or malignant, where they might express mutant proteins. T cells recognize target cells via their T cell receptor (TCR) engaging intracellular peptides presented by major histocompatibility complex proteins on target cells. Individual T cells typically recognize target cells bearing specific MHC-peptide complexes, but novel agents have been developed that usurp and amplify this natural process for therapeutic benefit. Bi-specific T cell engagers link antigen binding site(s) of tumor-associated antigens to antigen binding site(s) of components of the TCR complex to redirect T cell activity towards desired target cells independent of native peptide-MHC recognition. For example, Blincyto is an FDA-approved T cell engager that targets CD19 on malignant B cells.

[0006] T cells can also be engineered to express chimeric antigen receptors (CAR) that endow it with target recognition capabilities of its CAR. CARs contain antigen binding site(s) to tumor associated antigens linked to T cell activation domains. These CAR-T cells can also be employed to target malignant cells, and some have been FDA-approved for use against B cell malignancies.

[0007] Antibodies that bind to certain tumor-associated antigens and to certain immune cells have been described in the literature. *See, e.g.*, WO 2016/134371 and WO 2015/095412. Antibody-drug conjugates or immunocytokines using antigen binding sites targeting tumor associated antigens to deliver toxic agents or immune-modulatory cytokines to specific target cells.

[0008] Natural killer (NK) cells are a component of the innate immune system and make up approximately 15% of circulating lymphocytes. NK cells infiltrate virtually all tissues and were originally characterized by their ability to kill tumor cells effectively without the need for prior sensitization. Activated NK cells kill target cells by means similar to cytotoxic T cells – *i.e.*, via cytolytic granules that contain perforin and granzymes as well as via death receptor pathways. Activated NK cells also secrete inflammatory cytokines such as IFN-gamma and chemokines that promote the recruitment of other leukocytes to the target tissue.

[0009] NK cells respond to signals through a variety of activating and inhibitory receptors on their surface. For example, when NK cells encounter healthy self-cells, their activity is inhibited through activation of the killer-cell immunoglobulin-like receptors (KIRs). Alternatively, when NK cells encounter foreign cells or cancer cells, they are activated via their activating receptors (*e.g.*, NKG2D, NCRs, DNAM1). NK cells are also activated by the constant region of some immunoglobulins through CD16 receptors on their surface. The overall sensitivity of NK cells to activation depends on the sum of stimulatory and inhibitory signals.

[0010] CD33 is a member of the sialic acid-binding immunoglobulin-like lectins. As a transmembrane receptor mainly expressed on cells of myeloid lineage, CD33 modulates inflammatory and immune responses through a dampening effect on tyrosine kinase-driven signaling pathways. For example, CD33 was shown to constitutively suppress the production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-8 by human monocytes.

[0011] CD33 is associated with hematopoietic cancers. It is broadly expressed in blasts of nearly all acute myeloid leukemia (AML). Furthermore, hematopoietic cancer stem and/or progenitor cells are found to be $CD33^+$, implying that CD33-directed therapy could potentially eradicate malignant stem and/or progenitor cells in such cases while sparing normal hematopoietic stem cells. In addition to its expression in AML, CD33 is found on other myeloid neoplasms (*e.g.*, myelodysplastic syndromes and myeloproliferative neoplasms) and on subsets of B-cell and T-cell acute lymphoblastic leukemias (ALL)/lymphoblastic lymphomas. This expression pattern has led to the use of CD33-directed therapeutics in patients with malignancies including AML, myelodysplastic syndromes, chronic myelomonocytic leukemia, myeloid blast crisis of chronic myeloid leukemia, and ALLs.

SUMMARY OF THE INVENTION

[0012] The invention provides multi-specific binding proteins that bind to CD33 on a cancer cell and to the NKG2D receptor and CD16 receptor on natural killer cells. Such proteins can engage more than one kind of NK activating receptor, and may block the binding of natural ligands to NKG2D. In certain embodiments, the proteins can agonize NK cells in humans, and in other species such as rodents and cynomolgus monkeys. Various aspects and embodiments of the invention are described in further detail below.

[0013] In certain embodiments, the present invention provides a protein that includes a human CD33 antigen-binding site including a heavy chain variable domain, which includes an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, or 302, and further comprises a second antigen binding site same or different from the antigen-binding site that binds to human CD33.

[0014] In certain embodiments, the present invention provides an antigen-binding site in a protein (*e.g.*, a multi-specific binding protein) that binds to CD33 on a cancer cell, and the NKG2D receptor and CD16 receptor on natural killer cells to activate the natural killer cell.

The binding protein (*e.g.*, a multi-specific binding protein) is useful in the pharmaceutical compositions and therapeutic methods described herein. Binding of the protein including an antigen-binding site that binds to CD33, and to NKG2D receptor and CD16 receptor on natural killer cell enhances the activity of the natural killer cell toward destruction of a cancer cell. Binding of the protein including an antigen-binding site that binds to CD33 (*e.g.*, a multi-specific binding protein) on a cancer cell brings the cancer cell into proximity to the natural killer cell, which facilitates direct and indirect destruction of the cancer cell by the natural killer cell. Further description of exemplary multi-specific binding proteins is provided below.

[0015] The first component of the multi-specific binding proteins of the present disclosure binds to CD33-expressing cells, which can include but are not limited to AML, myelodysplastic syndromes, chronic myelomonocytic leukemia, myeloid blast crisis of chronic myeloid leukemia, and ALLs.

[0016] The second component of the multi-specific binding proteins of the present disclosure binds to NKG2D receptor-expressing cells, which can include but are not limited to NK cells, γδ T cells and $CD8^+$ αβ T cells. Upon NKG2D binding, the multi-specific binding proteins may block natural ligands, such as ULBP6 and MICA, from binding to NKG2D and activating NKG2D receptors. The NKG2D antigen binding site can include, for example:

(1) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:81 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:82 [ADI-29379];

(2) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:83 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:84 [ADI-29463];

(3) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:85 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:86 [ADI-27744];

(4) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:87 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:88 [ADI-27749];

(5) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:191 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:88 [A49MI]; or

(6) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:89 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:90 [ADI-29378].

[0017] The third component for the multi-specific binding proteins of the present disclosure binds to cells expressing CD16, an Fc receptor on the surface of leukocytes including natural killer cells, macrophages, neutrophils, eosinophils, mast cells, and follicular dendritic cells.

[0018] In certain embodiments, any of the foregoing isolated antibodies has a K_D of 1 nM or lower, 5 nM or lower, or 12 nM or lower for extracellular domain of human CD33, as measured by surface plasmon resonance (SPR) (*e.g.*, using the Biacore method described in Example 1 *infra*) or by bio-layer interferometry (BLI) (*e.g.*, using the Octet method described in Example 1 *infra*), and/or binds CD33 from a body fluid, tissue, and/or cell of a subject. In certain embodiments, any of the foregoing isolated antibodies has a K_d (*i.e.*, off-rate, also called K_{off}) equal to or lower than 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 5×10^{-3}, 0.01, 0.02, or 0.05 1/s, as measured by SPR (*e.g.*, using the Biacore method described in Example 1 *infra*) or by BLI (*e.g.*, using the Octet method described in Example 1 *infra*).

[0019] Some proteins of the present disclosure bind to NKG2D with a K_D of 10 nM or weaker affinity.

[0020] In another aspect, the invention provides one or more isolated nucleic acids comprising sequences encoding an immunoglobulin heavy chain and/or immunoglobulin light chain variable region of any one of the foregoing antibodies. The invention provides one or more expression vectors that express the immunoglobulin heavy chain and/or

immunoglobulin light chain variable region of any one of the foregoing antibodies. Similarly the invention provides host cells comprising one or more of the foregoing expression vectors and/or isolated nucleic acids.

[0021] Formulations including any of the proteins that include a CD33-binding domain described herein and methods of enhancing tumor cell death using these proteins and/or formulations are also provided.

[0022] In another aspect, the invention provides a method of treating a cancer, for example, a CD33-associated cancer, in a subject. The method comprises administering to the subject an effective amount of a protein containing any CD33-binding domain described herein, for example, a multi-specific protein containing a CD33binding domain, an NKG2D-binding domain and a CD16-binding domain, to treat the cancer in the subject.

[0023] In another aspect, the invention provides a method of inhibiting cancer growth, for example, the growth of a CD33-associated cancer, in a subject. The method comprises exposing the subject to an effective amount of an antibody comprising any CD33-binding domain described herein, for example, a multi-specific protein containing an CD33-binding domain, an NKG2D-binding domain and a CD16-binding domain, to inhibit cancer growth in the subject.

[0024] Another aspect of the invention provides a method of treating cancer in a patient. The method comprises administering to a patient in need thereof a therapeutically effective amount of the multi-specific binding protein described herein. Exemplary cancers for treatment using the multi-specific binding proteins include, for example, wherein the cancer is selected from the group consisting of AML, myelodysplastic syndromes, chronic myelomonocytic leukemia, myeloid blast crisis of chronic myeloid leukemia, and ALLs.

[0025] Another aspect of the invention provides a protein comprising:

(a) a first antigen-binding site comprising an Fab fragment that binds NKG2D;

(b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds CD33 comprising a heavy chain variable domain and a light chain variable domain; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16,

wherein the scFv is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser or Gly-Ala-Ser.

[0026] In certain embodiments, the scFv is linked to the antibody Fc domain. In certain embodiments, the heavy chain variable domain of the scFv forms a disulfide bridge with the

light chain variable domain of the scFv. In certain embodiments, the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

[0027] In certain embodiments, the scFv is linked to the antibody Fc domain, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv, and is linked to the heavy chain variable domain of the scFv via a flexible linker (GlyGlyGlyGlySer)4 ((G4S)4), and the Fab is linked to the antibody Fc domain.

[0028] In certain embodiments, the present invention provides a protein as disclosed herein, wherein the heavy chain variable domain of the scFv is linked to the light chain variable domain of the scFv via a flexible linker. In certain embodiments, the flexible linker comprises (GlyGlyGlyGlySer)4 ((G4S)4).

[0029] In certain embodiments, the present invention provides a protein as disclosed herein, wherein the heavy chain variable domain of the scFv is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv. In certain embodiments, the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv.

[0030] In certain embodiments, the present invention provides a protein as disclosed herein, wherein the Fab fragment is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16 or the third antigen-binding site that binds CD16. In certain embodiments, the heavy chain portion of the Fab fragment comprises a heavy chain variable domain and a CH1 domain, and wherein the heavy chain variable domain is linked to the CH1 domain. In certain embodiments, the Fab fragment is linked to the antibody Fc domain.

[0031] In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity-determining region 3 (CDR3) sequences represented by the amino acid sequences of SEQ ID NOs:93, 94, and 95, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:96, 97, and 98, respectively. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:99, 100, and 101, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:102, 103, and 104, respectively. In certain

embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:105, 106, and 107, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:108, 109, and 110, respectively. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 193, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 195, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:117, 118, and 119, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:120, 121, and 122, respectively.

[0032] In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:81 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:82. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:83 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:84. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:85 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:86. In certain

embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:87 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:88. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:191 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:88. In certain embodiments, the first antigen-binding site that binds NKG2D comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:89 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:90.

[0033] In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:181, 46, and 182, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:48, 49, and 50, respectively. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:183, 34, and 184, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:36, 185, and 38, respectively.

[0034] In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:9 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:10. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:5 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:6. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:1 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:2. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:3 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:4. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:7 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:11 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:12. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:13 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:14. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:15 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:16. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:17 and a light chain

variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:18. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:19 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:20. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:266 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:267. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:268 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:269. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:270 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:271. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:272 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:273. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:274 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:275. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:276 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:277. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:278 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:279. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:280 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:281. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:282 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:283. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:284 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:285. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:286 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:287. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:288 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:289. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain

variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:290 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:291. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:292 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:293. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:294 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:295. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:296 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:297. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:298 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:299. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:300 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:301. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:302 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:303. In certain

embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:418 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:419. In certain embodiments, the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:420 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:421.

[0035] In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence selected from SEQ ID NO:188, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, SEQ ID NO:484, SEQ ID NO:485, SEQ ID NO:486, SEQ ID NO:487, and SEQ ID NO:488.

[0036] In certain embodiments, the present invention provides a multi-specific binding protein disclosed herein comprising an scFv linked to an antibody Fc domain, wherein the scFv linked to the antibody Fc domain is represented by a sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243.

[0037] In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence selected from SEQ ID NO:189, SEQ ID NO:196, SEQ ID NO:244, and SEQ ID NO:245.

[0038] In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an amino acid sequence selected from SEQ ID NO:188, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, and SEQ ID NO:484. In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:188, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, and SEQ ID NO:484. In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:188, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209,

SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, and SEQ ID NO:484.

[0039] In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an amino acid sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243. In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243. In certain embodiments, the present invention provides a protein disclosed herein comprising a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243.

[0040] Another aspect of the present invention provides a formulation comprising a protein as disclosed herein, and a pharmaceutically acceptable carrier.

[0041] Another aspect of the present invention provides a method of treating a CD33-expressing cancer, the method comprising administering a therapeutically effective amount of a protein or formulation thereof disclosed herein to a subject in need thereof.

[0042] In certain embodiments, the cancer is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPNs), lymphoma, non-Hodgkin lymphomas, and classical Hodgkin lymphoma. In certain embodiments, 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). In certain embodiments, the AML is characterized by expression of CLL-1 on the AML leukemia stem cells (LSCs). In certain embodiments, the LSCs further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96.

[0043] In certain embodiments, the AML is a minimal residual disease (MRD). In certain embodiments, 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)). In certain embodiments, 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). In certain embodiments, the MDS is a primary MDS or a secondary MDS.

[0044] 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.

[0045] These and other aspects and advantages of the invention are illustrated by the following figures, detailed description and claims.

DESCRIPTION OF THE DRAWINGS

[0046] The invention can be more completely understood with reference to the following drawings.

[0047] **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.

[0048] **FIG. 2** shows an alignment of the primary sequences of full length human and cyno CD33 (SEQ ID NO:598 and SEQ ID NO:599, respectively). V domain is underlined in blue, C domain is underlined in green. Difference in sequences are framed in red.

[0049] **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 Biacore profile of ADI-11835; and FIG. 3K is a Biacore profile of Fab fragment from Lintuzumab.

[0050] **FIGs. 4A-4H** show SPR profiles of Fab fragments from CD33 monoclonal antibodies binding to cyno CD33 ECD measured by Biacore at 37 °C. Each Fab fragment includes a CD33-binding clone described herein. FIG. 4A is a Biacore profile of ADI-10159; FIG. 4B is a Biacore profile of ADI-10177; FIG. 4C is a Biacore profile of ADI-11776; FIG. 4D is a Biacore profile of ADI-11807; FIG. 4E is a Biacore profile of ADI-11809; FIG. 4F is a Biacore profile of ADI-11819; FIG. 4G is a Biacore profile of ADI-11830; and FIG. 4H is a Biacore profile of ADI-11835.

[0051] **FIGs. 5A-5T** show SPR profiles of FABs from CD33 monoclonal antibodies binding to V domain and C domain of human CD33 measured at 37 °C. Each Fab fragment includes a CD33-binding clone described herein. FIGs. 5A-5J represent binding to the V-domain; panels K-T represent binding to the C domain. FIGs. 5A and 5K are Biacore profiles of ADI-10159; FIGs. 5B and 5L are Biacore profiles of ADI-10177; FIGs. 5C and 5M are Biacore profiles of ADI-11776; FIGs. 5D and 5N are Biacore profiles of ADI-11801; FIGs. 5E and 5O are Biacore profiles of ADI-11807; FIGs. 5F and 5P are Biacore profiles of ADI-11809; FIGs. 5G and 5Q are Biacore profiles of ADI-11815; FIGs. 5H and 5R are Biacore profiles of ADI-11819; FIGs. 5I and 5S are Biacore profiles of ADI-11830; and FIGs. 5J and 5T are Biacore profiles of ADI-11835.

[0052] **FIGs. 6A-6D** show SPR profiles of an Fab that comprises ADI-11815 binding to different domains of human CD33 and human CD33 having an R69G point mutation. **FIG. 6**A: Fab binding to human CD33 ECD; **FIG. 6**B: Fab binding to V domain; **FIG. 6**C: Fab binding to C domain: **FIG. 6D**: Fab binding to human CD33 having R69G.

[0053] **FIGs. 7A-7D** show SPR profiles of a Fab that comprises ADI-11801 binding to different domains of human CD33 and human CD33 having an R69G point mutation. FIG. 7A: human CD33 ECD; FIG. 7B: V domain; FIG. 7C: C domain: FIG. 7D: human CD33 having R69G.

[0054] **FIG. 8** are bar graphs showing binding of monoclonal antibodies comprising CD33-binding clones to CD33 expressed on Molm-13 human AML cells. CD33 antibody Lintuzumab was also tested, and mean fluorescence intensity (MFI) was plotted. Five of the six antibodies show higher binding signal to CD33 compared to Lintuzumab.

[0055] **FIG. 9** are bar graphs showing internalization of CD33 antibodies on Molm-13 cells after 24 hours. All the CD33 antibodies showed similar internalization after 24 hours. Lintuzumab showed slightly higher internalization compare to other anti-CD33 antibodies.

[0056] **FIGs. 10A-10B** show binding of CD33-targeting TriNKETs to human NKG2D expressed on EL4-hNKG2D and KHYG-1 cells. FIG. 10A shows binding of CD33-targeting TriNKETs to human NKG2D recombinantly expressed on EL4 cells. FIG. 10B shows binding of CD33-targeting TriNKETs to human NKG2D expressed on KHYG-1 cells. For each TriNKET, signal fold-over-background (FOB) was similar on both EL4-hNKG2D cells and KHYG-1 cells, and the rank of binding was also maintain on both cell lines.

[0057] **FIG. 11** shows binding of CD33-targeting TriNKETs to CD33 expressed on human AML Molm-13 cells. Four different CD33-binding clones were used with five

NKG2D-binding clones to make a total of 20 different TriNKETs. NKG2D-binding domains TriNKET do not affect the binding of CD33-binding clones to CD33.

[0058] **FIG. 12** is a graph showing that rested human NK cells are activated by CD33-targeting TriNKETs in co-culture with CD33-expressing THP-1 AML cells.

[0059] **FIG. 13** is a bar graph showing that CD33 TriNKETs induce rested NK cell mediated killing of Molm-13 AML cells.

[0060] **FIG. 14** is a bar graph showing that CD33 TriNKETs induce activated NK cell mediated killing of THP-1 cells.

[0061] **FIG. 15A** are line graphs showing that TriNKETs mediate KHYG-1 killing of Molm-13 AML cells. **FIG. 15B** are line graphs showing that TriNKETs mediate rested human NK cell killing of Molm-13 human AML cells.

[0062] **FIG. 16** are line graphs showing that TriNKETs mediate KHYG-1 killing of EOL-1 AML cells.

[0063] **FIG. 17A** are line graphs showing that TriNKETs mediate KHYG-1 killing of THP-1 cells. **FIG. 17B** are line graphs showing that TriNKETs mediate rested human NK cell killing of THP-1 human AML cells.

[0064] **FIG. 18** is a representation of a multispecific binding protein that contains an NKG2D-binding domain (right arm), a CD33-binding domain (left arm), and an Fc domain or a portion thereof that binds to CD16.

[0065] **FIG. 19** is a representation of a multispecific binding protein that includes a NKG2D-binding domain or a CD33-binding domain, either one of which can be in a scFv format, and an Fc domain or a portion thereof that binds to CD16.

[0066] **FIG. 20** is a representation of a TriNKET in the Triomab form, which is a trifunctional, bispecific antibody that maintains an IgG-like shape. This chimera consists of two half antibodies, each with one light and one heavy chain, that originate from two parental antibodies.

[0067] **FIG. 21** is a representation of a TriNKET in the KiH Common Light Chain (LC) form, which involves the knobs-into-holes (KIHs) technology. KiH is a heterodimer containing 2 Fabs binding to target 1 and 2, and an Fc stabilized by heterodimerization mutations. TriNKET in the KiH format may be an heterodimeric construct with 2 Fabs binding to target 1 and target 2, containing two different heavy chains and a common light chain that pairs with both heavy chains.

[0068] **FIG. 22** is a representation of a TriNKET in the dual-variable domain immunoglobulin (DVD-Ig™) form, which combines the target binding domains of two

monoclonal antibodies via flexible naturally occurring linkers, and yields a tetravalent IgG - like molecule. DVD-Ig™ is a homodimeric construct where variable domain targeting antigen 2 is fused to the N terminus of variable domain of Fab targeting antigen 1 Construct contains normal Fc.

[0069] **FIG. 23** is a representation of a TriNKET in the Orthogonal Fab interface (Ortho-Fab) form, which is an heterodimeric construct that contains 2 Fabs binding to target1 and target 2 fused to Fc. LC-HC pairing is ensured by orthogonal interface. Heterodimerization is ensured by mutations in the Fc.

[0070] **FIG. 24** is a representation of a TrinKET in the 2-in-1 Ig format.

[0071] **FIG. 25** is a representation of a TriNKET in the ES form, which is an heterodimeric construct containing two different Fabs binding to target 1 and target 2 fused to the Fc. Heterodimerization is ensured by electrostatic steering mutations in the Fc.

[0072] **FIG. 26** is a representation of a TriNKET in the Fab Arm Exchange form: antibodies that exchange Fab arms by swapping a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule, resulting in bispecific antibodies. Fab Arm Exchange form (cFae) is a heterodimer containing 2 Fabs binding to target 1 and 2, and an Fc stabilized by heterodimerization mutations.

[0073] **FIG. 27** is a representation of a TriNKET in the SEED Body form, which is an heterodimer containing two Fabs binding to target 1 and 2, and an Fc stabilized by heterodimerization mutations.

[0074] **FIG. 28** is a representation of a TriNKET in the LuZ-Y form, in which leucine zipper is used to induce heterodimerization of two different HCs. LuZ-Y form is a heterodimer containing two different scFabs binding to target 1 and 2, fused to Fc.

[0075] **FIG. 29** is a representation of a TriNKET in the Cov-X-Body form.

[0076] **FIGs. 30A-30B** represent TriNKETs in the κλ-Body forms, which are an heterodimeric constructs with two different Fabs fused to Fc stabilized by heterodimerization 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 κλ-Body; FIG. 30B is an exemplary representation of another κλ-Body.

[0077] **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.

[0078] **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.

[0079] **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.

[0080] **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.

[0081] **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.

[0082] **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).

[0083] **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).

[0084] **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.

[0085] **FIG. 39** is a series of flow cytograms showing the expression level of CD3, CD8, NKG2D, and CD16 on isolated primary $CD8^+$ T cells.

[0086] **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 FIG. 40B were isolated from PBMCs of donor 2. The dotted lines indicate specific lysis of Molm-13 cells by $CD8^+$ T cells in the absence of TriNKET or antibody.

[0087] **FIGs. 41A-41E** are histograms showing the binding of A49-F3'-TriNKET-I07 to NK cells (FIG. 41A), $CD8^+$ T cells (FIG. 41B), $CD4^+$ T cells (FIG. 41C), B cells (FIG. 41D), and monocytes (FIG. 41E) in human whole blood. The dotted lines without fill represent binding of A49-F3'-TriNKET-I07 to the cells; the solid lines with fill represent binding of human IgG1 isotype control to the cells.

[0088] **FIGs. 42A-42B** are graphs showing CD33 expression on monocytes. FIG. 42A shows CD33 expression on monocytes from four healthy donors (dark gray) and Molm-13

(light grey). The bottom five rows are signals from the cell samples stained with an anti-CD33 antibody; the top five rows are signals from the same samples stained with an isotype antibody. FIG. 42B shows CD33 expression on monocytes from the same donor before (light grey) and after (dark grey) negative selection for monocytes.

[0089] **FIGs. 43A-43B** are graphs showing long-term cytotoxicity of NK cells against Molm-13 AML cells and human primary monocytes in the presence of A49-F3'-TriNKET-I07. Proliferation of the target cells are plotted against the time of co-culture with NK cells in the presence of A49-F3'-TriNKET-I07 or PMA + ionomycin. FIG. 43A represents the results from an experiment using NK cells from one donor, and FIG. 43B represents the results from another experiment using NK cells from a different donor.

[0090] **FIG. 44** illustrates a trispecific antibody (TriNKET) that contains a CD33-binding scFv, a NKG2D-targeting Fab, and a heterodimerized antibody constant domain that binds CD16. The antibody format is referred to herein as F3'-TriNKET.

DETAILED DESCRIPTION

[0091] The invention provides multi-specific binding proteins that bind a CD33 on a cancer cell and the NKG2D receptor and CD16 receptor on natural killer cells to activate the natural killer cell, pharmaceutical compositions comprising such multi-specific binding proteins, and therapeutic methods using such multi-specific proteins and pharmaceutical compositions, including for the treatment of cancer. Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

[0092] In one aspect, the invention provides a multi-specific binding protein comprising an antigen binding site that binds an epitope on an extracellular domain of human CD33 and/or Cynomolgus/Rhesus (cyno) CD33. In one aspect, the present invention provides an antigen binding site that recognizes and binds one or more conformational epitopes on the extracellular domain of human CD33 and/or Cynomolgus/Rhesus (cyno) CD33. In one aspect, the present invention provides an antigen binding site that recognizes and binds one or more conformational epitopes on the extracellular domain of human CD33 but does not recognize and/or bind one or more conformational epitopes on the extracellular domain of cyno CD33. In one aspect, the present invention provides an antigen binding site that binds to the R69G allele of human CD33. In one aspect, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the R69G allele of human CD33. In

one aspect, the present invention provides an antigen binding site that binds to an epitope on human CD33 that includes R69. In one aspect, the present invention provides an antigen binding site that binds to the S128N allele of human CD33. In one aspect, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33. In one aspect, the present invention provides an antigen binding site that binds to an epitope on human CD33 that includes S128. In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain, which binds to the extracellular domain in human CD33 and/or cyno CD33, irrespective of the glycosylation profile of the targeted CD33.

[0093] In certain embodiments the present invention provides a multi-specific binding protein comprising an antigen binding site, which binds to the extracellular domain in human CD33 and/or cyno CD33, such that the epitopes are unique compared to the epitopes targeted by one or more known anti-CD33 antibodies in the art. In certain embodiments, the present invention provides an antigen binding site, which binds to the extracellular domain in human CD33 and/or cyno CD33, and shows human or Cynomolgus/Rhesus (cyno) CD33 cross reactivity and high affinity binding to the target CD33.

[0094] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0095] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0096] As used herein, the term "antigen-binding site" refers to the part of the immunoglobulin molecule that participates in antigen binding. In human antibodies, the antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FR." Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In a human antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." In certain animals, such as camels and cartilaginous fish, the antigen-binding site is formed by a single

antibody chain providing a "single domain antibody." Antigen-binding sites can exist in an intact antibody, in an antigen-binding fragment of an antibody that retains the antigen-binding surface, or in a recombinant polypeptide such as an scFv, using a peptide linker to connect the heavy chain variable domain to the light chain variable domain in a single polypeptide. All the amino acid positions in heavy or light chain variable regions disclosed herein are numbered according to Kabat numbering.

[0097] The CDRs of an antigen-binding site can be determined by the methods described in Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al., Sequences of protein of immunological interest. (1991), Chothia et al., J. Mol. Biol. 196:901-917 (1987), and MacCallum et al., J. Mol. Biol. 262:732-745 (1996). The CDRs determined under these definitions typically include overlapping or subsets of amino acid residues when compared against each other. In certain embodiments, the term "CDR" is a CDR as defined by MacCallum et al., J. Mol. Biol. 262:732-745 (1996) and Martin A., Protein Sequence and Structure Analysis of Antibody Variable Domains, in Antibody Engineering, Kontermann and Dubel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In certain embodiments, the term "CDR" is a CDR as defined by Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al., Sequences of protein of immunological interest. (1991). In certain embodiments, heavy chain CDRs and light chain CDRs of an antibody are defined using different conventions. For example, in certain embodiments, the heavy chain CDRs are defined according to MacCallum (*supra*), and the light CDRs are defined according to Kabat (*supra*). CDRH1, CDRH2 and CDRH3 denote the heavy chain CDRs, and CDRL1, CDRL2 and CDRL3 denote the light chain CDRs.

[0098] As used herein, the terms "subject" and "patient" refer to an organism to be treated by the methods and compositions described herein. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and more preferably include humans.

[0099] As used herein, the term "effective amount" refers to the amount of a compound (*e.g.*, a compound of the present invention) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0100] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0101] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, s*ee e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0102] As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (*e.g.*, acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Exemplary acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0103] Exemplary bases include, but are not limited to, alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

[0104] Exemplary salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

[0105] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0106] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0107] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

[0108] Various features and aspects of the invention are discussed in more detail below.

I. Antigen-Binding Site

[0109] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:2. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:21, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:22, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:23. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:434, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:22, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:435. In certain embodiments, an antigen-binding site

that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:2, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:24, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:25, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:26.

[0110] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:4. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:27, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:28, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:29. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:181, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:28, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:436. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:4, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:30, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:31, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:32.

[0111] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5, and an antibody light chain variable

domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:6. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:33, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:34, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:35. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:183, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:34, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:184. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:36, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:37, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:38. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:36, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:185, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:38. In certain embodiments, the antigen-binding site comprises an amino acid sequence at least 90% (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:188. In certain embodiments, the antigen-binding site comprises an amino acid sequence at least 95% identical to SEQ ID NO:188. In certain embodiments, the antigen-binding site comprises an amino acid sequence at least 99% identical to SEQ ID NO:188. In certain embodiments, the antigen-binding site comprises the amino acid sequence of SEQ ID NO:188.

[0112] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence

at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:39, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:40, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:41. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:437, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:40, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:438. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:42, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:43, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:44.

[0113] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:10. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:45, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:46, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:47. In certain embodiments, an

antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:181, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:46, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:182. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:10, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:48, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:49, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:50. In certain embodiments, the antigen-binding site comprises an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:198. In certain embodiments, the antigen-binding site comprises an amino acid sequence at least 95% identical to SEQ ID NO:198. In certain embodiments, the antigen-binding site comprises an amino acid sequence at least 99% identical to SEQ ID NO:198. In certain embodiments, the antigen-binding site comprises the amino acid sequence of SEQ ID NO:198.

[0114] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:12. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:51, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:52, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:53. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:181, a CDR2 sequence represented

by the amino acid sequence of SEQ ID NO:52, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:439. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:12, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:54, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:55, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:56.

[0115] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:14. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:57, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:58, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:59. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:440, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:58, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:441. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:60, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:61, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:62.

[0116] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence

at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:16. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:63, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:64, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:65. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:442, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:64, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:443. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:16, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:66, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:67, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:68.

[0117] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:18. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:69, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:70, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:71. In certain embodiments, an

antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:181, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:70, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:444. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:18, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:72, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:73, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:74.

[0118] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:20. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:75, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:76, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:77. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:445, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:76, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:446. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:20, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:78, a CDR2 sequence represented by the amino acid

sequence of SEQ ID NO:79, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:80.

[0119] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:267. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:304, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:305, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:306. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:528, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:305, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:529. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:307, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:308, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:309.

[0120] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:269. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:310, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:311, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:312. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:530, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:311, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:531. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:313, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:314, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:315.

[0121] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:271. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:316, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:317, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:318. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:532, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:317, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:533. In certain embodiments, an

antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:319, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:320, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:321.

[0122] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:273. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:322, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:323, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:324. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:534, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:323, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:535. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:325, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:326, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:327.

[0123] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274, and an antibody light chain variable

domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:275. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:328, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:329, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:330. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:536, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:329, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:537. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:331, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:332, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:333.

[0124] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:277. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:334, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:335, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:336. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%,

or 100%) identical to the amino acid sequence of SEQ ID NO:276, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:538, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:335, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:539. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:277, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:337, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:338, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:339.

[0125] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:279. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:340, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:341, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:342. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:540, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:341, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:541. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:343, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:344, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:345.

[0126] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:281. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:346, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:347, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:348. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:542, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:347, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:543. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:349, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:350, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:351.

[0127] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:283. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:352, a CDR2

sequence represented by the amino acid sequence of SEQ ID NO:353, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:354. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:544, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:353, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:545. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:355, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:356, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:357.

[0128] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:285. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:358, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:359, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:360. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:546, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:359, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:547. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or

100%) identical to the amino acid sequence of SEQ ID NO:285, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:361, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:362, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:363.

[0129] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:287. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:364, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:365, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:366. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:548, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:365, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:549. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:367, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:368, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:369.

[0130] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:289. In certain

embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:370, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:371, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:372. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:550, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:371, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:551. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:373, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:374, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:375.

[0131] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:291. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:376, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:377, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:378. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:552, a CDR2 sequence

represented by the amino acid sequence of SEQ ID NO:377, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:553. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:379, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:380, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:381.

[0132] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:293. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:382, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:383, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:384. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:554, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:383, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:555. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:293, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:385, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:386, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:387.

[0133] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence

at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:295. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:388, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:389, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:390. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:556, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:389, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:557. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:295, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:391, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:392, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:393.

[0134] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:297. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:394, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:395, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:396. In certain embodiments, an

antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:558, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:395, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:559. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:397, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:398, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:399.

[0135] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:299. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:400, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:401, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:402. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:560, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:401, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:561. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:403, a CDR2 sequence represented

by the amino acid sequence of SEQ ID NO:404, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:405.

[0136] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:301. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:406, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:407, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:408. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:562, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:407, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:563. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:409, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:410, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:411.

[0137] In certain embodiments, the present invention provides an antigen-binding site that includes an antibody heavy chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302, and an antibody light chain variable domain that includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:303. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:412, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:413, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:414. In certain embodiments, an antigen-binding site that includes an antibody heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:564, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:413, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:565. In certain embodiments, an antigen-binding site that includes an antibody light chain variable domain with an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303, includes a CDR1 sequence represented by the amino acid sequence of SEQ ID NO:415, a CDR2 sequence represented by the amino acid sequence of SEQ ID NO:416, and a CDR3 sequence represented by the amino acid sequence of SEQ ID NO:417.

[0138] In each of the foregoing embodiments, it is contemplated herein that immunoglobulin heavy chain variable region sequences and/or light chain variable region sequences that together bind CD33 may contain amino acid alterations (*e.g.*, at least 1, 2, 3, 4, 5, or 10 amino acid substitutions, deletions, or additions) in the framework regions of the heavy and/or light chain variable regions without affecting their ability to bind to CD33 significantly.

[0139] Table 1 lists peptide sequences of heavy chain variable domains and light chain variable domains that, in combination (either as a Fab fragment or a single-chain variable fragment (scFv)), can bind to CD33. Unless indicated otherwise, the CDR sequences provided in Table 1 are determined under Kabat. The CD33-binding domains can vary in their binding affinity to CD33. Table 1 also lists scFv forms of the CD33-binding heavy and light chain variable domains. The exemplary nucleic acid sequences listed in Table 1 are predicted possible nucleic acid sequences that the listed corresponding peptide sequences originated from, and were generated using EMBL-EBI's Protein Sequence Back-translation program.

Table 1	VH	VL
ADI-10159 [Ab1] (G59)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:1] CDR1: FTFSSYGMS [SEQ ID NO:21] (non-Kabat) or SYGMS [SEQ ID NO:434] CDR2: NIKQDGSEKYYVDSVKG [SEQ ID NO:22] CDR3: AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:23] (non-Kabat) or EGGPYYDSSGYFVYYGMDV [SEQ ID NO:435]	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYESFPTFGGGTKVEIK [SEQ ID NO:2] CDR1: RASQSISSWLA [SEQ ID NO:24] CDR2: DASSLES [SEQ ID NO:25] CDR3: QQYESFPT [SEQ ID NO:26]
scFv of Ab1	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYESFPTFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGK***C***LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:206] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGK***C***LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYESFPTFG***C***GTKVEIK [SEQ ID NO:207]	
Exemplary nucleotide sequence of Ab1 scFv	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACGCCAGCAGCCTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGACCCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTGCCAGCAGTACGAGAGCTTCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGGCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAACATCAAGCAGGACGGCAGCGAGAAGTACTACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACC	

Table 1	VH	VL
	TGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTAC TGCGCCAGGGAGGGCGGCCCCTACTACGACAGCAGCGGCTACTTC GTGTACTACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGAC CGTGAGCAGC [SEQ ID NO:246] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACGGCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAAGCAGGACGGCAGCGAGAAGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCGGCCCCTACT ACGACAGCAGCGGCTACTTCGTGTACTACGGCATGGACGTGTGGG GCCAGGGCACCACCGTGACCGTGAGCAGCGGCGGCGGCGGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGC GTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCAT CAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCC CCAAGCTGCTGATCTACGACGCCAGCAGCCTGGAGAGCGGCGTG CCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCT GACCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTG CCAGCAGTACGAGAGCTTCCCCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAG [SEQ ID NO:247]	
ADI-10177 [Ab2]	EVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGK GLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARPLNAGELDV WGQGTMVTVSS [SEQ ID NO:3] CDR1: FTFSSYWMS [SEQ ID NO:27] (non-Kabat) or SYWMS [SEQ ID NO:181] CDR2: NIKQDGSEKYYVDSVKG [SEQ ID NO:28] CDR3: ARPLNAGELDV [SEQ ID NO:29] (non-Kabat) or PLNAGELDV [SEQ ID NO:436]	DIQMTQSPSTLSASVGDRVTITCR ASQSISSWLAWYQQKPGKAPKL LIYEASSLESGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQLESY PLTFGGGTKVEIK [SEQ ID NO:4] CDR1: RASQSISSWLA [SEQ ID NO:30] CDR2: EASSLES [SEQ ID NO:31] CDR3: QQLESYPLT [SEQ ID NO:32]
scFv of Ab2	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQLESYPLT FG<u>C</u>GTKVEIK<u>GGGGSGGGGSGGGGSGGGGS</u>EVQLVESGGGLVQP GGSLRLSCAASGFTFSSYWMSWVRQAPGK<u>C</u>LEWVANIKQDGSEKY YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGEL DVWGQGTMVTVSS [SEQ ID NO:208] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK<u>C</u>LE	

Table 1	VH	VL
	WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARPLNAGELDVWGQGTMVTVSS**GGGGSGGGGSGGGGSGG GGS**DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAP KLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQLES YPLTFG*C*GTKVEIK [SEQ ID NO:209]	
Exemplary nucleotide sequence of Ab2 scFv	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCA GCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGAGGCCAGCAGCCTGGAGAGCGGCGTGCC CAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGA CCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTGCC AGCAGCTGGAGAGCTACCCCCTGACCTTCGGCTGCGGCACCAAGG TGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGA GAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGA GCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCT GGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAAC ATCAAGCAGGACGGCAGCGAGAAGTACTACGTGGACAGCGTGAA GGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGT ACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGGCCCCTGAACGCCGGCGAGCTGGACGTGTGGGG CCAGGGCACCATGGTGACCGTGAGCAGC [SEQ ID NO:248] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAAGCAGGACGGCAGCGAGAAGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGCCCCTGAACGCCGGCG AGCTGGACGTGTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGAGCCCCAGC ACCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAG GGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGA AGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGAGGCCAGCAGC CTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGG CACCGAGTTCACCCTGACCATCAGCAGCCTGCAGCCCGACGACTT CGCCACCTACTACTGCCAGCAGCTGGAGAGCTACCCCCTGACCTT CGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:249]	
ADI-11776 [Ab3] (H76)	EVQLLESGGGLVQPGGSLRLSC AASGFTFSKYTMSWVRQAPGK GLEWVSAIVGSGESTYFADSVK GRFTISRDNSKNTLYLQMNSLR AEDTAVYYCAREGGPYYDSSG YFVYYGMDVWGQGTTVTVSS	DIQMTQSPSTLSASVGDRVTITCR ASQSISSWLAWYQQKPGKAPKL LIYKASSLESGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYDD LPTFGGGTKVEIK [SEQ ID NO:6] CDR1: RASQSISSWLA [SEQ ID

Table 1	VH	VL
	[SEQ ID NO:5] CDR1: FTFSKYTMS [SEQ ID NO:33] (non-Kabat) or KYTMS [SEQ ID NO:183] CDR2: AIVGSGESTYFADSVKG [SEQ ID NO:34] CDR3: AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:35] (non-Kabat) or EGGPYYDSSGYFVYYGMDV [SEQ ID NO:184]	NO:36] CDR2: KASSLES [SEQ ID NO:37] or KASSLE [SEQ ID NO:185] (non-Kabat) CDR3: QQYDDLPT [SEQ ID NO:38]
scFv of Ab3	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK*C*LEWVSAIVGSGESTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:198] EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK*C*LEWVSAIVGSGESTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG*C*GTKVEIK [SEQ ID NO:210]
Exemplary nucleotide sequence of Ab3 scFv	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACAAGGCCAGCAGCCTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGACCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTGCCAGCAGTACGACGACCTGCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAAGTACACCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGAGCGCCATCGTGGGCAGCGGCGAGAGCACCTACTTCGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCGGCCCCTACTACGACAGCAGCGGCTACTTCGTGTACTACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGAC

Table 1	VH	VL
	CGTGAGCAGC [SEQ ID NO:250] GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAAGTACACCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGAGCGCCATCGTGGGCAGCGGCGAGAGCACCTAC TTCGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCGGCCCCTACT ACGACAGCAGCGGCTACTTCGTGTACTACGGCATGGACGTGTGGG GCCAGGGCACCACCGTGACCGTGAGCAGCGGCGGCGGCGGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGC GTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCAT CAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCC CCAAGCTGCTGATCTACAAGGCCAGCAGCCTGGAGAGCGGCGTG CCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCT GACCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTG CCAGCAGTACGACGACCTGCCCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAG [SEQ ID NO:251]	
ADI-11801 [Ab4]	QVQLVQSGAEVKKPGASVKVS CKASGYTFSDYYMHWVRQAPG QGLEWMGMINPSWGSTSYAQK FQGRVTMTRDTSTSTVYMELSS LRSEDTAVYYCAREAADGFVGE RYFDLWGRGTLVTVSS [SEQ ID NO:7] CDR1: YTFSDYYMH [SEQ ID NO:39] (non-Kabat) or DYYMH [SEQ ID NO:437] CDR2: MINPSWGSTSYAQKFQG [SEQ ID NO:40] CDR3: AREAADGFVGERYFDL [SEQ ID NO:41] (non-Kabat) or EAADGFVGERYFDL [SEQ ID NO:438]	DIVMTQSPLSLPVTPGEPASISCR SSQSLLYSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYC MQDVALPITFGGGTKVEIK [SEQ ID NO:8] CDR1: RSSQSLLYSNGYNYLD [SEQ ID NO:42] CDR2: LGSNRAS [SEQ ID NO:43] CDR3: MQDVALPIT [SEQ ID NO:44]
scFv of Ab4	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ DVALPITFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSG AEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQ***C***LEWMGMIN PSWGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR EAADGFVGERYFDLWGRGTLVTVSS [SEQ ID NO:211] QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQ***C***L EWMGMINPSWGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT	

Table 1	VH	VL
	AVYYCAREAADGFVGERYFDLWGRGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFG**C**GTKVEIK [SEQ ID NO:212]	
Exemplary nucleotide sequence of Ab4 scFv	GACATCGTGATGACCCAGAGCCCCCTGAGCCTGCCCGTGACCCCCGGCGAGCCCGCCAGCATCAGCTGCAGGAGCAGCCAGAGCCTGCTGTACAGCAACGGCTACAACTACCTGGACTGGTACCTGCAGAAGCCCGGCCAGAGCCCCCAGCTGCTGATCTACCTGGGCAGCAACAGGGCCAGCGGCGTGCCCGACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGACGTGGGCGTGTACTACTGCATGCAGGACGTGGCCCTGCCCATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCAGCGACTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCATGATCAACCCCAGCTGGGGCAGCACCAGCTACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCGCCGACGGCTTCGTGGGCGAGAGGTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:252] CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCAGCGACTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCATGATCAACCCCAGCTGGGGCAGCACCAGCTACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCGCCGACGGCTTCGTGGGCGAGAGGTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCGTGATGACCCAGAGCCCCCTGAGCCTGCCCGTGACCCCCGGCGAGCCCGCCAGCATCAGCTGCAGGAGCAGCCAGAGCCTGCTGTACAGCAACGGCTACAACTACCTGGACTGGTACCTGCAGAAGCCCGGCCAGAGCCCCCAGCTGCTGATCTACCTGGGCAGCAACAGGGCCAGCGGCGTGCCCGACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGACGTGGGCGTGTACTACTGCATGCAGGACGTGGCCCTGCCCATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:253]	
ADI-11807 [Ab5] (I07)	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGKGLEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVW	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIK [SEQ ID

Table 1	VH	VL
	GQGTMVTVSS [SEQ ID NO:9] CDR1: FTFGSYWMS [SEQ ID NO:45] (non-Kabat) or SYWMS [SEQ ID NO:181] CDR2: TIKQDGSEKSYVDSVKG [SEQ ID NO:46] CDR3: ARPLNAGELDV [SEQ ID NO:47] (non-Kabat) or RPLNAGELDV [SEQ ID NO:182]	NO:10] CDR1: RASQSISSWLA [SEQ ID NO:48] CDR2: EASSLES [SEQ ID NO:49] CDR3: QQSQSYPPIT [SEQ ID NO:50]
scFv of Ab5	***I07 scFv*** DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGK***C***LEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQGTMVTVSS [SEQ ID NO:188] EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGK***C***LEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQGTMVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFG***C***GTKVEIK [SEQ ID NO:213]
Exemplary nucleotide sequence of Ab5 scFv	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGAGGCCAGCAGCCTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGACCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTGCCAGCAGAGCCAGAGCTACCCCCCCATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCGGCAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCACCATCAAGCAGGACGGCAGCGAGAAGAGCTACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGCCCCTGAACGCCGGCGAGCTGGACGTGTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC [SEQ ID NO:254] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG

Table 1	VH	VL
	CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCGG CAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCACCATCAAGCAGGACGGCAGCGAGAAGAGC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGCCCCTGAACGCCGGCG AGCTGGACGTGTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGAGCCCCAGC ACCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAG GGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGA AGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGAGGCCAGCAGC CTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGG CACCGAGTTCACCCTGACCATCAGCAGCCTGCAGCCCGACGACTT CGCCACCTACTACTGCCAGCAGAGCCAGAGCTACCCCCCCATCAC CTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:255]	
ADI-11809 [Ab6]	EVQLVESGGGLVQPGGSLRLSC AASGFTFPSYWMSWVRQAPGK GLEWVATIKRDGSEKGYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARPLNAGELDV WGQGTMVTVSS [SEQ ID NO:11] CDR1: FTFPSYWMS [SEQ ID NO:51] (non-Kabat) or SYWMS [SEQ ID NO:181] CDR2: TIKRDGSEKGYVDSVKG [SEQ ID NO:52] CDR3: ARPLNAGELDV [SEQ ID NO:53] (non-Kabat) or PLNAGELDV [SEQ ID NO:439]	DIQMTQSPSTLSASVGDRVTITCR ASQSISSWLAWYQQKPGKAPKL LIYEASSLESGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQSQSY PPITFGGGTKVEIK [SEQ ID NO:12] CDR1: RASQSISSWLA [SEQ ID NO:54] CDR2: EASSLES [SEQ ID NO:55] CDR3: QQSQSYPPIT [SEQ ID NO:56]
scFv of Ab6	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPI TFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQ PGGSLRLSCAASGFTFPSYWMSWVRQAPGK***C***LEWVATIKRDGSEKG YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGEL DVWGQGTMVTVSS [SEQ ID NO:214] EVQLVESGGGLVQPGGSLRLSCAASGFTFPSYWMSWVRQAPGK***C***LE WVATIKRDGSEKGYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARPLNAGELDVWGQGTMVTVSS**GGGGSGGGGSGGGGSGG GGS**DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAP KLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQS YPPITFG***C***GTKVEIK [SEQ ID NO:215]	

Table 1	VH	VL
Exemplary nucleotide sequence of Ab6 scFv	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCA GCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGAGGCCAGCAGCCTGGAGAGCGGCGTGCC CAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGA CCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTGCC AGCAGAGCCAGAGCTACCCCCCCATCACCTTCGGCTGCGGCACCA AGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGT GGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGC TGAGCTGCGCCGCCAGCGGCTTCACCTTCCCCAGCTACTGGATGA GCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCC ACCATCAAGAGGGACGGCAGCGAGAAGGGCTACGTGGACAGCGT GAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCC TGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTG TACTACTGCGCCAGGCCCCTGAACGCCGGCGAGCTGGACGTGTGG GGCCAGGGCACCATGGTGACCGTGAGCAGC [SEQ ID NO:256] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCCC CAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCACCATCAAGAGGGACGGCAGCGAGAAGGGC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGCCCCTGAACGCCGGCG AGCTGGACGTGTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGAGCCCCAGC ACCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAG GGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGA AGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGAGGCCAGCAGC CTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGG CACCGAGTTCACCCTGACCATCAGCAGCCTGCAGCCCGACGACTT CGCCACCTACTACTGCCAGCAGAGCCAGAGCTACCCCCCCATCAC CTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:257]	
ADI-11815 [Ab7]	QVQLVQSGAEVKKPGASVKVS CKASGYTFGTYYMHWVRQAPG QGLEWMGIINPSRGSTVYAQKF QGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARGAGYDDEDM DVWGKGTTVTVSS [SEQ ID NO:13] CDR1: YTFGTYYMH [SEQ ID NO:57] (non-Kabat) or TYYMH [SEQ ID NO:440] CDR2: IINPSRGSTVYAQKFQG	DIQMTQSPSSVSASVGDRVTITC RASQGIDSWLAWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQAHS YPLTFGGGTKVEIK [SEQ ID NO:14] CDR1: RASQGIDSWLA [SEQ ID NO:60] CDR2: AASSLQS [SEQ ID NO:61] CDR3: QQAHSYPLT [SEQ ID

Table 1	VH	VL
	[SEQ ID NO:58] CDR3: ARGAGYDDEDMDV [SEQ ID NO:59] (non-Kabat) or GAGYDDEDMDV [SEQ ID NO:441]	NO:62]
scFv of Ab7	DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPL TFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKK PGASVKVSCKASGYTFGTYYMHWVRQAPGQ***C***LEWMGIINPSRGSTV YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDD EDMDVWGKGTTVTVSS [SEQ ID NO:216] QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQAPGQ***C*** LEWMGIINPSRGSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGAGYDDEDMDVWGKGTTVTVSS**GGGGSGGGGSGGGG SGGGGS**DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKP GKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QAHSYPLTFG***C***GTKVEIK [SEQ ID NO:217]
Exemplary nucleotide sequence of Ab7 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCGTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGGGCATCG ACAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAGCCTGCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGCCCACAGCTACCCCCTGACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGGTGCA GAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGA GCTGCAAGGCCAGCGGCTACACCTTCGGCACCTACTACATGCACT GGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCATC ATCAACCCCAGCAGGGGCAGCACCGTGTACGCCCAGAAGTTCCA GGGCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGT ACATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTAC TACTGCGCCAGGGGCGCCGGCTACGACGACGAGGACATGGACGT GTGGGGCAAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:258] CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGG CGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCG GCACCTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCC TGGAGTGGATGGGCATCATCAACCCCAGCAGGGGCAGCACCGTG TACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACAC CAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCG AGGACACCGCCGTGTACTACTGCGCCAGGGGCGCCGGCTACGAC GACGAGGACATGGACGTGTGGGGCAAGGGCACCACCGTGACCGT GAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC

Table 1	VH	VL
	GGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGAG CCCCAGCAGCGTGAGCGCCAGCGTGGGCGACAGGGTGACCATCA CCTGCAGGGCCAGCCAGGGCATCGACAGCTGGCTGGCCTGGTACC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCC AGCAGCCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGG CAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGA GGACTTCGCCACCTACTACTGCCAGCAGGCCCACAGCTACCCCCT GACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO: 259]	
ADI-11819 [Ab8]	EVQLVESGGGLVKPGGSLRLSC AASGFTFSSYAMSWVRQAPGK GLEWVSSISSSSEGIYYADSVKG RFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREGGPYYDSSGYF VYYGMDVWGQGTTVTVSS [SEQ ID NO:15] CDR1: FTFSSYAMS [SEQ ID NO:63] (non-Kabat) or SYAMS [SEQ ID NO:442] CDR2: SISSSSEGIYYADSVKG [SEQ ID NO:64] CDR3: AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:65] (non-Kabat) or EGGPYYDSSGYFVYYGMDV [SEQ ID NO:443]	DIQMTQSPSTLSASVGDRVTITCR ASNSISSWLAWYQQKPGKAPKL LIYEASSTKSGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYDD LPTFGGGTKVEIK [SEQ ID NO:16] CDR1: RASNSISSWLA [SEQ ID NO:66] CDR2: EASSTKS [SEQ ID NO:67] CDR3: QQYDDLPT [SEQ ID NO:68]
scFv of Ab8	DIQMTQSPSTLSASVGDRVTITCRASNSISSWLAWYQQKPGKAPKLLI YEASSTKSGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPT FG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVKP GGSLRLSCAASGFTFSSYAMSWVRQAPGK***C***LEWVSSISSSSEGIYYA DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSS GYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:218] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMSWVRQAPGK***C***LE WVSSISSSSEGIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS**GGGGSGGGG SGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASNSISSWLAW YQQKPGKAPKLLIYEASSTKSGVPSRFSGSGSGTEFTLTISSLQPDDFA TYYCQQYDDLPTFG***C***GTKVEIK [SEQ ID NO:219]	
Exemplary nucleotide sequence of Ab8	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCAACAGCATCA GCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGAGGCCAGCAGCACCAAGAGCGGCGTGCC CAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGA	

Table 1	VH	VL
scFv	CCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTGCC AGCAGTACGACGACCTGCCCACCTTCGGCTGCGGCACCAAGGTGG AGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGAGAG CGGCGGCGGCCTGGTGAAGCCCGGCGGCAGCCTGAGGCTGAGCT GCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAGCTGGG TGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGAGCAGCATC AGCAGCAGCAGCGAGGGCATCTACTACGCCGACAGCGTGAAGGG CAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACC TGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTAC TGCGCCAGGGAGGGCGGCCCCTACTACGACAGCAGCGGCTACTTC GTGTACTACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGAC CGTGAGCAGC [SEQ ID NO:260] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGAAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGAGCAGCATCAGCAGCAGCAGCGAGGGCATCTAC TACGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCGGCCCCTACT ACGACAGCAGCGGCTACTTCGTGTACTACGGCATGGACGTGTGGG GCCAGGGCACCACCGTGACCGTGAGCAGCGGCGGCGGCGGCAGC GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGC GTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCAACAGCAT CAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCC CCAAGCTGCTGATCTACGAGGCCAGCAGCACCAAGAGCGGCGTG CCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCT GACCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTACTG CCAGCAGTACGACGACCTGCCCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAG [SEQ ID NO:261]	
ADI-11830 [Ab9]	EVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGK GLEWVANINTDGSEVYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARDVGPGIAYQ GHFDYWGQGTLVTVSS [SEQ ID NO:17] CDR1: FTFSSYWMS [SEQ ID NO:69] (non-Kabat) or SYWMS [SEQ ID NO:181] CDR2: NINTDGSEVYYVDSVKG [SEQ ID NO:70] CDR3: ARDVGPGIAYQGHFDY	DIQMTQSPSSLSASVGDRVTITCR ASQVIYSYLNWYQQKPGKAPKL LIYAASSLKSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQVYD TPLTFGGGTKVEIK [SEQ ID NO:18] CDR1: RASQVIYSYLN [SEQ ID NO:72] CDR2: AASSLKS [SEQ ID NO:73] CDR3: QQVYDTPLT [SEQ ID NO:74]

Table 1	VH	VL
	[SEQ ID NO:71] (non-Kabat) or DVGPGIAYQGHFDY [SEQ ID NO:444]	
scFv of Ab9	DIQMTQSPSSLSASVGDRVTITCRASQVIYSYLNWYQQKPGKAPKLLI YAASSLKSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPL TFG**C**GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQ PGGSLRLSCAASGFTFSSYWMSWVRQAPGK**C**LEWVANINTDGSEVY YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIA YQGHFDYWGQGTLVTVSS [SEQ ID NO:220] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK**C**LE WVANINTDGSEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARDVGPGIAYQGHFDYWGQGTLVTVSS**GGGGSGGGGSGGG GSGGGGS**DIQMTQSPSSLSASVGDRVTITCRASQVIYSYLNWYQQKP GKAPKLLIYAASSLKSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QVYDTPLTFG**C**GTKVEIK [SEQ ID NO:221]
Exemplary nucleotide sequence of Ab9 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGGTGATCT ACAGCTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAGCCTGAAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGTGTACGACACCCCCCTGACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGA GAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGA GCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCT GGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAAC ATCAACACCGACGGCAGCGAGGTGTACTACGTGGACAGCGTGAA GGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGT ACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGGGACGTGGGCCCCGGCATCGCCTACCAGGGCCAC TTCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:262] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAACACCGACGGCAGCGAGGTGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGACGTGGGCCCCGGC ATCGCCTACCAGGGCCACTTCGACTACTGGGGCCAGGGCACCCTG GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGA CCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTG

Table 1	VH	VL
	ACCATCACCTGCAGGGCCAGCCAGGTGATCTACAGCTACCTGAAC TGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTAC GCCGCCAGCAGCCTGAAGAGCGGCGTGCCCAGCAGGTTCAGCGG CAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCA GCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGTGTACGACAC CCCCCTGACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:263]	
ADI-11835 [Ab10] (I35)	QLQLQESGPGLVKPSETLSLTCT VSGGSISSTDYYWGWIRQPPGK GLEWIGSIGYSGTYYNPSLKSRV TISVDTSKNQFSLKLSSVTAADT AVYYCARETAHDVHGMDVWG QGTTVTVSS [SEQ ID NO:19] CDR1: GSISSTDYYWG [SEQ ID NO:75] (non-Kabat) or STDYYWG [SEQ ID NO:445] CDR2: SIGYSGTYYNPSLKS [SEQ ID NO:76] CDR3: ARETAHDVHGMDV [SEQ ID NO:77] (non-Kabat) or ETAHDVHGMDV [SEQ ID NO:446]	EIVLTQSPATLSLSPGERATLSCR ASHSVYSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQYDN LPTFGGGTKVEIK [SEQ ID NO:20] CDR1: RASHSVYSYLA [SEQ ID NO:78] CDR2: DASNRAT [SEQ ID NO:79] CDR3: QQYDNLPT [SEQ ID NO:80]
scFv of Ab10	EIVLTQSPATLSLSPGERATLSCRASHSVYSYLAWYQQKPGQAPRLLI YDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLPT FG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QLQLQESGPGLVKPS ETLSLTCTVSGGSISSTDYYWGWIRQPPGK*C*LEWIGSIGYSGTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARETAHDVHGMDV WGQGTTVTVSS [SEQ ID NO:222] QLQLQESGPGLVKPSETLSLTCTVSGGSISSTDYYWGWIRQPPGK*C*LE WIGSIGYSGTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC ARETAHDVHGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGG S**EIVLTQSPATLSLSPGERATLSCRASHSVYSYLAWYQQKPGQAPRLL IYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLPT FG*C*GTKVEIK [SEQ ID NO:223]	
Exemplary nucleotide sequence of Ab10 scFv	GAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCC GGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCACAGCGTGTA CAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCA GGCTGCTGATCTACGACGCCAGCAACAGGGCCACCGGCATCCCCG CCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCA TCAGCAGCCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGC AGTACGACAACCTGCCCACCTTCGGCTGCGGCACCAAGGTGGAG ATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGG CGGCAGCGGCGGCGGCGGCAGCCAGCTGCAGCTGCAGGAGAGCG	

Table 1	VH	VL
	GCCCCGGCCTGGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCA CCGTGAGCGGCGGCAGCATCAGCAGCACCGACTACTACTGGGGC TGGATCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCAG CATCGGCTACAGCGGCACCTACTACAACCCCAGCCTGAAGAGCA GGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTG AAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGC GCCAGGGAGACCGCCCACGACGTGCACGGCATGGACGTGTGGGG CCAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:264] CAGCTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAG CGAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCA GCAGCACCGACTACTACTGGGGCTGGATCAGGCAGCCCCCCGGC AAGTGCCTGGAGTGGATCGGCAGCATCGGCTACAGCGGCACCTA CTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACA CCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCC GCCGACACCGCCGTGTACTACTGCGCCAGGGAGACCGCCCACGA CGTGCACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGACCG TGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGCTGACCCAGAG CCCCGCCACCCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGA GCTGCAGGGCCAGCCACAGCGTGTACAGCTACCTGGCCTGGTACC AGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGACGCC AGCAACAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGG CAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAGCCCGA GGACTTCGCCGTGTACTACTGCCAGCAGTACGACAACCTGCCCAC CTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:265]
ADI-10154 [Ab11]	EVQLLESGGGLVQPGGSLRLSC AASGFTFSSYAMSWVRQAPGK GLEWVSAISASGGSTYYADSVK GRFTISRDNSKNTLYLQMNSLR AEDTAVYYCARPRAYYDSSGFK VNYGMDVWGQGTTVTVSS [SEQ ID NO:266] CDR1: SYAMS [SEQ ID NO:304] or FTFSSYAMS [SEQ ID NO:528] (non-Kabat) CDR2: AISASGGSTYYADSVKG [SEQ ID NO:305] CDR3: PRAYYDSSGFKVNYGMDV [SEQ ID NO:306] or ARPRAYYDSSGFKVNYGMDV [SEQ ID NO:529] (non-Kabat)	EIVLTQSPGTLSLSPGERATLSCR ASQSVSSSFLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQASS SPPTFGGGTKVEIK [SEQ ID NO:267] CDR1: RASQSVSSSFLA [SEQ ID NO:307] CDR2: GASSRAT [SEQ ID NO:308] CDR3: QQASSSPPT [SEQ ID NO:309]
scFv of	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQASSSPPT	

Table 1	VH	VL
Ab11	FG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQP GGSLRLSCAASGFTFSSYAMSWVRQAPGK*C*LEWVSAISASGGSTYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPRAYYDSS GFKVNYGMDVWGQGTTVTVSS [SEQ ID NO:447] EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK*C*LE WVSAISASGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCARPRAYYDSSGFKVNYGMDVWGQGTTVTVSS**GGGGSGGGG SGGGGSGGGGS**EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAW YQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFA VYYCQQASSSPPTFG*C*GTKVEIK [SEQ ID NO:448]
Exemplary nucleotide sequence of Ab11 scFv	GAGATCGTGCTGACCCAGAGCCCCGGCACCCTGAGCCTGAGCCCC GGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCAGCTTCCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCC CAGGCTGCTGATCTACGGCGCCAGCAGCAGGGCCACCGGCATCCC CGACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGA CCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCC AGCAGGCCAGCAGCAGCCCCCCCACCTTCGGCTGCGGCACCAAG GTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGG CGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGCTGG AGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTG AGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAGC TGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGAGCGC CATCAGCGCCAGCGGCGGCAGCACCTACTACGCCGACAGCGTGA AGGGCAGGTTCACCATCAGCAGGGACAACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTA CTACTGCGCCAGGCCCAGGGCCTACTACGACAGCAGCGGCTTCAA GGTGAACTACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGA CCGTGAGCAGC [SEQ ID NO:489] GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGAGCGCCATCAGCGCCAGCGGCGGCAGCACCTAC TACGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGCCCAGGGCCTACTACG ACAGCAGCGGCTTCAAGGTGAACTACGGCATGGACGTGTGGGGC CAGGGCACCACCGTGACCGTGAGCAGCGGCGGCGGCGGCAGCGG CGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCG AGATCGTGCTGACCCAGAGCCCCGGCACCCTGAGCCTGAGCCCCG GCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGC AGCAGCTTCCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCC AGGCTGCTGATCTACGGCGCCAGCAGCAGGGCCACCGGCATCCCC GACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCA GCAGGCCAGCAGCAGCCCCCCCACCTTCGGCTGCGGCACCAAGGT

Table 1	VH	VL
	GGAGATCAAG [SEQ ID NO:490]	
ADI-10155 [Ab12]	EVQLLESGGGLVQPGGSLRLSC AASGFTFSSYAMSWVRQAPGK GLEWVSGISGSGGSTYYADSVK GRFTISRDNSKNTLYLQMNSLR AEDTAVYYCAREGHSSSYYDH AFDIWGQGTMVTVSS [SEQ ID NO:268] CDR1: SYAMS [SEQ ID NO:310] or FTFSSYAMS [SEQ ID NO:530] (non-Kabat) CDR2: GISGSGGSTYYADSVKG [SEQ ID NO:311] CDR3: EGHSSSYYDHAFDI [SEQ ID NO:312] or AREGHSSSYYDHAFDI [SEQ ID NO:531] (non-Kabat)	EIVLTQSPGTLSLSPGERATLSCR ASQSVSSDYLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQHSS APPTFGGGTKVEIK [SEQ ID NO:269] CDR1: RASQSVSSDYLA [SEQ ID NO:313] CDR2: GASSRAT [SEQ ID NO:314] CDR3: QQHSSAPPT [SEQ ID NO:315]
scFv of Ab12	EIVLTQSPGTLSLSPGERATLSCRASQSVSSDYLAWYQQKPGQAPRLL IYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHSSAPP TFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLLESGGGLVQP GGSLRLSCAASGFTFSSYAMSWVRQAPGK***C***LEWVSGISGSGGSTYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGHSSSYY DHAFDIWGQGTMVTVSS [SEQ ID NO:449] EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK***C***LE WVSGISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREGHSSSYYDHAFDIWGQGTMVTVSS**GGGGSGGGGSGGG GSGGGGS**EIVLTQSPGTLSLSPGERATLSCRASQSVSSDYLAWYQQK PGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC QQHSSAPPTFG***C***GTKVEIK [SEQ ID NO:450]
Exemplary nucleotide sequence of Ab12 scFv	GAGATCGTGCTGACCCAGAGCCCCGGCACCCTGAGCCTGAGCCCC GGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCGACTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCC CCAGGCTGCTGATCTACGGCGCCAGCAGCAGGGCCACCGGCATCC CCGACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTG ACCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGC CAGCAGCACAGCAGCGCCCCCCCCACCTTCGGCTGCGGCACCAAG GTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGG CGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGCTGG AGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTG AGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAGC TGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGAGCGG CATCAGCGGCAGCGGCGGCAGCACCTACTACGCCGACAGCGTGA AGGGCAGGTTCACCATCAGCAGGGACAACAGCAAGAACACCCTG

Table 1	VH	VL
	TACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTA CTACTGCGCCAGGGAGGGCCACAGCAGCAGCTACTACGACCACG CCTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC [SEQ ID NO:491] GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGAGCGGCATCAGCGGCAGCGGCGGCAGCACCTAC TACGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCCACAGCAGC AGCTACTACGACCACGCCTTCGACATCTGGGGCCAGGGCACCATG GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGCTGA CCCAGAGCCCCGGCACCCTGAGCCTGAGCCCCGGCGAGAGGGCC ACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCGACTACCT GGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGA TCTACGGCGCCAGCAGCAGGGCCACCGGCATCCCCGACAGGTTCA GCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGG CTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCAGCACAGC AGCGCCCCCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:492]	
ADI-10157 [Ab13]	QVQLQESGPGLVKPSETLSLTCT VSGGSISSYYWSWIRQPPGKGLE WIGSIYYSGSTNYNPSLKSRVTIS VDTSKNQFSLKLSSVTAADTAV YYCARVGGVYSTIETYGMDVW GQGTTVTVSS [SEQ ID NO:270] CDR1: SYYWS [SEQ ID NO:316] or GSISSYYWS [SEQ ID NO:532] (non-Kabat) CDR2: SIYYSGSTNYNPSLKS [SEQ ID NO:317] CDR3: VGGVYSTIETYGMDV [SEQ ID NO:318] or ARVGGVYSTIETYGMDV [SEQ ID NO:533] (non-Kabat)	EIVMTQSPATLSVSPGERATLSCR ASQSVSSNLAWYQQKPGQAPRL LIYGASTRATGIPARFSGSGSGTE FTLTISSLQSEDFAVYYCQQYTV YPPTFGGGTKVEIK [SEQ ID NO:271] CDR1: RASQSVSSNLA [SEQ ID NO:319] CDR2: GASTRAT [SEQ ID NO:320] CDR3: QQYTVYPPT [SEQ ID NO:321]
scFv of Ab13	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYTVYPP TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLQESGPGLVKP SETLSLTCTVSGGSISSYYWSWIRQPPGK*C*LEWIGSIYYSGSTNYNPSL KSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVGGVYSTIETYGM DVWGQGTTVTVSS [SEQ ID NO:451]	

Table 1	VH	VL
	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGK*C*LEWIGSIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVGGVYSTIETYGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYTVYPPTFG*C*GTKVEIK [SEQ ID NO:452]	
Exemplary nucleotide sequence of Ab13 scFv	GAGATCGTGATGACCCAGAGCCCCGCCACCCTGAGCGTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCAACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGGCGCCAGCACCAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGACCATCAGCAGCCTGCAGAGCGAGGACTTCGCCGTGTACTACTGCCAGCAGTACACCGTGTACCCCCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCAGCAGCTACTACTGGAGCTGGATCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAGCACCAACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGGGTGGGCGGCGTGTACAGCACCATCGAGACCTACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:493] CAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCAGCAGCTACTACTGGAGCTGGATCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAGCACCAACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGGGTGGGCGGCGTGTACAGCACCATCGAGACCTACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGATGACCCAGAGCCCCGCCACCCTGAGCGTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCAACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGGCGCCAGCACCAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCACCGAGTTCACCCTGACCATCAGCAGCCTGCAGAGCGAGGACTTCGCCGTGTACTACTGCCAGCAGTACACCGTGTACCCCCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:494]	
ADI-10158 [Ab14]	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEIDHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAAD	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQDHNF

Table 1	VH	VL
	TAVYYCARQGIHGLRYFDLWG RGTLVTVSS [SEQ ID NO:272] CDR1: GYYWS [SEQ ID NO:322] or GSFSGYYWS [SEQ ID NO:534] (non-Kabat) CDR2: EIDHSGSTNYNPSLKS [SEQ ID NO:323] CDR3: QGIHGLRYFDL [SEQ ID NO:324] or ARQGIHGLRYFDL [SEQ ID NO:535] (non-Kabat)	PYTFGGGTKVEIK [SEQ ID NO:273] CDR1: RASQSVSSYLA [SEQ ID NO:325] CDR2: DASNRAT [SEQ ID NO:326] CDR3: QQDHNFPYT [SEQ ID NO:327]
scFv of Ab14	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLI YDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQDHNFPY TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLQQWGAGLLK PSETLSLTCAVYGGSFSGYYWSWIRQPPGK*C*LEWIGEIDHSGSTNYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARQGIHGLRYFD LWGRGTLVTVSS [SEQ ID NO:453] QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGK*C*LE WIGEIDHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARQGIHGLRYFDLWGRGTLVTVSS**GGGGSGGGGSGGGGSGGGG S**EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQDHNFP YTFG*C*GTKVEIK [SEQ ID NO:454]
Exemplary nucleotide sequence of Ab14 scFv	GAGATCGTGATGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCC GGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCA GGCTGCTGATCTACGACGCCAGCAACAGGGCCACCGGCATCCCCG CCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCA TCAGCAGCCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGC AGGACCACAACTTCCCCTACACCTTCGGCTGCGGCACCAAGGTGG AGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGCAGCAGTG GGGCGCCGGCCTGCTGAAGCCCAGCGAGACCCTGAGCCTGACCT GCGCCGTGTACGGCGGCAGCTTCAGCGGCTACTACTGGAGCTGGA TCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCGAGATC GACCACAGCGGCAGCACCAACTACAACCCCAGCCTGAAGAGCAG GGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGA AGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCG CCAGGCAGGGCATCCACGGCCTGAGGTACTTCGACCTGTGGGGCA GGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:495] CAGGTGCAGCTGCAGCAGTGGGGCGCCGGCCTGCTGAAGCCCAG CGAGACCCTGAGCCTGACCTGCGCCGTGTACGGCGGCAGCTTCAG CGGCTACTACTGGAGCTGGATCAGGCAGCCCCCCGGCAAGTGCCT

Table 1	VH	VL
	GGAGTGGATCGGCGAGATCGACCACAGCGGCAGCACCAACTACA ACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACACCAGC AAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGA CACCGCCGTGTACTACTGCGCCAGGCAGGGCATCCACGGCCTGAG GTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCA GCGGCGGCGGCGGCAGCGAGATCGTGATGACCCAGAGCCCCGCC ACCCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAG GGCCAGCCAGAGCGTGAGCAGCTACCTGGCCTGGTACCAGCAGA AGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGACGCCAGCAAC AGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGG CACCGACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAGGACTT CGCCGTGTACTACTGCCAGCAGGACCACAACTTCCCCTACACCTT CGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:496]	
ADI-10160 [Ab15]	EVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGK GLEWVANINQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCAREANYYGNVG DDYWGQGTLVTVSS [SEQ ID NO:274] CDR1: SYWMS [SEQ ID NO:328] or FTFSSYWMS [SEQ ID NO:536] (non-Kabat) CDR2: NINQDGSEKYYVDSVKG [SEQ ID NO:329] CDR3: EANYYGNVGDDY [SEQ ID NO:330] or AREANYYGNVGDDY [SEQ ID NO:537] (non-Kabat)	DIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQQYVT PITFGGGTKVEIK [SEQ ID NO:275] CDR1: RASQSISSYLN [SEQ ID NO:331] CDR2: AASSLQS [SEQ ID NO:332] CDR3: QQQYVTPIT [SEQ ID NO:333]
scFv of Ab15	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQQYVTPIT FG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQP GGSLRLSCAASGFTFSSYWMSWVRQAPGK*C*LEWVANINQDGSEKY YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREANYYG NVGDDYWGQGTLVTVSS [SEQ ID NO:455] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK*C*LE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCAREANYYGNVGDDYWGQGTLVTVSS**GGGGSGGGGSGGGG SGGGGS**DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ QYVTPITFG*C*GTKVEIK [SEQ ID NO:456]	
Exemplary	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGT	

Table 1	VH	VL
nucleotide sequence of Ab15 scFv	GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCA GCAGCTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAGCCTGCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGCAGTACGTGACCCCCATCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGA GAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGA GCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCT GGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAAC ATCAACCAGGACGGCAGCGAGAAGTACTACGTGGACAGCGTGAA GGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGT ACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGGGAGGCCAACTACTACGGCAACGTGGGCGACGA CTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:497] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGAAGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCAACTACTAC GGCAACGTGGGCGACGACTACTGGGGCCAGGGCACCCTGGTGAC CGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCG GCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAG AGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCAT CACCTGCAGGGCCAGCCAGAGCATCAGCAGCTACCTGAACTGGT ACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCC GCCAGCAGCCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAG CGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCC CGAGGACTTCGCCACCTACTACTGCCAGCAGCAGTACGTGACCCC CATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:498]	
ADI-10161 [Ab16]	EVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGK GLEWVANINQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCAREGGDSWYHA FDIWGQGTMVTVSS [SEQ ID NO:276] CDR1: SYWMS [SEQ ID NO:334] or FTFSSYWMS [SEQ ID NO:538] (non-Kabat)	DIQMTQSPSSVSASVGDRVTITC RASQGISSWLAWYQQKPGKAPK LLIYAASNLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQKLS LPLTFGGGTKVEIK [SEQ ID NO:277] CDR1: RASQGISSWLA [SEQ ID NO:337] CDR2: AASNLQS [SEQ ID

Table 1	VH	VL
	CDR2: NINQDGSEKYYVDSVKG [SEQ ID NO:335] CDR3: EGGDSWYHAFDI [SEQ ID NO:336] or AREGGDSWYHAFDI [SEQ ID NO:539] (non-Kabat)	NO:338] CDR3: QQKLSLPLT [SEQ ID NO:339]
scFv of Ab16	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQKLSLPLTFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK*C*LEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGDSWYHAFDIWGQGTMVTVSS [SEQ ID NO:457] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK*C*LEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGDSWYHAFDIWGQGTMVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQKLSLPLTFG*C*GTKVEIK [SEQ ID NO:458]
Exemplary nucleotide sequence of Ab16 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCGTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGGGCATCAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCCAGCAACCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGAAGCTGAGCCTGCCCCTGACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGAAGTACTACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCGGCGACAGCTGGTACCACGCCTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC [SEQ ID NO:499] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGAAGTACTACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGGCGGCGACAGCTGGTACCACGCCTTCGACATCTGGGGCCAGGGCACCATGGTGACC

Table 1	VH	VL
	GTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGG CGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGA GCCCCAGCAGCGTGAGCGCCAGCGTGGGCGACAGGGTGACCATC ACCTGCAGGGCCAGCCAGGGCATCAGCAGCTGGCTGGCCTGGTA CCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCG CCAGCAACCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGC GGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCC GAGGACTTCGCCACCTACTACTGCCAGCAGAAGCTGAGCCTGCCC CTGACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:500]	
ADI-10163 [Ab17]	QVQLQESGPGLVKPSQTLSLTCT VSGGSISSGGYYWSWIRQHPGK GLEWIGSIYYSGSTYYNPSLKSR VTISVDTSKNQFSLKLSSVTAAD TAVYYCARDRLDYSYNYGMDV WGQGTTVTVSS [SEQ ID NO:278] CDR1: SGGYYWS [SEQ ID NO:340] or GSISSGGYYWS [SEQ ID NO:540] (non-Kabat) CDR2: SIYYSGSTYYNPSLKS [SEQ ID NO:341] CDR3: DRLDYSYNYGMDV [SEQ ID NO:342] or ARDRLDYSYNYGMDV [SEQ ID NO:541] (non-Kabat)	DIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLL IYGASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQVYSAP FTFGGGTKVEIK [SEQ ID NO:279] CDR1: RASQSISSYLN [SEQ ID NO:343] CDR2: GASSLQS [SEQ ID NO:344] CDR3: QQVYSAPFT [SEQ ID NO:345]
scFv of Ab17	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYSAPF TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLQESGPGLVKP SQTLSLTCTVSGGSISSGGYYWSWIRQHPGK*C*LEWIGSIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDRLDYSYNYG MDVWGQGTTVTVSS [SEQ ID NO:459] QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGK*C*L EWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARDRLDYSYNYGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGS GGGGS**DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGK APKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQV YSAPFTFG*C*GTKVEIK [SEQ ID NO:460]	
Exemplary nucleotide sequence of Ab17	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCA GCAGCTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGGCGCCAGCAGCCTGCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC	

Table 1	VH	VL
scFv	CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGTGTACAGCGCCCCCTTCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGCAGGA GAGCGGCCCCGGCCTGGTGAAGCCCAGCCAGACCCTGAGCCTGA CCTGCACCGTGAGCGGCGGCAGCATCAGCAGCGGCGGCTACTACT GGAGCTGGATCAGGCAGCACCCCGGCAAGTGCCTGGAGTGGATC GGCAGCATCTACTACAGCGGCAGCACCTACTACAACCCCAGCCTG AAGAGCAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTT CAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGT ACTACTGCGCCAGGGACAGGCTGGACTACAGCTACAACTACGGC ATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:501] CAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAG CCAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCA GCAGCGGCGGCTACTACTGGAGCTGGATCAGGCAGCACCCCGGC AAGTGCCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAGCAC CTACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGG ACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACC GCCGCCGACACCGCCGTGTACTACTGCGCCAGGGACAGGCTGGA CTACAGCTACAACTACGGCATGGACGTGTGGGGCCAGGGCACCA CCGTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGC AGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGAT GACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGG TGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCAGCTACCTGA ACTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCT ACGGCGCCAGCAGCCTGCAGAGCGGCGTGCCCAGCAGGTTCAGC GGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTG CAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGTGTACAGC GCCCCCTTCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:502]	
ADI-10164 [Ab18]	QVQLQESGPGLVKPSETLSLTCA VSGYSISSGYYWGWIRQPPGKG LEWIGSIYHSGSTNYNPSLKSRV TISVDTSKNQFSLKLSSVTAADT AVYYCARLPPWFGFSYFDLWG RGTLVTVSS [SEQ ID NO:280] CDR1: SGYYWG [SEQ ID NO:346] or YSISSGYYWG [SEQ ID NO:542] (non-Kabat) CDR2: SIYHSGSTNYNPSLKS [SEQ ID NO:347] CDR3: LPPWFGFSYFDL [SEQ ID NO:348] or ARLPPWFGFSYFDL	EIVLTQSPATLSLSPGERATLSCR ASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQVDN YPPTFGGGTKVEIK [SEQ ID NO:281] CDR1: RASQSVSSYLA [SEQ ID NO:349] CDR2: DASNRAT [SEQ ID NO:350] CDR3: QQVDNYPPT [SEQ ID NO:351]

Table 1	VH	VL
	[SEQ ID NO:543] (non-Kabat)	
scFv of Ab18	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQVDNYPPTFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLQESGPGLVKPSETLSLTCAVSGYSISSGYYWGWIRQPPGK*C*LEWIGSIYHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLPPWFGFSYFDLWGRGTLVTVSS [SEQ ID NO:461] QVQLQESGPGLVKPSETLSLTCAVSGYSISSGYYWGWIRQPPGK*C*LEWIGSIYHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLPPWFGFSYFDLWGRGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQVDNYPPTFG*C*GTKVEIK [SEQ ID NO:462]
Exemplary nucleotide sequence of Ab18 scFv	GAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGACGCCAGCAACAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCAGGTGGACAACTACCCCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCGCCGTGAGCGGCTACAGCATCAGCAGCGGCTACTACTGGGGCTGGATCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCAGCATCTACCACAGCGGCAGCACCAACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGGCTGCCCCCCTGGTTCGGCTTCAGCTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:503] CAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCGCCGTGAGCGGCTACAGCATCAGCAGCGGCTACTACTGGGGCTGGATCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCAGCATCTACCACAGCGGCAGCACCAACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGGCTGCCCCCCTGGTTCGGCTTCAGCTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGACGCCAGCAACAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCG

Table 1	VH	VL
	GCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAGCCCG AGGACTTCGCCGTGTACTACTGCCAGCAGGTGGACAACTACCCCC CCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:504]	
ADI-10165 [Ab19]	EVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGK GLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARDVGPGIAYQ GHFDYWGQGTLVTVSS [SEQ ID NO:282] CDR1: SYWMS [SEQ ID NO:352] or FTFSSYWMS [SEQ ID NO:544] (non-Kabat) CDR2: NIKQDGSEKYYVDSVKG [SEQ ID NO:353] CDR3: DVGPGIAYQGHFDY [SEQ ID NO:354] or ARDVGPGIAYQGHFDY [SEQ ID NO:545] (non-Kabat)	DIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQVYDT PLTFGGGTKVEIK [SEQ ID NO:283] CDR1: RASQSISSYLN [SEQ ID NO:355] CDR2: AASSLQS [SEQ ID NO:356] CDR3: QQVYDTPLT [SEQ ID NO:357]
scFv of Ab19	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPL TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQ PGGSLRLSCAASGFTFSSYWMSWVRQAPGK*C*LEWVANIKQDGSEKY YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIA YQGHFDYWGQGTLVTVSS [SEQ ID NO:463] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK*C*LE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARDVGPGIAYQGHFDYWGQGTLVTVSS**GGGGSGGGGSGGG GSGGGGS**DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKP GKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QVYDTPLTFG*C*GTKVEIK [SEQ ID NO:464]	
Exemplary nucleotide sequence of Ab19 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCA GCAGCTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAGCCTGCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGTGTACGACACCCCCCTGACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGA GAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGA GCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCT	

Table 1	VH	VL
	GGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAAC ATCAAGCAGGACGGCAGCGAGAAGTACTACGTGGACAGCGTGAA GGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGT ACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGGGACGTGGGCCCCGGCATCGCCTACCAGGGCCAC TTCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:505] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAG CAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAAGCAGGACGGCAGCGAGAAGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGACGTGGGCCCCGGC ATCGCCTACCAGGGCCACTTCGACTACTGGGGCCAGGGCACCCTG GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGA CCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTG ACCATCACCTGCAGGGCCAGCCAGAGCATCAGCAGCTACCTGAA CTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTA CGCCGCCAGCAGCCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCG GCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGC AGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGTGTACGACA CCCCCCTGACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:506]	
ADI-10167 [Ab20]	QLQLQESGPGLVKPSETLSLTCT VSGGSISSSSYYWGWIRQPPGK GLEWIGSIYYSGSTYYNPSLKSR VTISVDTSKNQFSLKLSSVTAAD TAVYYCARETAHDVHGMDVW GQGTTVTVSS [SEQ ID NO:284] CDR1: SSSYYWG [SEQ ID NO:358] or GSISSSSYYWG [SEQ ID NO:546] (non-Kabat) CDR2: SIYYSGSTYYNPSLKS [SEQ ID NO:359] CDR3: ETAHDVHGMDV [SEQ ID NO:360] or ARETAHDVHGMDV [SEQ ID NO:547] (non-Kabat)	EIVLTQSPATLSLSPGERATLSCR ASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTD FTLTISSLEPEDFAVYYCQQYDN LPTFGGGTKVEIK [SEQ ID NO:285] CDR1: RASQSVSSYLA [SEQ ID NO:361] CDR2: DASNRAT [SEQ ID NO:362] CDR3: QQYDNLPT [SEQ ID NO:363]
scFv of Ab20	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLI YDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLPT FG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QLQLQESGPGLVKPS ETLSLTCTVSGGSISSSSYYWGWIRQPPGK*C*LEWIGSIYYSGSTYYNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARETAHDVHGMD	

Table 1	VH	VL
	VWGQGTTVTVSS [SEQ ID NO:465] QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKCLE WIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARETAHDVHGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGG GSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLP TFGCGTKVEIK [SEQ ID NO:466]	
Exemplary nucleotide sequence of Ab20 scFv	GAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCC GGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCA GGCTGCTGATCTACGACGCCAGCAACAGGGCCACCGGCATCCCCG CCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCA TCAGCAGCCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGC AGTACGACAACCTGCCCACCTTCGGCTGCGGCACCAAGGTGGAG ATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGG CGGCAGCGGCGGCGGCGGCAGCCAGCTGCAGCTGCAGGAGAGCG GCCCCGGCCTGGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCA CCGTGAGCGGCGGCAGCATCAGCAGCAGCAGCTACTACTGGGGC TGGATCAGGCAGCCCCCCGGCAAGTGCCTGGAGTGGATCGGCAG CATCTACTACAGCGGCAGCACCTACTACAACCCCAGCCTGAAGAG CAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCC TGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACT GCGCCAGGGAGACCGCCCACGACGTGCACGGCATGGACGTGTGG GGCCAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:507] CAGCTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAG CGAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCA GCAGCAGCAGCTACTACTGGGGCTGGATCAGGCAGCCCCCCGGC AAGTGCCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAGCAC CTACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGG ACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACC GCCGCCGACACCGCCGTGTACTACTGCGCCAGGGAGACCGCCCAC GACGTGCACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGAC CGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCG GCGGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGCTGACCCAG AGCCCCGCCACCCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCT GAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCTACCTGGCCTGGT ACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGAC GCCAGCAACAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAG CGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAGCC CGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGACAACCTGCC CACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:508]	
ADI-10168 [Ab21]	QVQLVQSGAEVKKPGSSVKVSC KASGGTFSSYAISWVRQAPGQG LEWMGSIIPIFGTANYAQKFQGR	EIVLTQSPATLSLSPGERATLSCR ASQSVSSYLAWYQQKPGQAPRL LIYDASKRATGIPARFSGSGSGTD

Table 1	VH	VL
	VTITADESTSTAYMELSSLRSED TAVYYCAREVGYGWYTKIAFDI WGQGTMVTVSS [SEQ ID NO:286] CDR1: SYAIS [SEQ ID NO:364] or GTFSSYAIS [SEQ ID NO:548] (non-Kabat) CDR2: SIIPIFGTANYAQKFQG [SEQ ID NO:365] CDR3: EVGYGWYTKIAFDI [SEQ ID NO:366] or AREVGYGWYTKIAFDI [SEQ ID NO:549] (non-Kabat)	FTLTISSLEPEDFAVYYCQQSSNH PSTFGGGTKVEIK [SEQ ID NO:287] CDR1: RASQSVSSYLA [SEQ ID NO:367] CDR2: DASKRAT [SEQ ID NO:368] CDR3: QQSSNHPST [SEQ ID NO:369]
scFv of Ab21	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLI YDASKRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNHPST FG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKKP GSSVKVSCKASGGTFSSYAISWVRQAPGQ*C*LEWMGSIIPIFGTANYA QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAREVGYGWYTK IAFDIWGQGTMVTVSS [SEQ ID NO:467] QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQ*C*LE WMGSIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVY YCAREVGYGWYTKIAFDIWGQGTMVTVSS**GGGGSGGGGSGGGGS GGGGS**EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQ APRLLIYDASKRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQS SNHPSTFG*C*GTKVEIK [SEQ ID NO:468]
Exemplary nucleotide sequence of Ab21 scFv	GAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCC GGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCA GGCTGCTGATCTACGACGCCAGCAAGAGGGCCACCGGCATCCCC GCCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACC ATCAGCAGCCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAG CAGAGCAGCAACCACCCCAGCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGGTGCA GAGCGGCGCCGAGGTGAAGAAGCCCGGCAGCAGCGTGAAGGTGA GCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTACGCCATCAGCT GGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCAGC ATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAGTTCCAG GGCAGGGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTA CATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTACT ACTGCGCCAGGGAGGTGGGCTACGGCTGGTACACCAAGATCGCC TTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGC [SEQ ID NO:509]	

Table 1	VH	VL
	CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGG CAGCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCGGCACCTTCA GCAGCTACGCCATCAGCTGGGTGAGGCAGGCCCCCGGCCAGTGC CTGGAGTGGATGGGCAGCATCATCCCCATCTTCGGCACCGCCAAC TACGCCCAGAAGTTCCAGGGCAGGGTGACCATCACCGCCGACGA GAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAGGAGCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGTGGGCTACGGC TGGTACACCAAGATCGCCTTCGACATCTGGGGCCAGGGCACCATG GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGCTGA CCCAGAGCCCCGCCACCCTGAGCCTGAGCCCCGGCGAGAGGGCC ACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCTACCTGGC CTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTA CGACGCCAGCAAGAGGGCCACCGGCATCCCCGCCAGGTTCAGCG GCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGG AGCCCGAGGACTTCGCCGTGTACTACTGCCAGCAGAGCAGCAACC ACCCCAGCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:510]	
ADI-10173 [Ab22]	QVQLVQSGAEVKKPGASVKVS CKASGYTFTSYYMHWVRQAPG QGLEWMGIINPSGGSTTYAQKF QGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCAREAADGFVGE RYFDLWGRGTLVTVSS [SEQ ID NO:288] CDR1: SYYMH [SEQ ID NO:370] or YTFTSYYMH [SEQ ID NO:550] (non-Kabat) CDR2: IINPSGGSTTYAQKFQG [SEQ ID NO:371] CDR3: EAADGFVGERYFDL [SEQ ID NO:372] or AREAADGFVGERYFDL [SEQ ID NO:551] (non-Kabat)	DIVMTQSPLSLPVTPGEPASISCR SSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYC MQALGVPLTFGGGTKVEIK [SEQ ID NO:289] CDR1: RSSQSLLHSNGYNYLD [SEQ ID NO:373] CDR2: LGSNRAS [SEQ ID NO:374] CDR3: MQALGVPLT [SEQ ID NO:375]
scFv of Ab22	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ ALGVPLTFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQS GAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ*C*LEWMGIIN PSGGSTTYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR EAADGFVGERYFDLWGRGTLVTVSS [SEQ ID NO:469] QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ*C*L EWMGIINPSGGSTTYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCAREAADGFVGERYFDLWGRGTLVTVSS**GGGGSGGGGSGGG**	

Table 1	VH	VL
	GSGGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDW YLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDV GVYYCMQALGVPLTFG**C**GTKVEIK [SEQ ID NO:470]	
Exemplary nucleotide sequence of Ab22 scFv	GACATCGTGATGACCCAGAGCCCCCTGAGCCTGCCCGTGACCCCC GGCGAGCCCGCCAGCATCAGCTGCAGGAGCAGCCAGAGCCTGCT GCACAGCAACGGCTACAACTACCTGGACTGGTACCTGCAGAAGC CCGGCCAGAGCCCCCAGCTGCTGATCTACCTGGGCAGCAACAGG GCCAGCGGCGTGCCCGACAGGTTCAGCGGCAGCGGCAGCGGCAC CGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGACGTGG GCGTGTACTACTGCATGCAGGCCCTGGGCGTGCCCCTGACCTTCG GCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCCA GGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCG CCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCACC AGCTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCCTG GAGTGGATGGGCATCATCAACCCCAGCGGCGGCAGCACCACCTA CGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACACCA GCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCGAG GACACCGCCGTGTACTACTGCGCCAGGGAGGCCGCCGACGGCTTC GTGGGCGAGAGGTACTTCGACCTGTGGGGCAGGGGCACCCTGGT GACCGTGAGCAGC [SEQ ID NO:511] CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGG CGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCA CCAGCTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCC TGGAGTGGATGGGCATCATCAACCCCAGCGGCGGCAGCACCACC TACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACAC CAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCGCCGACGGC TTCGTGGGCGAGAGGTACTTCGACCTGTGGGGCAGGGGCACCCTG GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCGTGATGA CCCAGAGCCCCCTGAGCCTGCCCGTGACCCCCGGCGAGCCCGCCA GCATCAGCTGCAGGAGCAGCCAGAGCCTGCTGCACAGCAACGGC TACAACTACCTGGACTGGTACCTGCAGAAGCCCGGCCAGAGCCCC CAGCTGCTGATCTACCTGGGCAGCAACAGGGCCAGCGGCGTGCCC GACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAA GATCAGCAGGGTGGAGGCCGAGGACGTGGGCGTGTACTACTGCA TGCAGGCCCTGGGCGTGCCCCTGACCTTCGGCTGCGGCACCAAGG TGGAGATCAAG [SEQ ID NO:512]	
ADI-11802 [Ab23]	QVQLVQSGAEVKKPGASVKVS CKASGYTFSGYYMHWVRQAPG QGLEWMGMINPYGGSTRYAQK FQGRVTMTRDTSTSTVYMELSS LRSEDTAVYYCAREAADGFVGE RYFDLWGRGTLVTVSS [SEQ ID	DIVMTQSPLSLPVTPGEPASISCR SSQSLLYSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYC MQDVALPITFGGGTKVEIK [SEQ ID NO:291]

Table 1	VH	VL
	NO:290] CDR1: GYYMH [SEQ ID NO:376] or YTFSGYYMH [SEQ ID NO:552] (non-Kabat) CDR2: MINPYGGSTRYAQKFQG [SEQ ID NO:377] CDR3: EAADGFVGERYFDL [SEQ ID NO:378] or AREAADGFVGERYFDL [SEQ ID NO:553] (non-Kabat)	CDR1: RSSQSLLYSNGYNYLD [SEQ ID NO:379] CDR2: LGSNRAS [SEQ ID NO:380] CDR3: MQDVALPIT [SEQ ID NO:381]
scFv of Ab23	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKKPGASVKVSCKASGYTFSGYYMHWVRQAPGQ*C*LEWMGMINPYGGSTRYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYFDLWGRGTLVTVSS [SEQ ID NO:471] QVQLVQSGAEVKKPGASVKVSCKASGYTFSGYYMHWVRQAPGQ*C*LEWMGMINPYGGSTRYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYFDLWGRGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFG*C*GTKVEIK [SEQ ID NO:472]
Exemplary nucleotide sequence of Ab23 scFv	GACATCGTGATGACCCAGAGCCCCCTGAGCCTGCCCGTGACCCCCGGCGAGCCCGCCAGCATCAGCTGCAGGAGCAGCCAGAGCCTGCTGTACAGCAACGGCTACAACTACCTGGACTGGTACCTGCAGAAGCCCGGCCAGAGCCCCCAGCTGCTGATCTACCTGGGCAGCAACAGGGCCAGCGGCGTGCCCGACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGACGTGGGCGTGTACTACTGCATGCAGGACGTGGCCCTGCCCATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCAGCGGCTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCATGATCAACCCCTACGGCGGCAGCACCAGGTACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCGCCGACGGCTTCGTGGGCGAGAGGTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:513] CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCA

Table 1	VH	VL
	GCGGCTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCC TGGAGTGGATGGGCATGATCAACCCCTACGGCGGCAGCACCAGG TACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACAC CAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCGCCGACGGC TTCGTGGGCGAGAGGTACTTCGACCTGTGGGGCAGGGGCACCCTG GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCGTGATGA CCCAGAGCCCCCTGAGCCTGCCCGTGACCCCCGGCGAGCCCGCCA GCATCAGCTGCAGGAGCAGCCAGAGCCTGCTGTACAGCAACGGC TACAACTACCTGGACTGGTACCTGCAGAAGCCCGGCCAGAGCCCC CAGCTGCTGATCTACCTGGGCAGCAACAGGGCCAGCGGCGTGCCC GACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAA GATCAGCAGGGTGGAGGCCGAGGACGTGGGCGTGTACTACTGCA TGCAGGACGTGGCCCTGCCCATCACCTTCGGCTGCGGCACCAAGG TGGAGATCAAG [SEQ ID NO:514]	
ADI-11812 [Ab24]	QVQLVQSGAEVKKPGASVKVS CKASGYTFEIYYMHWVRQAPG QGLEWMGIINPSSGSTVYAQKF QGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARGAGYDDEDM DVWGKGTTVTVSS [SEQ ID NO:292] CDR1: IYYMH [SEQ ID NO:382] or YTFEIYYMH [SEQ ID NO:554] (non-Kabat) CDR2: IINPSSGSTVYAQKFQG [SEQ ID NO:383] CDR3: GAGYDDEDMDV [SEQ ID NO:384] or ARGAGYDDEDMDV [SEQ ID NO:555] (non-Kabat)	DIQMTQSPSSVSASVGDRVTITC RASQGIDSWLAWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQAHS YPLTFGGGTKVEIK [SEQ ID NO:293] CDR1: RASQGIDSWLA [SEQ ID NO:385] CDR2: AASSLQS [SEQ ID NO:386] CDR3: QQAHSYPLT [SEQ ID NO:387]
scFv of Ab24	DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPL TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKK PGASVKVSCKASGYTFEIYYMHWVRQAPGQ*C*LEWMGIINPSSGSTV YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDD EDMDVWGKGTTVTVSS [SEQ ID NO:473] QVQLVQSGAEVKKPGASVKVSCKASGYTFEIYYMHWVRQAPGQ*C*L EWMGIINPSSGSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTA VYYCARGAGYDDEDMDVWGKGTTVTVSS**GGGGSGGGGSGGGGS GGGGS**DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ	

Table 1	VH	VL
	AHSYPLTFGCGTKVEIK [SEQ ID NO:474]	
Exemplary nucleotide sequence of Ab24 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCGTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGGGCATCG ACAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAGCCTGCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGCCCACAGCTACCCCCTGACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGGTGCA GAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGA GCTGCAAGGCCAGCGGCTACACCTTCGAGATCTACTACATGCACT GGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCATC ATCAACCCCAGCAGCGGCAGCACCGTGTACGCCCAGAAGTTCCA GGGCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGT ACATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTAC TACTGCGCCAGGGGCGCCGGCTACGACGACGAGGACATGGACGT GTGGGGCAAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:515] CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGG CGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCG AGATCTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCC TGGAGTGGATGGGCATCATCAACCCCAGCAGCGGCAGCACCGTG TACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACAC CAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCG AGGACACCGCCGTGTACTACTGCGCCAGGGGCGCCGGCTACGAC GACGAGGACATGGACGTGTGGGGCAAGGGCACCACCGTGACCGT GAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGAG CCCCAGCAGCGTGAGCGCCAGCGTGGGCGACAGGGTGACCATCA CCTGCAGGGCCAGCCAGGGCATCGACAGCTGGCTGGCCTGGTACC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCC AGCAGCCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGG CAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGA GGACTTCGCCACCTACTACTGCCAGCAGGCCCACAGCTACCCCCT GACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:516]	
ADI-11825 [Ab25]	EVQLVESGGGLVQPGGSLRLSC AASGFTFGGYWMSWVRQAPGK GLEWVANINQDGSEEYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCAREANYYGNVG DDYWGQGTLVTVSS [SEQ ID NO:294] CDR1: GYWMS [SEQ ID NO:388]	DIQMTQSPSSLSASVGDRVTITCR ASQSIYNYLNWYQQKPGKAPKL LIYAASNLHSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQAFH VPITFGGGTKVEIK [SEQ ID NO:295] CDR1: RASQSIYNYLN [SEQ ID

Table 1	VH	VL
	or FTFGGYWMS [SEQ ID NO:556] (non-Kabat) CDR2: NINQDGSEEYYVDSVKG [SEQ ID NO:389] CDR3: EANYYGNVGDDY [SEQ ID NO:390] or AREANYYGNVGDDY [SEQ ID NO:557] (non-Kabat)	NO:391] CDR2: AASNLHS [SEQ ID NO:392] CDR3: QQAFHVPIT [SEQ ID NO:393]
scFv of Ab25	DIQMTQSPSSLSASVGDRVTITCRASQSIYNYLNWYQQKPGKAPKLLI YAASNLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAFHVPI TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQ PGGSLRLSCAASGFTFGGYWMSWVRQAPGK*C*LEWVANINQDGSEE YYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREANYY GNVGDDYWGQGTLVTVSS [SEQ ID NO:475] EVQLVESGGGLVQPGGSLRLSCAASGFTFGGYWMSWVRQAPGK*C*L EWVANINQDGSEEYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCAREANYYGNVGDDYWGQGTLVTVSS**GGGGSGGGGSGGG GSGGGGS**DIQMTQSPSSLSASVGDRVTITCRASQSIYNYLNWYQQKP GKAPKLLIYAASNLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAFHVPITFG*C*GTKVEIK [SEQ ID NO:476]
Exemplary nucleotide sequence of Ab25 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCT ACAACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAACCTGCACAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGCCTTCCACGTGCCCATCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGA GAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGA GCTGCGCCGCCAGCGGCTTCACCTTCGGCGGCTACTGGATGAGCT GGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAAC ATCAACCAGGACGGCAGCGAGGAGTACTACGTGGACAGCGTGAA GGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGT ACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGGGAGGCCAACTACTACGGCAACGTGGGCGACGA CTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:517] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCGG CGGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGGAGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA

Table 1	VH	VL
	CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCAACTACTAC GGCAACGTGGGCGACGACTACTGGGGCCAGGGCACCCTGGTGAC CGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCG GCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAG AGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCAT CACCTGCAGGGCCAGCCAGAGCATCTACAACTACCTGAACTGGTA CCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCG CCAGCAACCTGCACAGCGGCGTGCCCAGCAGGTTCAGCGGCAGC GGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCC GAGGACTTCGCCACCTACTACTGCCAGCAGGCCTTCCACGTGCCC ATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:518]	
ADI-11826 [Ab26]	EVQLVESGGGLVQPGGSLRLSC AASGFTFPGYWMSWVRQAPGK GLEWVANINQDGSEVYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCAREANYYGNVG DDYWGQGTLVTVSS [SEQ ID NO:296] CDR1: GYWMS [SEQ ID NO:394] or FTFPGYWMS [SEQ ID NO:558] (non-Kabat) CDR2: NINQDGSEVYYVDSVKG [SEQ ID NO:395] CDR3: EANYYGNVGDDY [SEQ ID NO:396] or AREANYYGNVGDDY [SEQ ID NO:559] (non-Kabat)	DIQMTQSPSSLSASVGDRVTITCR ASQSIYNYLNWYQQKPGKAPKL LIYAASSTQSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQAFHV PITFGGGTKVEIK [SEQ ID NO:297] CDR1: RASQSIYNYLN [SEQ ID NO:397] CDR2: AASSTQS [SEQ ID NO:398] CDR3: QQAFHVPIT [SEQ ID NO:399]
scFv of Ab26	DIQMTQSPSSLSASVGDRVTITCRASQSIYNYLNWYQQKPGKAPKLLI YAASSTQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAFHVPIT FG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQP GGSLRLSCAASGFTFPGYWMSWVRQAPGK*C*LEWVANINQDGSEVY YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREANYYG NVGDDYWGQGTLVTVSS [SEQ ID NO:477] EVQLVESGGGLVQPGGSLRLSCAASGFTFPGYWMSWVRQAPGK*C*LE WVANINQDGSEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCAREANYYGNVGDDYWGQGTLVTVSS**GGGGSGGGGSGGGG SGGGGS**DIQMTQSPSSLSASVGDRVTITCRASQSIYNYLNWYQQKPG KAPKLLIYAASSTQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ AFHVPITFG*C*GTKVEIK [SEQ ID NO:478]	
Exemplary nucleotide	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCT	

Table 1	VH	VL
sequence of Ab26 scFv	ACAACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCAGCACCCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGCCTTCCACGTGCCCATCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGA GAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGA GCTGCGCCGCCAGCGGCTTCACCTTCCCCGGCTACTGGATGAGCT GGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAAC ATCAACCAGGACGGCAGCGAGGTGTACTACGTGGACAGCGTGAA GGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGT ACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGGGAGGCCAACTACTACGGCAACGTGGGCGACGA CTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:519] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG CGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCCC CGGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCC TGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGGTGTAC TACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAA CGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGAGGCCAACTACTAC GGCAACGTGGGCGACGACTACTGGGGCCAGGGCACCCTGGTGAC CGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCG GCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAG AGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCAT CACCTGCAGGGCCAGCCAGAGCATCTACAACTACCTGAACTGGTA CCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCG CCAGCAGCACCCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGC GGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCC GAGGACTTCGCCACCTACTACTGCCAGCAGGCCTTCCACGTGCCC ATCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:520]	
ADI-11828 [Ab27]	EVQLVESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGK GLEWVANINQDGSEVYYVDSV KGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARDVGPGIAYQ GHFDYWGQGTLVTVSS [SEQ ID NO:298] CDR1: SYWMS [SEQ ID NO:400] or FTFSSYWMS [SEQ ID NO:560] (non-Kabat) CDR2: NINQDGSEVYYVDSVKG	DIQMTQSPSSLSASVGDRVTITCR ASQSIYYYLNWYQQKPGKAPKL LIYAASSRQSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQVYD TPLTFGGGTKVEIK [SEQ ID NO:299] CDR1: RASQSIYYYLN [SEQ ID NO:403] CDR2: AASSRQS [SEQ ID NO:404] CDR3: QQVYDTPLT [SEQ ID

Table 1	VH	VL
	[SEQ ID NO:401] CDR3: DVGPGIAYQGHFDY [SEQ ID NO:402] or ARDVGPGIAYQGHFDY [SEQ ID NO:561] (non-Kabat)	NO:405]
scFv of Ab27	DIQMTQSPSSLSASVGDRVTITCRASQSIYYYLNWYQQKPGKAPKLLIYAASSRQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPLTFG***C***GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK***C***LEWVANINQDGSEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIAYQGHFDYWGQGTLVTVSS [SEQ ID NO:479] EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK***C***LEWVANINQDGSEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIAYQGHFDYWGQGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSSLSASVGDRVTITCRASQSIYYYLNWYQQKPGKAPKLLIYAASSRQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPLTFG***C***GTKVEIK [SEQ ID NO:480]
Exemplary nucleotide sequence of Ab27 scFv	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCTACTACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCCAGCAGCAGGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGTGTACGACACCCCCCTGACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGGTGTACTACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGACGTGGGCCCCGGCATCGCCTACCAGGGCCACTTCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:521] GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACTGGATGAGCTGGGTGAGGCAGGCCCCCGGCAAGTGCCTGGAGTGGGTGGCCAACATCAACCAGGACGGCAGCGAGGTGTACTACGTGGACAGCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGACGTGGGCCCCGGCATCGCCTACCAGGGCCACTTCGACTACTGGGGCCAGGGCACCCTG

Table 1	VH	VL
	GTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAG CGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGA CCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTG ACCATCACCTGCAGGGCCAGCCAGAGCATCTACTACTACCTGAAC TGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTAC GCCGCCAGCAGCAGGCAGAGCGGCGTGCCCAGCAGGTTCAGCGG CAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCA GCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGTGTACGACAC CCCCCTGACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:522]	
ADI-11839 [Ab28]	QVQLVQSGAEVKKPGASVKVS CKASGYTFSNYYMHWVRQAPG QGLEWMGWINPFSGGTRYAQK FQGRVTMTRDTSTSTVYMELSS LRSEDTAVYYCARDVGSSAYY YMDVWGKGTTVTVSS [SEQ ID NO:300] CDR1: NYYMH [SEQ ID NO:406] or YTFSNYYMH [SEQ ID NO:562] (non-Kabat) CDR2: WINPFSGGTRYAQKFQG [SEQ ID NO:407] CDR3: DVGSSAYYYMDV [SEQ ID NO:408] or ARDVGSSAYYYMDV [SEQ ID NO:563] (non-Kabat)	DIQMTQSPSSVSASVGDRVTITCE ASKGISSWLAWYQQKPGKAPKL LIYAASDLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQAFL FPPTFGGGTKVEIK [SEQ ID NO:301] CDR1: EASKGISSWLA [SEQ ID NO:409] CDR2: AASDLQS [SEQ ID NO:410] CDR3: QQAFLFPPT [SEQ ID NO:411]
scFv of Ab28	DIQMTQSPSSVSASVGDRVTITCEASKGISSWLAWYQQKPGKAPKLL IYAASDLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAFLFPP TFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKK PGASVKVSCKASGYTFSNYYMHWVRQAPGQ*C*LEWMGWINPFSGGT RYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDVGSSA YYYMDVWGKGTTVTVSS [SEQ ID NO:481] QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYYMHWVRQAPGQ*C*L EWMGWINPFSGGTRYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARDVGSSAYYYMDVWGKGTTVTVSS**GGGGSGGGGSGGG GSGGGGS**DIQMTQSPSSVSASVGDRVTITCEASKGISSWLAWYQQK PGKAPKLLIYAASDLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAFLFPPTFG*C*GTKVEIK [SEQ ID NO:482]	
Exemplary nucleotide sequence of Ab28	GACATCCAGATGACCCAGAGCCCCAGCAGCGTGAGCGCCAGCGT GGGCGACAGGGTGACCATCACCTGCGAGGCCAGCAAGGGCATCA GCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC AAGCTGCTGATCTACGCCGCCAGCGACCTGCAGAGCGGCGTGCCC AGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAC	

Table 1	VH	VL
scFv	CATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGGCCTTCCTGTTCCCCCCCACCTTCGGCTGCGGCACCAAGGT GGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCGGCAGCGGCGGCGGCGGCAGCCAGGTGCAGCTGGTGCA GAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCGTGAAGGTGA GCTGCAAGGCCAGCGGCTACACCTTCAGCAACTACTACATGCACT GGGTGAGGCAGGCCCCCGGCCAGTGCCTGGAGTGGATGGGCTGG ATCAACCCCTTCAGCGGCGGCACCAGGTACGCCCAGAAGTTCCAG GGCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGTA CATGGAGCTGAGCAGCCTGAGGAGCGAGGACACCGCCGTGTACT ACTGCGCCAGGGACGTGGGCAGCAGCGCCTACTACTACATGGAC GTGTGGGGCAAGGGCACCACCGTGACCGTGAGCAGC [SEQ ID NO:523] CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGG CGCCAGCGTGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCA GCAACTACTACATGCACTGGGTGAGGCAGGCCCCCGGCCAGTGCC TGGAGTGGATGGGCTGGATCAACCCCTTCAGCGGCGGCACCAGGT ACGCCCAGAAGTTCCAGGGCAGGGTGACCATGACCAGGGACACC AGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAGGAGCGA GGACACCGCCGTGTACTACTGCGCCAGGGACGTGGGCAGCAGCG CCTACTACTACATGGACGTGTGGGGCAAGGGCACCACCGTGACCG TGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGACATCCAGATGACCCAGAG CCCCAGCAGCGTGAGCGCCAGCGTGGGCGACAGGGTGACCATCA CCTGCGAGGCCAGCAAGGGCATCAGCAGCTGGCTGGCCTGGTAC CAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGC CAGCGACCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCG GCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCG AGGACTTCGCCACCTACTACTGCCAGCAGGCCTTCCTGTTCCCCCC CACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:524]	
ADI-10152 [Ab29]	EVQLVQSGAEVKKPGESLKISC KGSGYSFTSYWIGWVRQMPGK GLEWMGSIYPGDSDTRYSPSFQ GQVTISADKSISTAYLQWSSLKA SDTAMYYCARELAYGDYKGGV DYWGQGTLVTVSS [SEQ ID NO:302] CDR1: SYWIG [SEQ ID NO:412] or YSFTSYWIG [SEQ ID NO:564] (non-Kabat) CDR2: SIYPGDSDTRYSPSFQG [SEQ ID NO:413] CDR3: ELAYGDYKGGVDY [SEQ	EIVLTQSPGTLSLSPGERATLSCR ASQSVSSSFLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQLDS PPPTFGGGTKVEIK [SEQ ID NO:303] CDR1: RASQSVSSSFLA [SEQ ID NO:415] CDR2: GASSRAT [SEQ ID NO:416] CDR3: QQLDSPPPT [SEQ ID NO:417]

Table 1	VH	VL
	ID NO:414] or ARELAYGDYKGGVDY [SEQ ID NO:565] (non-Kabat)	
scFv of Ab29	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQLDSPPPTFG*C*GTKVEIK**GGGGSGGGGSGGGGSGGGGS**EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGK*C*LEWMGSIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARELAYGDYKGGVDYWGQGTLVTVSS [SEQ ID NO:483] EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGK*C*LEWMGSIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARELAYGDYKGGVDYWGQGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQLDSPPPTFG*C*GTKVEIK [SEQ ID NO:484]
Exemplary nucleotide sequence of Ab29 scFv	GAGATCGTGCTGACCCAGAGCCCCGGCACCCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCAGCTTCCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGGCGCCAGCAGCAGGGCCACCGGCATCCCCGACAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCAGCTGGACAGCCCCCCCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGAGAGCCTGAAGATCAGCTGCAAGGGCAGCGGCTACAGCTTCACCAGCTACTGGATCGGCTGGGTGAGGCAGATGCCCGGCAAGTGCCTGGAGTGGATGGGCAGCATCTACCCCGGCGACAGCGACACCAGGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGCGCCAGGGAGCTGGCCTACGGCGACTACAAGGGCGGCGTGGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGC [SEQ ID NO:525] GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGAGAGCCTGAAGATCAGCTGCAAGGGCAGCGGCTACAGCTTCACCAGCTACTGGATCGGCTGGGTGAGGCAGATGCCCGGCAAGTGCCTGGAGTGGATGGGCAGCATCTACCCCGGCGACAGCGACACCAGGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGCGCCAGGGAGCTGGCCTACGGCGACTACAAGGGCGGCGTGGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGAGATCGTGCTGACCCAGAGCCCCGGCACCCTGAGCCTGAGCCCCGGCGAGAGGGCCAC

Table 1	VH	VL
	CCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCAGCTTCCTGG CCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCT ACGGCGCCAGCAGCAGGGCCACCGGCATCCCCGACAGGTTCAGC GGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGGCT GGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCAGCTGGACAG CCCCCCCCCCACCTTCGGCTGCGGCACCAAGGTGGAGATCAAG [SEQ ID NO:526]	
Clone 280-31-01 (mut) of WO2012045752	QVQLVQSGAEVKKPGSSVKVSC KASGGTFSDYAISWVRQAPGQG LEWMGRIIPILGVADYAQKFQG RVTITADKSTRTAYMELSSLRSE DTAVYYCARNWADAFDIWGQG TMVTVSS [SEQ ID NO:418] CDR1: DYAIS [SEQ ID NO:422] CDR2: RIIPILGVADYAQKFQG [SEQ ID NO:423] CDR3: NWADAFDI [SEQ ID NO:424]	DIQLTQSPSSLSASVGDRVTITCR ASQGISSVLAWYQQKPGKAPKL LIYDASSLESGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQFDSSI TFGQGTKLEIK [SEQ ID NO:419] CDR1: RASQGISSVLA [SEQ ID NO:425] CDR2: DASSLES [SEQ ID NO:426] CDR3: QQFDSSIT [SEQ ID NO:427]
scFv of clone 280-31-01 (mut) of WO2012045752	DIQLTQSPSSLSASVGDRVTITCRASQGISSVLAWYQQKPGKAPKLLI YDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFDSSITF G*C*GTKLEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKKPG SSVKVSCKASGGTFSDYAISWVRQAPGQ*C*LEWMGRIIPILGVADYAQ KFQGRVTITADKSTRTAYMELSSLRSEDTAVYYCARNWADAFDIWG QGTMVTVSS [SEQ ID NO:485] QVQLVQSGAEVKKPGSSVKVSCKASGGTFSDYAISWVRQAPGQ*C*LE WMGRIIPILGVADYAQKFQGRVTITADKSTRTAYMELSSLRSEDTAV YYCARNWADAFDIWGQGTMVTVSS**GGGGSGGGGSGGGGSGGGG S**DIQLTQSPSSLSASVGDRVTITCRASQGISSVLAWYQQKPGKAPKLL IYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFDSSITF G*C*GTKLEIK [SEQ ID NO:486]	
lintuzumab	QVQLVQSGAEVKKPGSSVKVSC KASGYTFTDYNMHWVRQAPGQ GLEWIGYIYPYNGGTGYNQKFK SKATITADESTNTAYMELSSLRS EDTAVYYCARGRPAMDYWGQ GTLVTVSS [SEQ ID NO:420] CDR1: DYNMH [SEQ ID NO:428] CDR2: YIYPYNGGTGYNQKFKS [SEQ ID NO:429] CDR3: GRPAMDY [SEQ ID	DIQMTQSPSSLSASVGDRVTITCR ASESVDNYGISFMNWFQQKPGK APKLLIYAASNQGSGVPSRFSGS GSGTDFTLTISSLQPDDFATYYCQ QSKEVPWTFGQGTKVEIK [SEQ ID NO:421] CDR1: RASESVDNYGISFMN [SEQ ID NO:431] CDR2: AASNQGS [SEQ ID NO:432]

Table 1	VH	VL
	NO:430]	CDR3: QQSKEVPWT [SEQ ID NO:433]
scFv of lintuzumab	DIQMTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKLLIYAASNQGSGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQSKEVPWTFGCGTKVEIK**GGGGSGGGGSGGGGSGGGGS**QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYNMHWVRQAPGQCLEWIGYIYPYNGGTGYNQKFKSKATITADESTNTAYMELSSLRSEDTAVYYCARGRPAMDYWGQGTLVTVSS [SEQ ID NO:487] QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYNMHWVRQAPGQCLEWIGYIYPYNGGTGYNQKFKSKATITADESTNTAYMELSSLRSEDTAVYYCARGRPAMDYWGQGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKLLIYAASNQGSGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQSKEVPWTFGCGTKVEIK [SEQ ID NO:488]

An antigen binding site that binds an epitope on an extracellular domain of human CD33 and/or Cynomolgus/Rhesus (cyno) CD33

[0140] In one aspect, the invention provides an antigen binding site including a heavy chain variable domain that binds an epitope on an extracellular domain of human CD33 and/or Cynomolgus/Rhesus (cyno) CD33.

[0141] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:1]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:1. In some embodiments, the heavy chain variable domain includes amino acid sequences FTFSSYGMS [SEQ ID NO:21] as the first complementarity-determining region 1 ("CDR1"), NIKQDGSEKYYVDSVKG [SEQ ID NO:22] as the second CDR ("CDR2"), and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:23] as the third CDR ("CDR3") of SEQ ID NO:1. In some embodiments, the heavy chain variable domain includes amino acid sequences SYGMS [SEQ ID NO:434] as the first complementarity-determining region 1 ("CDR1"), NIKQDGSEKYYVDSVKG [SEQ ID NO:22] as the second CDR ("CDR2"), and EGGPYYDSSGYFVYYGMDV [SEQ ID

NO:435] as the third CDR ("CDR3") of SEQ ID NO:1. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYESFPTFGGGTKVEIK [SEQ ID NO:2]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:2, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:24] as CDR1, DASSLES [SEQ ID NO:25] as CDR2, and QQYESFPT [SEQ ID NO:26] as CDR3 of SEQ ID NO:2.

[0142] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDG SEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ GTMVTVSS [SEQ ID NO:3]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:3. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYWMS [SEQ ID NO:27] as CDR1, NIKQDGSEKYYVDSVKG [SEQ ID NO:28] as CDR2, and ARPLNAGELDV [SEQ ID NO:29] as CDR3 of SEQ ID NO:3. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SYWMS [SEQ ID NO:181] as CDR1, NIKQDGSEKYYVDSVKG [SEQ ID NO:28] as CDR2, and PLNAGELDV [SEQ ID NO:436] as CDR3 of SEQ ID NO:3. In certain embodiments, the antibody heavy chain variable domain, which includes an amino acid sequence at least 90% (*e.g.*, at least 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3, is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQLESYPLTFGGGTKVEIK [SEQ ID NO:4]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:4, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:30] as CDR1, EASSLES [SEQ ID NO:31] as CDR2, and QQLESYPLT [SEQ ID NO:32] as CDR3 of SEQ ID NO:4.

[0143] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGKGLEWVSAIVGSGE STYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVY YGMDVWGQGTTVTVSS [SEQ ID NO:5]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:5. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSKYTMS [SEQ ID NO:33] as CDR1, AIVGSGESTYFADSVKG [SEQ ID NO:34] as CDR2, and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:35] as CDR3 of SEQ ID NO:5. In some embodiments, the heavy chain variable domain incorporates amino acid sequences KYTMS [SEQ ID NO:183] as CDR1, AIVGSGESTYFADSVKG [SEQ ID NO:34] as CDR2, and EGGPYYDSSGYFVYYGMDV [SEQ ID NO:184] as CDR3 of SEQ ID NO:5. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 is combined with a light chain

variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFGGGTKVEIK [SEQ ID NO:6]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:36] as CDR1, KASSLES [SEQ ID NO:37] or KASSLE [SEQ ID NO:185] as CDR2, and QQYDDLPT [SEQ ID NO:38] as CDR3 of SEQ ID NO:6.

[0144] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQGLEWMGMINPS WGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYF DLWGRGTLVTVSS [SEQ ID NO:7]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:7. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFSDYYMH [SEQ ID NO:39] as CDR1, MINPSWGSTSYAQKFQG [SEQ ID NO:40] as CDR2, and AREAADGFVGERYFDL [SEQ ID NO:41] as CDR3 of SEQ ID NO:7. In some embodiments, the heavy chain variable domain incorporates amino acid sequences DYYMH [SEQ ID NO:437] as CDR1, AIVGSGESTYFADSVKG [SEQ ID NO:34] as CDR2, and EAADGFVGERYFDL [SEQ ID NO:438] as CDR3 of SEQ ID NO:7. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSN RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFGGGTKVEIK [SEQ ID NO:8]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8, which includes amino acid sequences RSSQSLLYSNGYNYLD [SEQ ID NO:42] as CDR1, LGSNRAS [SEQ ID NO:43] as CDR2, and MQDVALPIT [SEQ ID NO:44] as CDR3 of SEQ ID NO:8.

[0145] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGKGLEWVATIKQDG SEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ GTMVTVSS [SEQ ID NO:9]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:9. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFGSYWMS [SEQ ID NO:45] as CDR1, TIKQDGSEKSYVDSVKG [SEQ ID NO:46] as CDR2, and ARPLNAGELDV [SEQ ID NO:47] as CDR3 of SEQ ID NO:9. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SYWMS [SEQ ID NO:181] as CDR1, TIKQDGSEKSYVDSVKG [SEQ ID NO:46] as CDR2, and RPLNAGELDV [SEQ ID NO:182] as CDR3 of SEQ ID NO:9. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIK [SEQ ID NO:10]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:10, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:48] as CDR1, EASSLES [SEQ ID NO:49] as CDR2, and QQSQSYPPIT [SEQ ID NO:50] as CDR3 of SEQ ID NO:10.

[0146] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFPSYWMSWVRQAPGKGLEWVATIKRDGS EKGYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQG TMVTVSS [SEQ ID NO:11]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:11. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFPSYWMS [SEQ ID NO:51] as CDR1, TIKRDGSEKGYVDSVKG [SEQ ID NO:52] as CDR2, and ARPLNAGELDV [SEQ ID NO:53] as CDR3 of SEQ ID NO:11. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SYWMS [SEQ ID NO:181] as CDR1, TIKRDGSEKGYVDSVKG [SEQ ID NO:52] as CDR2, and PLNAGELDV [SEQ ID NO:439] as CDR3 of SEQ ID NO:11. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV

PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIK [SEQ ID NO:12]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:12, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:54] as CDR1, EASSLES [SEQ ID NO:55] as CDR2, and QQSQSYPPIT [SEQ ID NO:56] as CDR3 of SEQ ID NO:12.

[0147] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQAPGQGLEWMGIINPSR GSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDDEDMDV WGKGTTVTVSS [SEQ ID NO:13]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:13. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFGTYYMH [SEQ ID NO:57] as CDR1, IINPSRGSTVYAQKFQG [SEQ ID NO:58] as CDR2, and ARGAGYDDEDMDV [SEQ ID NO:59] as CDR3 of SEQ ID NO:13. In some embodiments, the heavy chain variable domain incorporates amino acid sequences TYYMH [SEQ ID NO:440] as CDR1, TIKRDGSEKGYVDSVKG [SEQ ID NO:52] as CDR2, and GAGYDDEDMDV [SEQ ID NO:441] as CDR3 of SEQ ID NO:13. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPLTFGGGTKVEIK [SEQ ID NO:14]. In certain embodiments, an antibody heavy chain variable domain at least 90%

(*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14, which includes amino acid sequences RASQGIDSWLA [SEQ ID NO:60] as CDR1, AASSLQS [SEQ ID NO:61] as CDR2, and QQAHSYPLT [SEQ ID NO:62] as CDR3 of SEQ ID NO:14.

[0148] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSSSEGIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:15]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:15. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYAMS [SEQ ID NO:63] as CDR1, SISSSSEGIYYADSVKG [SEQ ID NO:64] as CDR2, and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:65] as CDR3 of SEQ ID NO:15. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SYAMS [SEQ ID NO:442] as CDR1, SISSSSEGIYYADSVKG [SEQ ID NO:64] as CDR2, and EGGPYYDSSGYFVYYGMDV [SEQ ID NO:443] as CDR3 of SEQ ID NO:15. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASNSISSWLAWYQQKPGKAPKLLIYEASSTKSGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFGGGTKVEIK [SEQ ID NO:16]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 can be paired with an antibody light chain variable

domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:16, which includes amino acid sequences RASNSISSWLA [SEQ ID NO:66] as CDR1, EASSTKS [SEQ ID NO:67] as CDR2, and QQYDDLPT [SEQ ID NO:68] as CDR3 of SEQ ID NO:16.

[0149] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANINTDG SEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIAYQGHFD YWGQGTLVTVSS [SEQ ID NO:17]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:17. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYWMS [SEQ ID NO:69] as CDR1, NINTDGSEVYYVDSVKG [SEQ ID NO:70] as CDR2, and ARDVGPGIAYQGHFDY [SEQ ID NO:71] as CDR3 of SEQ ID NO:17. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SYWMS [SEQ ID NO:181] as CDR1, NINTDGSEVYYVDSVKG [SEQ ID NO:70] as CDR2, and DVGPGIAYQGHFDY [SEQ ID NO:444] as CDR3 of SEQ ID NO:17. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSSLSASVGDRVTITCRASQVIYSYLNWYQQKPGKAPKLLIYAASSLKSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPLTFGGGTKVEIK [SEQ ID NO:18]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:18, which includes amino acid

sequences RASQVIYSYLN [SEQ ID NO:72] as CDR1, AASSLKS [SEQ ID NO:73] as CDR2, and QQVYDTPLT [SEQ ID NO:74] as CDR3 of SEQ ID NO:18.

[0150] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QLQLQESGPGLVKPSETLSLTCTVSGGSISSTDYYWGWIRQPPGKGLEWIGSIGYSGT YYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARETAHDVHGMDVWGQG TTVTVSS [SEQ ID NO:19]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:19. In some embodiments, the heavy chain variable domain incorporates amino acid sequences GSISSTDYYWG [SEQ ID NO:75] as CDR1, SIGYSGTYYNPSLKS [SEQ ID NO:76] as CDR2, and ARETAHDVHGMDV [SEQ ID NO:77] as CDR3 of SEQ ID NO:19. In some embodiments, the heavy chain variable domain incorporates amino acid sequences STDYYWG [SEQ ID NO:445] as CDR1, SIGYSGTYYNPSLKS [SEQ ID NO:76] as CDR2, and ETAHDVHGMDV [SEQ ID NO:446] as CDR3 of SEQ ID NO:19. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence EIVLTQSPATLSLSPGERATLSCRASHSVYSYLAWYQQKPGQAPRLLIYDASNRATGI PARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLPTFGGGTKVEIK [SEQ ID NO:20]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:20, which includes amino acid sequences RASHSVYSYLA [SEQ ID NO:78] as CDR1, DASNRAT [SEQ ID NO:79] as CDR2, and QQYDNLPT [SEQ ID NO:80] as CDR3 of SEQ ID NO:20.

[0151] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:304 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:306 as CDR3 of SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:528 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:529 as CDR3 of SEQ ID NO:266. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267, which includes amino acid sequences SEQ ID NO:307 as CDR1, SEQ ID NO:308 as CDR2, and SEQ ID NO:309 as CDR3 of SEQ ID NO:267.

[0152] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:268. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:310 as CDR1, SEQ ID NO:311 as CDR2, and SEQ ID NO:312 as CDR3 of SEQ ID NO:268. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:530 as

CDR1, SEQ ID NO:311 as CDR2, and SEQ ID NO:531 as CDR3 of SEQ ID NO:268. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269, which includes amino acid sequences SEQ ID NO:313 as CDR1, SEQ ID NO:314 as CDR2, and SEQ ID NO:315 as CDR3 of SEQ ID NO:269.

[0153] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:316 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:318 as CDR3 of SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:532 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:533 as CDR3 of SEQ ID NO:270. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the

amino acid sequence of SEQ ID NO:271. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271, which includes amino acid sequences SEQ ID NO:319 as CDR1, SEQ ID NO:320 as CDR2, and SEQ ID NO:321 as CDR3 of SEQ ID NO:271.

[0154] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:322 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:324 as CDR3 of SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:534 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:535 as CDR3 of SEQ ID NO:272. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273, which includes amino acid sequences SEQ ID NO:325 as CDR1, SEQ ID NO:326 as CDR2, and SEQ ID NO:327 as CDR3 of SEQ ID NO:273.

[0155] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site

includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:274. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:328 as CDR1, SEQ ID NO:329 as CDR2, and SEQ ID NO:330 as CDR3 of SEQ ID NO:274. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:536 as CDR1, SEQ ID NO:329 as CDR2, and SEQ ID NO:537 as CDR3 of SEQ ID NO:274. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275, which includes amino acid sequences SEQ ID NO:331 as CDR1, SEQ ID NO:332 as CDR2, and SEQ ID NO:333 as CDR3 of SEQ ID NO:275.

[0156] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:276. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:334 as CDR1, SEQ ID NO:335 as CDR2, and SEQ ID NO:336 as CDR3 of SEQ ID NO:276. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:538 as CDR1, SEQ ID NO:335 as CDR2, and SEQ ID NO:539 as CDR3 of SEQ ID NO:276. In certain embodiments, the antibody heavy chain variable domain which includes an amino

acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:277. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:277, which includes amino acid sequences SEQ ID NO:337 as CDR1, SEQ ID NO:338 as CDR2, and SEQ ID NO:339 as CDR3 of SEQ ID NO:277.

[0157] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:340 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:342 as CDR3 of SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:540 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:541 as CDR3 of SEQ ID NO:278. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279, which includes amino acid sequences SEQ ID NO:343 as CDR1, SEQ ID NO:344 as CDR2, and SEQ ID NO:345 as CDR3 of SEQ ID NO:279.

[0158] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:346 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:348 as CDR3 of SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:542 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:543 as CDR3 of SEQ ID NO:280. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281, which includes amino acid sequences SEQ ID NO:349 as CDR1, SEQ ID NO:350 as CDR2, and SEQ ID NO:351 as CDR3 of SEQ ID NO:281.

[0159] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino

acid sequence of SEQ ID NO:282. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:352 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:354 as CDR3 of SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:544 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:545 as CDR3 of SEQ ID NO:282. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283, which includes amino acid sequences SEQ ID NO:355 as CDR1, SEQ ID NO:356 as CDR2, and SEQ ID NO:357 as CDR3 of SEQ ID NO:283.

[0160] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:358 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:546 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:547. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 is combined with a light

chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285, which includes amino acid sequences SEQ ID NO:361 as CDR1, SEQ ID NO:362 as CDR2, and SEQ ID NO:363 as CDR3 of SEQ ID NO:285.

[0161] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:364 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:366 as CDR3 of SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:548 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:549 as CDR3 of SEQ ID NO:286. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287, which includes amino acid sequences SEQ ID NO:367 as CDR1, SEQ ID NO:368 as CDR2, and SEQ ID NO:369 as CDR3 of SEQ ID NO:287.

[0162] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:370 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:372 as CDR3 of SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:550 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:551 as CDR3 of SEQ ID NO:288. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, which includes amino acid sequences SEQ ID NO:373 as CDR1, SEQ ID NO:374 as CDR2, and SEQ ID NO:375 as CDR3 of SEQ ID NO:289.

[0163] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:290. In some embodiments, the heavy chain

variable domain incorporates amino acid sequences SEQ ID NO:376 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:378 as CDR3 of SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:552 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:553 as CDR3 of SEQ ID NO:290. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291, which includes amino acid sequences SEQ ID NO:379 as CDR1, SEQ ID NO:380 as CDR2, and SEQ ID NO:381 as CDR3 of SEQ ID NO:291.

[0164] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:292. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:382 as CDR1, SEQ ID NO:383 as CDR2, and SEQ ID NO:384 as CDR3 of SEQ ID NO:292. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:554 as CDR1, SEQ ID NO:383 as CDR2, and SEQ ID NO:555 as CDR3 of SEQ ID NO:292. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:293. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:293, which includes amino acid sequences SEQ ID NO:385 as CDR1, SEQ ID NO:386 as CDR2, and SEQ ID NO:387 as CDR3 of SEQ ID NO:293.

[0165] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:294. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:388 as CDR1, SEQ ID NO:389 as CDR2, and SEQ ID NO:390 as CDR3 of SEQ ID NO:294. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:556 as CDR1, SEQ ID NO:389 as CDR2, and SEQ ID NO:557 as CDR3 of SEQ ID NO:294. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:295. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID

NO:295, which includes amino acid sequences SEQ ID NO:391 as CDR1, SEQ ID NO:392 as CDR2, and SEQ ID NO:393 as CDR3 of SEQ ID NO:295.

[0166] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:296. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:394 as CDR1, SEQ ID NO:395 as CDR2, and SEQ ID NO:396 as CDR3 of SEQ ID NO:296. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:558 as CDR1, SEQ ID NO:395 as CDR2, and SEQ ID NO:559 as CDR3 of SEQ ID NO:296. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297, which includes amino acid sequences SEQ ID NO:397 as CDR1, SEQ ID NO:398 as CDR2, and SEQ ID NO:399 as CDR3 of SEQ ID NO:297.

[0167] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33 and Cynomolgus/Rhesus (cyno) CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:298. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID

NO:400 as CDR1, SEQ ID NO:401 as CDR2, and SEQ ID NO:402 as CDR3 of SEQ ID NO:298. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:560 as CDR1, SEQ ID NO:401 as CDR2, and SEQ ID NO:561 as CDR3 of SEQ ID NO:298. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299, which includes amino acid sequences SEQ ID NO:403 as CDR1, SEQ ID NO:404 as CDR2, and SEQ ID NO:405 as CDR3 of SEQ ID NO:299.

[0168] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:406 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:408 as CDR3 of SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:562 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:563 as CDR3 of SEQ ID NO:300. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301, which includes amino acid sequences SEQ ID NO:409 as CDR1, SEQ ID NO:410 as CDR2, and SEQ ID NO:411 as CDR3 of SEQ ID NO:301.

[0169] In certain embodiments, the present invention provides an antigen binding site that binds an epitope on an extracellular domain of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:412 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:414 as CDR3 of SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:564 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:565 as CDR3 of SEQ ID NO:302. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID

NO:303, which includes amino acid sequences SEQ ID NO:415 as CDR1, SEQ ID NO:416 as CDR2, and SEQ ID NO:417 as CDR3 of SEQ ID NO:303.

An antigen binding site that recognizes and binds a conformational epitope on an extracellular domain of the human CD33 and/or the Cynomolgus/Rhesus (cyno) CD33

[0170] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain that recognizes and binds one or more conformational epitopes on the extracellular domain of the human CD33 and/or the Cynomolgus/Rhesus (cyno) CD33.

[0171] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds a conformational epitope partially located in the V domain of human CD33 extracellular domain; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDG SEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ GTMVTVSS [SEQ ID NO:3]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:3. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYWMS [SEQ ID NO:27] as CDR1, NIKQDGSEKYYVDSVKG [SEQ ID NO:28] as CDR2, and ARPLNAGELDV [SEQ ID NO:29] as CDR3 of SEQ ID NO:3. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQLESYPLTFGGGTKVEIK [SEQ ID NO:4]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 can be paired with an antibody light chain variable domain at least 90%

(*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:4, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:30] as CDR1, EASSLES [SEQ ID NO:31] as CDR2, and QQLESYPLT [SEQ ID NO:32] as CDR3 of SEQ ID NO:4.

[0172] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds a conformational epitope partially located in the V domain of the human CD33 extracellular domain; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFPSYWMSWVRQAPGKGLEWVATIKRDGS EKGYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQG TMVTVSS [SEQ ID NO:11]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:11. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFPSYWMS [SEQ ID NO:51] as CDR1, TIKRDGSEKGYVDSVKG [SEQ ID NO:52] as CDR2, and ARPLNAGELDV [SEQ ID NO:53] as CDR3 of SEQ ID NO:11. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIK [SEQ ID NO:12]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:12, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:54] as CDR1, EASSLES [SEQ ID NO:55] as CDR2, and QQSQSYPPIT [SEQ ID NO:56] as CDR3 of SEQ ID NO:12.

[0173] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds a conformational epitope partially located in the V domain of the human CD33 extracellular domain; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSSSEGIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYYGMDVWGQGTTVTVSS [SEQ ID NO:15]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:15. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYAMS [SEQ ID NO:63] as CDR1, SISSSSEGIYYADSVKG [SEQ ID NO:64] as CDR2, and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:65] as CDR3 of SEQ ID NO:15. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASNSISSWLAWYQQKPGKAPKLLIYEASSTKSGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFGGGTKVEIK [SEQ ID NO:16]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:16, which includes amino acid sequences RASNSISSWLA [SEQ ID NO:66] as CDR1, EASSTKS [SEQ ID NO:67] as CDR2, and QQYDDLPT [SEQ ID NO:68] as CDR3 of SEQ ID NO:16.

[0174] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds a conformational epitope partially located in the V domain of the human CD33 extracellular domain; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270. In

some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:316 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:318 as CDR3 of SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:532 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:533 as CDR3 of SEQ ID NO:270. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271, which includes amino acid sequences SEQ ID NO:319 as CDR1, SEQ ID NO:320 as CDR2, and SEQ ID NO:321 as CDR3 of SEQ ID NO:271.

[0175] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds a conformational epitope partially located in the V domain of the human CD33 extracellular domain; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:322 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:324 as CDR3 of SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:534 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:535 as CDR3 of SEQ ID NO:272. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino

acid sequence of SEQ ID NO:272 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273, which includes amino acid sequences SEQ ID NO:325 as CDR1, SEQ ID NO:326 as CDR2, and SEQ ID NO:327 as CDR3 of SEQ ID NO:273.

[0176] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds a conformational epitope partially located in the V domain of the human CD33 extracellular domain; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:346 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:348 as CDR3 of SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:542 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:543 as CDR3 of SEQ ID NO:280. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the

amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281, which includes amino acid sequences SEQ ID NO:349 as CDR1, SEQ ID NO:350 as CDR2, and SEQ ID NO:351 as CDR3 of SEQ ID NO:281.

An antigen binding site that recognizes and binds a conformational epitope on an extracellular domain of the human CD33 but not a conformational epitope on an extracellular domain of the Cynomolgus/Rhesus (cyno) CD33

[0177] In one aspect, the present invention provides an antigen binding site that recognizes and binds one or more conformational epitopes on the extracellular domain of the human CD33 but does not recognize and/or bind one or more conformational epitopes on the extracellular domain of the cyno CD33.

[0178] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds one or more conformational epitopes on the extracellular domain of the human CD33 but does not recognize and/or bind one or more conformational epitopes on the extracellular domain of the cyno CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQGLEWMGMINPS WGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYF DLWGRGTLVTVSS [SEQ ID NO:7]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:7. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFSDYYMH [SEQ ID NO:39] as CDR1, MINPSWGSTSYAQKFQG [SEQ ID NO:40] as CDR2, and AREAADGFVGERYFDL [SEQ ID NO:41] as CDR3 of SEQ ID NO:7. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence

DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSN RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFGGGTKVEIK [SEQ ID NO:8]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8, which includes amino acid sequences RSSQSLLYSNGYNYLD [SEQ ID NO:42] as CDR1, LGSNRAS [SEQ ID NO:43] as CDR2, and MQDVALPIT [SEQ ID NO:44] as CDR3 of SEQ ID NO:8.

[0179] In certain embodiments, the present invention provides an antigen binding site that recognizes and binds one or more conformational epitopes on the extracellular domain of the human CD33 but does not recognize and/or bind one or more conformational epitopes on the extracellular domain of the cyno CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQAPGQGLEWMGIINPSR GSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDDEDMDV WGKGTTVTVSS [SEQ ID NO:13]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:13. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFGTYYMH [SEQ ID NO:57] as CDR1, IINPSRGSTVYAQKFQG [SEQ ID NO:58] as CDR2, and ARGAGYDDEDMDV [SEQ ID NO:59] as CDR3 of SEQ ID NO:13. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPLTFGGGTKVEIK [SEQ ID NO:14]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino

acid sequence of SEQ ID NO:13 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14, which includes amino acid sequences RASQGIDSWLA [SEQ ID NO:60] as CDR1, AASSLQS [SEQ ID NO:61] as CDR2, and QQAHSYPLT [SEQ ID NO:62] as CDR3 of SEQ ID NO:14.

[0180] In certain embodiments, an antibody binding site that includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQAPGQGLEWMGIINPSR GSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDDEDMDV WGKGTTVTVSS [SEQ ID NO:13] binds to the full-length extracellular domain of human CD33, but does not bind human CD33 V domain or C domain individually, and does not cross-block binding to human CD33 with lintuzumab. In certain embodiments, an antibody binding site that includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13, and is paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPLTFGGGTKVEIK [SEQ ID NO:14], binds to the full-length extracellular domain of human CD33, but does not bind human CD33 V domain or C domain individually, and does not cross-block binding to human CD33 with lintuzumab. In certain embodiments, an antibody binding site that includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13, and is paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14, which includes amino acid sequences RASQGIDSWLA [SEQ ID NO:60] as CDR1, AASSLQS [SEQ ID NO:61] as CDR2, and QQAHSYPLT [SEQ ID NO:62] as CDR3 of SEQ ID NO:14, binds to the full-length extracellular domain of human CD33, but does not bind human CD33 V domain or C domain individually, and does not cross-block binding to human CD33 with lintuzumab.

An antigen binding site that binds to the R69G allele of human CD33

[0181] In one aspect, the present invention provides an antigen binding site that binds to the R69G allele of human CD33. In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVANIKQDGS EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVY YGMDVWGQGTTVTVSS [SEQ ID NO:1]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:1. In some embodiments, the heavy chain variable domain includes amino acid sequences FTFSSYGMS [SEQ ID NO:21] as the first complementarity-determining region 1 ("CDR1"), NIKQDGSEKYYVDSVKG [SEQ ID NO:22] as the second CDR ("CDR2"), and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:23] as the third CDR ("CDR3") of SEQ ID NO:1. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYESFPTFGGGTKVEIK [SEQ ID NO:2]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:2, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:24] as CDR1, DASSLES [SEQ ID NO:25] as CDR2, and QQYESFPT [SEQ ID NO:26] as CDR3 of SEQ ID NO:2.

[0182] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDG SEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ GTMVTVSS [SEQ ID NO:3]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:3. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYWMS [SEQ ID NO:27] as CDR1, NIKQDGSEKYYVDSVKG [SEQ ID NO:28] as CDR2, and ARPLNAGELDV [SEQ ID NO:29] as CDR3 of SEQ ID NO:3. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQLESYPLTFGGGTKVEIK [SEQ ID NO:4]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:4, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:30] as CDR1, EASSLES [SEQ ID NO:31] as CDR2, and QQLESYPLT [SEQ ID NO:32] as CDR3 of SEQ ID NO:4.

[0183] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGKGLEWVSAIVGSGE STYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVY

YGMDVWGQGTTVTVSS [SEQ ID NO:5]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:5. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSKYTMS [SEQ ID NO:33] as CDR1, AIVGSGESTYFADSVKG [SEQ ID NO:34] as CDR2, and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:35] as CDR3 of SEQ ID NO:5. In some embodiments, the heavy chain variable domain incorporates amino acid sequences KYTMS [SEQ ID NO:183] as CDR1, AIVGSGESTYFADSVKG [SEQ ID NO:34] as CDR2, and EGGPYYDSSGYFVYYGMDV [SEQ ID NO:184] as CDR3 of SEQ ID NO:5. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFGGGTKVEIK [SEQ ID NO:6]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:36] as CDR1, KASSLES [SEQ ID NO:37] or KASSLE [SEQ ID NO:185] as CDR2, and QQYDDLPT [SEQ ID NO:38] as CDR3 of SEQ ID NO:6.

[0184] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGKGLEWVATIKQDG SEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ GTMVTVSS [SEQ ID NO:9]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:9. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFGSYWMS [SEQ ID NO:45] as

CDR1, TIKQDGSEKSYVDSVKG [SEQ ID NO:46] as CDR2, and ARPLNAGELDV [SEQ ID NO:47] as CDR3 of SEQ ID NO:9. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SYWMS [SEQ ID NO:181] as CDR1, TIKQDGSEKSYVDSVKG [SEQ ID NO:46] as CDR2, and RPLNAGELDV [SEQ ID NO:182] as CDR3 of SEQ ID NO:9. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIK [SEQ ID NO:10]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:10, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:48] as CDR1, EASSLES [SEQ ID NO:49] as CDR2, and QQSQSYPPIT [SEQ ID NO:50] as CDR3 of SEQ ID NO:10.

[0185] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFPSYWMSWVRQAPGKGLEWVATIKRDGS EKGYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQG TMVTVSS [SEQ ID NO:11]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:11. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFPSYWMS [SEQ ID NO:51] as CDR1, TIKRDGSEKGYVDSVKG [SEQ ID NO:52] as CDR2, and ARPLNAGELDV [SEQ ID NO:53] as CDR3 of SEQ ID NO:11. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIK [SEQ ID NO:12]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:12, which includes amino acid sequences RASQSISSWLA [SEQ ID NO:54] as CDR1, EASSLES [SEQ ID NO:55] as CDR2, and QQSQSYPPIT [SEQ ID NO:56] as CDR3 of SEQ ID NO:12.

[0186] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQAPGQGLEWMGIINPSR GSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDDEDMDV WGKGTTVTVSS [SEQ ID NO:13]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:13. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFGTYYMH [SEQ ID NO:57] as CDR1, IINPSRGSTVYAQKFQG [SEQ ID NO:58] as CDR2, and ARGAGYDDEDMDV [SEQ ID NO:59] as CDR3 of SEQ ID NO:13. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%)

identical to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPLTFGGGTKVEIK [SEQ ID NO:14]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14, which includes amino acid sequences RASQGIDSWLA [SEQ ID NO:60] as CDR1, AASSLQS [SEQ ID NO:61] as CDR2, and QQAHSYPLT [SEQ ID NO:62] as CDR3 of SEQ ID NO:14.

[0187] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSSSEG IYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYY GMDVWGQGTTVTVSS [SEQ ID NO:15]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:15. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYAMS [SEQ ID NO:63] as CDR1, SISSSSEGIYYADSVKG [SEQ ID NO:64] as CDR2, and AREGGPYYDSSGYFVYYGMDV [SEQ ID NO:65] as CDR3 of SEQ ID NO:15. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSTLSASVGDRVTITCRASNSISSWLAWYQQKPGKAPKLLIYEASSTKSGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFGGGTKVEIK [SEQ ID NO:16]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 can be paired with an antibody light chain variable domain

at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:16, which includes amino acid sequences RASNSISSWLA [SEQ ID NO:66] as CDR1, EASSTKS [SEQ ID NO:67] as CDR2, and QQYDDLPT [SEQ ID NO:68] as CDR3 of SEQ ID NO:16.

[0188] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANINTDG SEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIAYQGHFD YWGQGTLVTVSS [SEQ ID NO:17]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:17. In some embodiments, the heavy chain variable domain incorporates amino acid sequences FTFSSYWMS [SEQ ID NO:69] as CDR1, NINTDGSEVYYVDSVKG [SEQ ID NO:70] as CDR2, and ARDVGPGIAYQGHFDY [SEQ ID NO:71] as CDR3 of SEQ ID NO:17. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIQMTQSPSSLSASVGDRVTITCRASQVIYSYLNWYQQKPGKAPKLLIYAASSLKSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPLTFGGGTKVEIK [SEQ ID NO:18]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:18, which includes amino acid sequences RASQVIYSYLN [SEQ ID NO:72] as CDR1, AASSLKS [SEQ ID NO:73] as CDR2, and QQVYDTPLT [SEQ ID NO:74] as CDR3 of SEQ ID NO:18.

[0189] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain

variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QLQLQESGPGLVKPSETLSLTCTVSGGSISSTDYYWGWIRQPPGKGLEWIGSIGYSGT YYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARETAHDVHGMDVWGQG TTVTVSS [SEQ ID NO:19]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:19. In some embodiments, the heavy chain variable domain incorporates amino acid sequences GSISSTDYYWG [SEQ ID NO:75] as CDR1, SIGYSGTYYNPSLKS [SEQ ID NO:76] as CDR2, and ARETAHDVHGMDV [SEQ ID NO:77] as CDR3 of SEQ ID NO:19. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence EIVLTQSPATLSLSPGERATLSCRASHSVYSYLAWYQQKPGQAPRLLIYDASNRATGI PARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLPTFGGGTKVEIK [SEQ ID NO:20]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:20, which includes amino acid sequences RASHSVYSYLA [SEQ ID NO:78] as CDR1, DASNRAT [SEQ ID NO:79] as CDR2, and QQYDNLPT [SEQ ID NO:80] as CDR3 of SEQ ID NO:20.

[0190] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:304 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:306 as CDR3 of SEQ ID NO:266. In some embodiments, the heavy chain

variable domain incorporates amino acid sequences SEQ ID NO:528 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:529 as CDR3 of SEQ ID NO:266. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267, which includes amino acid sequences SEQ ID NO:307 as CDR1, SEQ ID NO:308 as CDR2, and SEQ ID NO:309 as CDR3 of SEQ ID NO:267.

[0191] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:268. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:310 as CDR1, SEQ ID NO:311 as CDR2, and SEQ ID NO:312 as CDR3 of SEQ ID NO:268. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:530 as CDR1, SEQ ID NO:311 as CDR2, and SEQ ID NO:531 as CDR3 of SEQ ID NO:268. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 can be paired with an antibody light chain variable domain at least 90%

(*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269, which includes amino acid sequences SEQ ID NO:313 as CDR1, SEQ ID NO:314 as CDR2, and SEQ ID NO:315 as CDR3 of SEQ ID NO:269.

[0192] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:316 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:318 as CDR3 of SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:532 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:533 as CDR3 of SEQ ID NO:270. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271, which includes amino acid sequences SEQ ID NO:319 as CDR1, SEQ ID NO:320 as CDR2, and SEQ ID NO:321 as CDR3 of SEQ ID NO:271.

[0193] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:322 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:324 as CDR3 of SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:534 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:535 as CDR3 of SEQ ID NO:272. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273, which includes amino acid sequences SEQ ID NO:325 as CDR1, SEQ ID NO:326 as CDR2, and SEQ ID NO:327 as CDR3 of SEQ ID NO:273.

[0194] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:274. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:328 as CDR1, SEQ ID NO:329 as CDR2, and SEQ ID NO:330 as CDR3 of SEQ ID NO:274. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:536 as CDR1, SEQ ID

NO:329 as CDR2, and SEQ ID NO:537 as CDR3 of SEQ ID NO:274. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275, which includes amino acid sequences SEQ ID NO:331 as CDR1, SEQ ID NO:332 as CDR2, and SEQ ID NO:333 as CDR3 of SEQ ID NO:275.

[0195] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:276. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:334 as CDR1, SEQ ID NO:335 as CDR2, and SEQ ID NO:336 as CDR3 of SEQ ID NO:276. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:538 as CDR1, SEQ ID NO:335 as CDR2, and SEQ ID NO:539 as CDR3 of SEQ ID NO:276. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the

amino acid sequence of SEQ ID NO:277. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:277, which includes amino acid sequences SEQ ID NO:337 as CDR1, SEQ ID NO:338 as CDR2, and SEQ ID NO:339 as CDR3 of SEQ ID NO:277.

[0196] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:340 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:342 as CDR3 of SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:540 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:541 as CDR3 of SEQ ID NO:278. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279, which includes amino acid sequences SEQ ID NO:343 as CDR1, SEQ ID NO:344 as CDR2, and SEQ ID NO:345 as CDR3 of SEQ ID NO:279.

[0197] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain

variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:346 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:348 as CDR3 of SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:542 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:543 as CDR3 of SEQ ID NO:280. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281, which includes amino acid sequences SEQ ID NO:349 as CDR1, SEQ ID NO:350 as CDR2, and SEQ ID NO:351 as CDR3 of SEQ ID NO:281.

[0198] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:352 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:354 as CDR3 of SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:544 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:545 as CDR3 of SEQ ID NO:282. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid

sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283, which includes amino acid sequences SEQ ID NO:355 as CDR1, SEQ ID NO:356 as CDR2, and SEQ ID NO:357 as CDR3 of SEQ ID NO:283.

[0199] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:358 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:546 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:547. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285, which includes amino acid sequences SEQ ID NO:361 as CDR1, SEQ ID NO:362 as CDR2, and SEQ ID NO:363 as CDR3 of SEQ ID NO:285.

[0200] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:364 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:366 as CDR3 of SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:548 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:549 as CDR3 of SEQ ID NO:286. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287, which includes amino acid sequences SEQ ID NO:367 as CDR1, SEQ ID NO:368 as CDR2, and SEQ ID NO:369 as CDR3 of SEQ ID NO:287.

[0201] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of

SEQ ID NO:292. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:292. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:382 as CDR1, SEQ ID NO:383 as CDR2, and SEQ ID NO:384 as CDR3 of SEQ ID NO:292. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:554 as CDR1, SEQ ID NO:383 as CDR2, and SEQ ID NO:555 as CDR3 of SEQ ID NO:292. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:293. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:293, which includes amino acid sequences SEQ ID NO:385 as CDR1, SEQ ID NO:386 as CDR2, and SEQ ID NO:387 as CDR3 of SEQ ID NO:293.

[0202] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:294. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:388 as CDR1, SEQ ID NO:389 as CDR2, and SEQ ID NO:390 as CDR3 of SEQ ID NO:294. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:556 as CDR1, SEQ ID NO:389 as CDR2, and SEQ ID NO:557 as CDR3 of SEQ ID NO:294. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 is combined with a light

chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:295. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:295, which includes amino acid sequences SEQ ID NO:391 as CDR1, SEQ ID NO:392 as CDR2, and SEQ ID NO:393 as CDR3 of SEQ ID NO:295.

[0203] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:296. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:394 as CDR1, SEQ ID NO:395 as CDR2, and SEQ ID NO:396 as CDR3 of SEQ ID NO:296. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:558 as CDR1, SEQ ID NO:395 as CDR2, and SEQ ID NO:559 as CDR3 of SEQ ID NO:296. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297, which includes amino acid sequences SEQ ID NO:397 as CDR1, SEQ ID NO:398 as CDR2, and SEQ ID NO:399 as CDR3 of SEQ ID NO:297.

[0204] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:298. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:400 as CDR1, SEQ ID NO:401 as CDR2, and SEQ ID NO:402 as CDR3 of SEQ ID NO:298. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:560 as CDR1, SEQ ID NO:401 as CDR2, and SEQ ID NO:561 as CDR3 of SEQ ID NO:298. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299, which includes amino acid sequences SEQ ID NO:403 as CDR1, SEQ ID NO:404 as CDR2, and SEQ ID NO:405 as CDR3 of SEQ ID NO:299.

[0205] In certain embodiments, the present invention provides an antigen binding site that binds to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:302. In some embodiments, the heavy chain variable domain

incorporates amino acid sequences SEQ ID NO:412 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:414 as CDR3 of SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:564 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:565 as CDR3 of SEQ ID NO:302. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303, which includes amino acid sequences SEQ ID NO:415 as CDR1, SEQ ID NO:416 as CDR2, and SEQ ID NO:417 as CDR3 of SEQ ID NO:303.

An antigen binding site that does not bind to the R69G allele of human CD33

[0206] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain that binds wild-type human CD33, but not the R69G allele of human CD33. In certain embodiments, the present invention provides an antigen binding site that does not bind to the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQGLEWMGMINPS WGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYF DLWGRGTLVTVSS [SEQ ID NO:7]. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:7. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFSDYYMH [SEQ ID NO:39] as CDR1, MINPSWGSTSYAQKFQG [SEQ ID NO:40] as CDR2, and AREAADGFVGERYFDL [SEQ ID NO:41] as CDR3 of SEQ ID NO:7. In certain

embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90%(*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSN RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFGGGTKVEIK [SEQ ID NO:8]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8, which includes amino acid sequences RSSQSLLYSNGYNYLD [SEQ ID NO:42] as CDR1, LGSNRAS [SEQ ID NO:43] as CDR2, and MQDVALPIT [SEQ ID NO:44] as CDR3 of SEQ ID NO:8.

[0207] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:370 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:372 as CDR3 of SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:550 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:551 as CDR3 of SEQ ID NO:288. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at

least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, which includes amino acid sequences SEQ ID NO:373 as CDR1, SEQ ID NO:374 as CDR2, and SEQ ID NO:375 as CDR3 of SEQ ID NO:289.

[0208] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:376 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:378 as CDR3 of SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:552 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:553 as CDR3 of SEQ ID NO:290. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291, which includes amino acid sequences SEQ ID NO:379 as CDR1, SEQ ID NO:380 as CDR2, and SEQ ID NO:381 as CDR3 of SEQ ID NO:291.

[0209] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the R69G allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:406 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:408 as CDR3 of SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:562 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:563 as CDR3 of SEQ ID NO:300. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301, which includes amino acid sequences SEQ ID NO:409 as CDR1, SEQ ID NO:410 as CDR2, and SEQ ID NO:411 as CDR3 of SEQ ID NO:301.

An antigen binding site that binds to a unique epitope including R69 on human CD33

[0210] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain that binds to a unique epitope on human CD33 that includes R69. In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes R69; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of

QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQGLEWMGMINPS WGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYF DLWGRGTLVTVSS [SEQ ID NO:7].

[0211] In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:7. In some embodiments, the heavy chain variable domain incorporates amino acid sequences YTFSDYYMH [SEQ ID NO:39] as CDR1, MINPSWGSTSYAQKFQG [SEQ ID NO:40] as CDR2, and AREAADGFVGERYFDL [SEQ ID NO:41] as CDR3 of SEQ ID NO:7. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSN RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFGGGTKVEIK [SEQ ID NO:8]. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8, which includes amino acid sequences RSSQSLLYSNGYNYLD [SEQ ID NO:42] as CDR1, LGSNRAS [SEQ ID NO:43] as CDR2, and MQDVALPIT [SEQ ID NO:44] as CDR3 of SEQ ID NO:8.

[0212] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes R69; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:370 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:372 as CDR3 of SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:550 as

CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:551 as CDR3 of SEQ ID NO:288. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, which includes amino acid sequences SEQ ID NO:373 as CDR1, SEQ ID NO:374 as CDR2, and SEQ ID NO:375 as CDR3 of SEQ ID NO:289.

[0213] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes R69; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:376 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:378 as CDR3 of SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:552 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:553 as CDR3 of SEQ ID NO:290. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the

amino acid sequence of SEQ ID NO:291. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291, which includes amino acid sequences SEQ ID NO:379 as CDR1, SEQ ID NO:380 as CDR2, and SEQ ID NO:381 as CDR3 of SEQ ID NO:291.

[0214] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes R69; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:406 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:408 as CDR3 of SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:562 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:563 as CDR3 of SEQ ID NO:300. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301, which includes amino acid sequences SEQ ID NO:409 as CDR1, SEQ ID NO:410 as CDR2, and SEQ ID NO:411 as CDR3 of SEQ ID NO:301.

An antigen binding site that binds to the S128N allele of human CD33

[0215] In one aspect, the present invention provides an antigen binding site that binds to the S128N allele of human CD33.

[0216] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:268. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:310 as CDR1, SEQ ID NO:311 as CDR2, and SEQ ID NO:312 as CDR3 of SEQ ID NO:268. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:530 as CDR1, SEQ ID NO:311 as CDR2, and SEQ ID NO:531 as CDR3 of SEQ ID NO:268. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:268 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:269, which includes amino acid sequences SEQ ID NO:313 as CDR1, SEQ ID NO:314 as CDR2, and SEQ ID NO:315 as CDR3 of SEQ ID NO:269.

[0217] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274. In some embodiments, the antibody heavy chain variable domain is at least

95% identical to SEQ ID NO:274. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:328 as CDR1, SEQ ID NO:329 as CDR2, and SEQ ID NO:330 as CDR3 of SEQ ID NO:274. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:536 as CDR1, SEQ ID NO:329 as CDR2, and SEQ ID NO:537 as CDR3 of SEQ ID NO:274. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:274 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:275, which includes amino acid sequences SEQ ID NO:331 as CDR1, SEQ ID NO:332 as CDR2, and SEQ ID NO:333 as CDR3 of SEQ ID NO:275.

[0218] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:276. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:334 as CDR1, SEQ ID NO:335 as CDR2, and SEQ ID NO:336 as CDR3 of SEQ ID NO:276. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:538 as CDR1, SEQ ID NO:335 as CDR2, and SEQ ID NO:539 as CDR3 of SEQ ID NO:276. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For

example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:277. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:276 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:277, which includes amino acid sequences SEQ ID NO:337 as CDR1, SEQ ID NO:338 as CDR2, and SEQ ID NO:339 as CDR3 of SEQ ID NO:277.

[0219] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:292. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:382 as CDR1, SEQ ID NO:383 as CDR2, and SEQ ID NO:384 as CDR3 of SEQ ID NO:292. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:554 as CDR1, SEQ ID NO:383 as CDR2, and SEQ ID NO:555 as CDR3 of SEQ ID NO:292. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:293. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:292 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID

NO:293, which includes amino acid sequences SEQ ID NO:385 as CDR1, SEQ ID NO:386 as CDR2, and SEQ ID NO:387 as CDR3 of SEQ ID NO:293.

[0220] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:294. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:388 as CDR1, SEQ ID NO:389 as CDR2, and SEQ ID NO:390 as CDR3 of SEQ ID NO:294. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:556 as CDR1, SEQ ID NO:389 as CDR2, and SEQ ID NO:557 as CDR3 of SEQ ID NO:294. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:295. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:294 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:295, which includes amino acid sequences SEQ ID NO:391 as CDR1, SEQ ID NO:392 as CDR2, and SEQ ID NO:393 as CDR3 of SEQ ID NO:295.

[0221] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:296. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:394 as CDR1, SEQ ID NO:395 as CDR2,

and SEQ ID NO:396 as CDR3 of SEQ ID NO:296. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:558 as CDR1, SEQ ID NO:395 as CDR2, and SEQ ID NO:559 as CDR3 of SEQ ID NO:296. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:296 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:297, which includes amino acid sequences SEQ ID NO:397 as CDR1, SEQ ID NO:398 as CDR2, and SEQ ID NO:399 as CDR3 of SEQ ID NO:297.

[0222] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:298. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:400 as CDR1, SEQ ID NO:401 as CDR2, and SEQ ID NO:402 as CDR3 of SEQ ID NO:298. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:560 as CDR1, SEQ ID NO:401 as CDR2, and SEQ ID NO:561 as CDR3 of SEQ ID NO:298. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of

SEQ ID NO:298 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:298 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:299, which includes amino acid sequences SEQ ID NO:403 as CDR1, SEQ ID NO:404 as CDR2, and SEQ ID NO:405 as CDR3 of SEQ ID NO:299.

[0223] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:376 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:378 as CDR3 of SEQ ID NO:290. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:552 as CDR1, SEQ ID NO:377 as CDR2, and SEQ ID NO:553 as CDR3 of SEQ ID NO:290. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:290 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:291, which includes amino acid sequences SEQ ID NO:379 as CDR1, SEQ ID NO:380 as CDR2, and SEQ ID NO:381 as CDR3 of SEQ ID NO:291.

[0224] In certain embodiments, the present invention provides an antigen binding site that binds to the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:406 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:408 as CDR3 of SEQ ID NO:300. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:562 as CDR1, SEQ ID NO:407 as CDR2, and SEQ ID NO:563 as CDR3 of SEQ ID NO:300. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:300 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:301, which includes amino acid sequences SEQ ID NO:409 as CDR1, SEQ ID NO:410 as CDR2, and SEQ ID NO:411 as CDR3 of SEQ ID NO:301.

An antigen binding site that does not bind to the S128N allele of human CD33

[0225] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain that binds to wild-type human CD33 but not the S128N allele of human CD33.

[0226] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to

the amino acid sequence of SEQ ID NO:302. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:412 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:414 as CDR3 of SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:564 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:565 as CDR3 of SEQ ID NO:302. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303, which includes amino acid sequences SEQ ID NO:415 as CDR1, SEQ ID NO:416 as CDR2, and SEQ ID NO:417 as CDR3 of SEQ ID NO:303.

[0227] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:304 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:306 as CDR3 of SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:528 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:529 as CDR3 of SEQ ID NO:266. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 is combined

with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267, which includes amino acid sequences SEQ ID NO:307 as CDR1, SEQ ID NO:308 as CDR2, and SEQ ID NO:309 as CDR3 of SEQ ID NO:267.

[0228] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:316 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:318 as CDR3 of SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:532 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:533 as CDR3 of SEQ ID NO:270. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271, which includes amino acid sequences SEQ ID NO:319 as CDR1, SEQ ID NO:320 as CDR2, and SEQ ID NO:321 as CDR3 of SEQ ID NO:271.

[0229] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:322 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:324 as CDR3 of SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:534 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:535 as CDR3 of SEQ ID NO:272. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273, which includes amino acid sequences SEQ ID NO:325 as CDR1, SEQ ID NO:326 as CDR2, and SEQ ID NO:327 as CDR3 of SEQ ID NO:273.

[0230] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:278. In some embodiments,

the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:340 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:342 as CDR3 of SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:540 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:541 as CDR3 of SEQ ID NO:278. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279, which includes amino acid sequences SEQ ID NO:343 as CDR1, SEQ ID NO:344 as CDR2, and SEQ ID NO:345 as CDR3 of SEQ ID NO:279.

[0231] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:346 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:348 as CDR3 of SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:542 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:543 as CDR3 of SEQ ID NO:280. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281, which includes amino acid sequences SEQ ID NO:349 as CDR1, SEQ ID NO:350 as CDR2, and SEQ ID NO:351 as CDR3 of SEQ ID NO:281.

[0232] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:352 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:354 as CDR3 of SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:544 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:545 as CDR3 of SEQ ID NO:282. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of

SEQ ID NO:283, which includes amino acid sequences SEQ ID NO:355 as CDR1, SEQ ID NO:356 as CDR2, and SEQ ID NO:357 as CDR3 of SEQ ID NO:283.

[0233] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:358 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:546 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:547. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285, which includes amino acid sequences SEQ ID NO:361 as CDR1, SEQ ID NO:362 as CDR2, and SEQ ID NO:363 as CDR3 of SEQ ID NO:285.

[0234] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:364 as

CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:366 as CDR3 of SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:548 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:549 as CDR3 of SEQ ID NO:286. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287, which includes amino acid sequences SEQ ID NO:367 as CDR1, SEQ ID NO:368 as CDR2, and SEQ ID NO:369 as CDR3 of SEQ ID NO:287.

[0235] In certain embodiments, the present invention provides an antigen binding site that binds to wild-type human CD33 but not the S128N allele of human CD33; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:370 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:372 as CDR3 of SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:550 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:551 as CDR3 of SEQ ID NO:288. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid

sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, which includes amino acid sequences SEQ ID NO:373 as CDR1, SEQ ID NO:374 as CDR2, and SEQ ID NO:375 as CDR3 of SEQ ID NO:289.

An antigen binding site that binds to a unique epitope including S128 on human CD33

[0236] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain that binds to a unique epitope on human CD33 that includes S128.

[0237] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:412 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:414 as CDR3 of SEQ ID NO:302. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:564 as CDR1, SEQ ID NO:413 as CDR2, and SEQ ID NO:565 as CDR3 of SEQ ID NO:302. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, or 100%) identical to the amino acid sequence of SEQ ID NO:302 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:303, which includes amino acid sequences SEQ ID NO:415 as CDR1, SEQ ID NO:416 as CDR2, and SEQ ID NO:417 as CDR3 of SEQ ID NO:303.

[0238] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:304 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:306 as CDR3 of SEQ ID NO:266. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:528 as CDR1, SEQ ID NO:305 as CDR2, and SEQ ID NO:529 as CDR3 of SEQ ID NO:266. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:266 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:267, which includes amino acid sequences SEQ ID NO:307 as CDR1, SEQ ID NO:308 as CDR2, and SEQ ID NO:309 as CDR3 of SEQ ID NO:267.

[0239] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino

acid sequence of SEQ ID NO:270. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:316 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:318 as CDR3 of SEQ ID NO:270. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:532 as CDR1, SEQ ID NO:317 as CDR2, and SEQ ID NO:533 as CDR3 of SEQ ID NO:270. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:270 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:271, which includes amino acid sequences SEQ ID NO:319 as CDR1, SEQ ID NO:320 as CDR2, and SEQ ID NO:321 as CDR3 of SEQ ID NO:271.

[0240] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:322 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:324 as CDR3 of SEQ ID NO:272. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:534 as CDR1, SEQ ID NO:323 as CDR2, and SEQ ID NO:535 as CDR3 of SEQ ID NO:272. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 is combined with a light

chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:272 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:273, which includes amino acid sequences SEQ ID NO:325 as CDR1, SEQ ID NO:326 as CDR2, and SEQ ID NO:327 as CDR3 of SEQ ID NO:273.

[0241] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:340 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:342 as CDR3 of SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:540 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:541 as CDR3 of SEQ ID NO:278. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279, which includes amino acid sequences SEQ ID NO:343 as CDR1, SEQ ID NO:344 as CDR2, and SEQ ID NO:345 as CDR3 of SEQ ID NO:279.

[0242] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:346 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:348 as CDR3 of SEQ ID NO:280. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:542 as CDR1, SEQ ID NO:347 as CDR2, and SEQ ID NO:543 as CDR3 of SEQ ID NO:280. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:280 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:281, which includes amino acid sequences SEQ ID NO:349 as CDR1, SEQ ID NO:350 as CDR2, and SEQ ID NO:351 as CDR3 of SEQ ID NO:281.

[0243] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:282. In some embodiments, the heavy chain

variable domain incorporates amino acid sequences SEQ ID NO:352 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:354 as CDR3 of SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:544 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:545 as CDR3 of SEQ ID NO:282. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283, which includes amino acid sequences SEQ ID NO:355 as CDR1, SEQ ID NO:356 as CDR2, and SEQ ID NO:357 as CDR3 of SEQ ID NO:283.

[0244] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:358 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:546 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:547. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285, which includes amino acid sequences SEQ ID NO:361 as CDR1, SEQ ID NO:362 as CDR2, and SEQ ID NO:363 as CDR3 of SEQ ID NO:285.

[0245] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:364 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:366 as CDR3 of SEQ ID NO:286. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:548 as CDR1, SEQ ID NO:365 as CDR2, and SEQ ID NO:549 as CDR3 of SEQ ID NO:286. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:287. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:286 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID

NO:287, which includes amino acid sequences SEQ ID NO:367 as CDR1, SEQ ID NO:368 as CDR2, and SEQ ID NO:369 as CDR3 of SEQ ID NO:287.

[0246] In certain embodiments, the present invention provides an antigen binding site that binds to a unique epitope on human CD33 that includes S128; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:370 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:372 as CDR3 of SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:550 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:551 as CDR3 of SEQ ID NO:288. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, which includes amino acid sequences SEQ ID NO:373 as CDR1, SEQ ID NO:374 as CDR2, and SEQ ID NO:375 as CDR3 of SEQ ID NO:289.

An antigen binding site binds to the V domain of human CD33 in a glycosylation sensitive manner

[0247] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain that binds to the V domain of human CD33 in a glycosylation sensitive manner, *e.g.*, binds to the V domain of CD33 only when the V domain is deglycosylated.

[0248] In certain embodiments, the present invention provides an antigen binding site that binds an epitope in the V domain of human CD33 only when the V domain is deglycosylated; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:340 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:342 as CDR3 of SEQ ID NO:278. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:540 as CDR1, SEQ ID NO:341 as CDR2, and SEQ ID NO:541 as CDR3 of SEQ ID NO:278. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:278 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:279, which includes amino acid sequences SEQ ID NO:343 as CDR1, SEQ ID NO:344 as CDR2, and SEQ ID NO:345 as CDR3 of SEQ ID NO:279.

[0249] In certain embodiments, the present invention provides an antigen binding site that binds an epitope in the V domain of human CD33 only when the V domain is deglycosylated; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:352 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:354 as CDR3 of SEQ ID

NO:282. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:544 as CDR1, SEQ ID NO:353 as CDR2, and SEQ ID NO:545 as CDR3 of SEQ ID NO:282. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:282 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:283, which includes amino acid sequences SEQ ID NO:355 as CDR1, SEQ ID NO:356 as CDR2, and SEQ ID NO:357 as CDR3 of SEQ ID NO:283.

[0250] In certain embodiments, the present invention provides an antigen binding site that binds an epitope in the V domain of human CD33 only when the V domain is deglycosylated; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:358 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:284. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:546 as CDR1, SEQ ID NO:359 as CDR2, and SEQ ID NO:360 as CDR3 of SEQ ID NO:547. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to

the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:284 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:285, which includes amino acid sequences SEQ ID NO:361 as CDR1, SEQ ID NO:362 as CDR2, and SEQ ID NO:363 as CDR3 of SEQ ID NO:285.

[0251] In certain embodiments, the present invention provides an antigen binding site that binds an epitope in the V domain of human CD33 only when the V domain is deglycosylated; the antigen binding site includes a heavy chain variable domain including an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288. In some embodiments, the antibody heavy chain variable domain is at least 95% identical to SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:370 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:372 as CDR3 of SEQ ID NO:288. In some embodiments, the heavy chain variable domain incorporates amino acid sequences SEQ ID NO:550 as CDR1, SEQ ID NO:371 as CDR2, and SEQ ID NO:551 as CDR3 of SEQ ID NO:288. In certain embodiments, the antibody heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 is combined with a light chain variable domain to form an antigen-binding site capable of binding to CD33. For example, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289. In certain embodiments, an antibody heavy chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:288 can be paired with an antibody light chain variable domain at least 90% (*e.g.*, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:289, which includes amino acid sequences SEQ ID

NO:373 as CDR1, SEQ ID NO:374 as CDR2, and SEQ ID NO:375 as CDR3 of SEQ ID NO:289.

An antigen binding site that binds to the extracellular domain in human CD33 and/or cyno CD33, irrespective of the glycosylation profile of the targeted CD33

[0252] In one aspect, the present invention provides an antigen binding site including a heavy chain variable domain which includes an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, or 302, which binds to the extracellular domain in human CD33 irrespective of the glycosylation profile of the targeted CD33.

[0253] In certain embodiments, the present invention provides an antigen binding site including a heavy chain variable domain that binds to the extracellular domain in human CD33 and/or cyno CD33, such that the epitopes are unique compared to the epitopes targeted by one or more known anti-CD33 antibodies in the art. In certain embodiments, the present invention provides an antigen binding site including a heavy chain variable domain that binds to the extracellular domain in human CD33 and/or cyno CD33, which shows human or Cynomolgus/Rhesus (cyno) CD33 cross reactivity and high affinity binding to the target CD33.

A second antigen binding site same or different from the antigen-binding site that binds human CD33

[0254] In certain embodiments, the present invention provides a protein that includes a human CD33 antigen-binding site including a heavy chain variable domain, which includes an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, or 302, and further comprises a second antigen binding site same or different from the antigen-binding site that binds to human CD33.

Proteins with antigen-binding sites

[0255] An antibody heavy chain variable domain of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296,

298, 300, and/or 302 can optionally be coupled to an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an antibody constant region, such as an IgG constant region including hinge, CH2 and CH3 domains with or without a CH1 domain. In some embodiments, the amino acid sequence of the constant region is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a human antibody constant region, such as an human IgG1 constant region, an IgG2 constant region, IgG3 constant region, or IgG4 constant region. In some other embodiments, the amino acid sequence of the constant region is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an antibody constant region from another mammal, such as rabbit, dog, cat, mouse, or horse. One or more mutations can be incorporated into the constant region as compared to human IgG1 constant region, for example at Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411 and/or K439. Exemplary substitutions include, for example, Q347E, Q347R, Y349S, Y349K, Y349T, Y349D, Y349E, Y349C, T350V, L351K, L351D, L351Y, S354C, E356K, E357Q, E357L, E357W, K360E, K360W, Q362E, S364K, S364E, S364H, S364D, T366V, T366I, T366L, T366M, T366K, T366W, T366S, L368E, L368A, L368D, K370S, N390D, N390E, K392L, K392M, K392V, K392F, K392D, K392E, T394F, T394W, D399R, D399K, D399V, S400K, S400R, D401K, F405A, F405T, Y407A, Y407I , Y407V, K409F, K409W, K409D, T411D, T411E, K439D, and K439E.

[0256] In certain embodiments, mutations that can be incorporated into the CH1 of a human IgG1 constant region may be at amino acid V125, F126, P127, T135, T139, A140, F170, P171, and/or V173. In certain embodiments, mutations that can be incorporated into the Cκ of a human IgG1 constant region may be at amino acid E123, F116, S176, V163, S174, and/or T164.

II. Multi-specific Binding Proteins

[0257] In certain embodiments, the present invention provides an antigen-binding site in a protein (*e.g.*, a multi-specific binding protein) that binds to CD33 on a cancer cell, and the NKG2D receptor and CD16 receptor on natural killer cells to activate the natural killer cell. As used herein, the term "antibody" encompasses proteins (*e.g.*, multi-specific binding proteins) that comprise one or more antigen-binding sites (*e.g.*, an antigen-binding site that binds CD33), and is not limited to single-specific antibodies. In certain embodiments, the

protein (*e.g.*, multi-specific binding protein) or antibody is a trispecific antibody, also called Trispecific NK cell Engagement Therapy (TriNKET). The protein (*e.g.*, a multi-specific binding protein) is useful in the pharmaceutical compositions and therapeutic methods described herein. Binding of the protein including an antigen-binding site that binds to CD33, and to NKG2D receptor and CD16 receptor on natural killer cell enhances the activity of the natural killer cell toward destruction of a cancer cell. Binding of the protein including an antigen-binding site that binds to CD33 (*e.g.*, a multi-specific binding protein) on a cancer cell brings the cancer cell into proximity to the natural killer cell, which facilitates direct and indirect destruction of the cancer cell by the natural killer cell. Further description of exemplary multi-specific binding proteins is provided below.

[0258] In certain embodiments of the present disclosure, the first component of the multi-specific binding proteins binds to CD33-expressing cells, which can include but are not limited to AML, myelodysplastic syndromes, chronic myelomonocytic leukemia, myeloid blast crisis of chronic myeloid leukemia, and ALLs.

[0259] In certain embodiments of the present disclosure, the second component of the multi-specific binding proteins binds to NKG2D receptor-expressing cells, which can include but are not limited to NK cells, γδ T cells and $CD8^+$ αβ T cells. Upon NKG2D binding, the multi-specific binding proteins may block natural ligands, such as ULBP6 and MICA, from binding to NKG2D and activating NKG2D receptors.

[0260] In certain embodiments of the present disclosure, the third component for the multi-specific binding proteins binds to cells expressing CD16, an Fc receptor on the surface of leukocytes including natural killer cells, macrophages, neutrophils, eosinophils, mast cells, and follicular dendritic cells.

[0261] Another aspect of the present invention provides a protein comprising an antigen-binding site that binds NKG2D, the antigen-binding site comprising a heavy chain variable domain comprising:

CDR1 comprising the amino acid sequence of SYSMN [SEQ ID NO:192];

CDR2 comprising the amino acid sequence of SISSSSSYIYYADSVKG [SEQ ID NO:112]; and

CDR3 comprising the amino acid sequence of GAPXGAAAGWFDP [SEQ ID NO:527], wherein X is A, V, L, I, P, F, W, G, S, T, C, N, Q, or Y; and

a light chain variable domain comprising:

CDR1 comprising the amino acid sequence of RASQGISSWLA [SEQ ID NO:114],

CDR2 comprising the amino acid sequence of AASSLQS [SEQ ID NO:115], and CDR3 comprising the amino acid sequence of QQGVSFPRT [SEQ ID NO:116].

[0262] In certain embodiments, X is A, V, L, I, P, F, or W. In certain embodiments, X is V, L, or I. In certain embodiments, the amino acid sequence of CDR3 in the heavy chain variable domain comprises the sequence of SEQ ID NO:123. In certain embodiments, the amino acid sequence of CDR3 in the heavy chain variable domain comprises the sequence of SEQ ID NO:195, SEQ ID NO:588, SEQ ID NO:591, SEQ ID NO:594, or SEQ ID NO:597.

[0263] In certain embodiments, the antigen-binding site comprises a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the amino acid sequence of SEQ ID NO:191; and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the amino acid sequence of SEQ ID NO:81. In certain embodiments, the antigen-binding site comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:191; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:81.

[0264] In certain embodiments, the antigen-binding site that binds NKG2D is in the form of an Fab fragment. In certain embodiments, the antigen-binding site that binds NKG2D is in the form of an scFv.

[0265] In certain embodiments, the present invention provides a protein comprising (a) a first antigen-binding site comprising an Fab fragment that binds NKG2D as disclosed herein; (b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds a tumor associated antigen (*e.g.*, CD33); and (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0266] The multi-specific binding proteins described herein can take various formats. For example, one format is a heterodimeric, multi-specific antibody which includes a first immunoglobulin heavy chain, a first immunoglobulin light chain, a second immunoglobulin heavy chain and a second immunoglobulin light chain. The first immunoglobulin heavy chain includes a first Fc (hinge-CH2-CH3) domain, a first heavy chain variable domain and optionally a first CH1 heavy chain domain. The first immunoglobulin light chain includes a first light chain variable domain and a first light chain constant domain. The first immunoglobulin light chain, together with the first immunoglobulin heavy chain, forms an antigen-binding site that binds CD33. The second immunoglobulin heavy chain comprises a second Fc (hinge-CH2-CH3) domain, a second heavy chain variable domain and optionally a second CH1 heavy chain domain. The second immunoglobulin light chain includes a second

light chain variable domain and a second light chain constant domain. The second immunoglobulin light chain, together with the second immunoglobulin heavy chain, forms an antigen-binding site that binds NKG2D. The first Fc domain and second Fc domain together are able to bind to CD16.

[0267] Another exemplary format involves a heterodimeric, multi-specific antibody which includes a first immunoglobulin heavy chain, a second immunoglobulin heavy chain and an immunoglobulin light chain. The first immunoglobulin heavy chain includes a first Fc (hinge-CH2-CH3) domain fused via either a linker or an antibody hinge to a single-chain variable fragment (scFv) composed of a heavy variable domain and light chain variable domain which pair and bind CD33 or NKG2D. The second immunoglobulin heavy chain includes a second Fc (hinge-CH2-CH3) domain, a second heavy chain variable domain and optionally a CH1 heavy chain domain. The immunoglobulin light chain includes a light chain variable domain and a constant light chain domain. The second immunoglobulin heavy chain pairs with the immunoglobulin light chain and binds to NKG2D or CD33. The first Fc domain and the second Fc domain together are able to bind to CD16.

[0268] One or more additional binding motifs may be fused to the C-terminus of the constant region CH3 domain, optionally via a linker sequence. In certain embodiments, the antigen-binding site could be a single-chain or disulfide-stabilized variable region (scFv) or could form a tetravalent or trivalent molecule.

[0269] In some embodiments, the multi-specific binding protein is in the Triomab form, which is a trifunctional, bispecific antibody that maintains an IgG-like shape. This chimera consists of two half antibodies, each with one light and one heavy chain, that originate from two parental antibodies.

[0270] In some embodiments, the multi-specific binding protein is the KiH Common Light Chain (LC) form, which involves the knobs-into-holes (KIHs) technology. The KIH involves engineering C_H3 domains to create either a "knob" or a "hole" in each heavy chain to promote heterodimerization. The concept behind the "Knobs-into-Holes (KiH)" Fc technology was to introduce a "knob" in one CH3 domain (CH3A) by substitution of a small residue with a bulky one (*e.g.*, $T366W_{CH3A}$ in EU numbering). To accommodate the "knob," a complementary "hole" surface was created on the other CH3 domain (CH3B) by replacing the closest neighboring residues to the knob with smaller ones (*e.g.*, $T366S/L368A/Y407V_{CH3B}$). The "hole" mutation was optimized by structured-guided phage library screening (Atwell S, Ridgway JB, Wells JA, Carter P., Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library, *J. Mol.*

Biol. (1997) 270(1):26–35). X-ray crystal structures of KiH Fc variants (Elliott JM, Ultsch M, Lee J, Tong R, Takeda K, Spiess C, *et al.*, Antiparallel conformation of knob and hole aglycosylated half-antibody homodimers is mediated by a CH2-CH3 hydrophobic interaction. *J. Mol. Biol.* (2014) 426(9):1947–57; Mimoto F, Kadono S, Katada H, Igawa T, Kamikawa T, Hattori K. Crystal structure of a novel asymmetrically engineered Fc variant with improved affinity for FcgammaRs. *Mol. Immunol.* (2014) 58(1):132–8) demonstrated that heterodimerization is thermodynamically favored by hydrophobic interactions driven by steric complementarity at the inter-CH3 domain core interface, whereas the knob–knob and the hole–hole interfaces do not favor homodimerization owing to steric hindrance and disruption of the favorable interactions, respectively.

[0271] In some embodiments, the multi-specific binding protein is in the dual-variable domain immunoglobulin (DVD-Ig™) form, which combines the target binding domains of two monoclonal antibodies via flexible naturally occurring linkers, and yields a tetravalent IgG - like molecule.

[0272] In some embodiments, the multi-specific binding protein is in the Orthogonal Fab interface (Ortho-Fab) form. In the ortho-Fab IgG approach (Lewis SM, Wu X, Pustilnik A, Sereno A, Huang F, Rick HL, *et al.*, Generation of bispecific IgG antibodies by structure-based design of an orthogonal Fab interface. *Nat. Biotechnol.* (2014) 32(2):191–8), structure-based regional design introduces complementary mutations at the LC and $HC_{VH\text{-}CH1}$ interface in only one Fab, without any changes being made to the other Fab.

[0273] In some embodiments, the multi-specific binding protein is in the 2-in-1 Ig format. In some embodiments, the multi-specific binding protein is in the ES form, which is a heterodimeric construct containing two different Fabs binding to targets 1 and target 2 fused to the Fc. Heterodimerization is ensured by electrostatic steering mutations in the Fc.

[0274] In some embodiments, the multi-specific binding protein is in the κλ-Body form, which is an heterodimeric constructs with two different Fabs fused to Fc stabilized by heterodimerization 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 κλ-Body; FIG. 30B is an exemplary representation of another κλ-Body.

[0275] In some embodiments, the multi-specific binding protein is in Fab Arm Exchange form (antibodies that exchange Fab arms by swapping a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule, which results in bispecific antibodies). In some embodiments, the multi-specific binding protein is in the SEED Body form. The strand-exchange engineered domain (SEED) platform was designed to

generate asymmetric and bispecific antibody-like molecules, a capability that expands therapeutic applications of natural antibodies. This protein engineered platform is based on exchanging structurally related sequences of immunoglobulin within the conserved CH3 domains. The SEED design allows efficient generation of AG/GA heterodimers, while disfavoring homodimerization of AG and GA SEED CH3 domains. (Muda M. *et al.*, *Protein Eng. Des. Sel.* (2011, 24(5):447-54)). In some embodiments, the multi-specific binding protein is in the LuZ-Y form, in which a leucine zipper is used to induce heterodimerization of two different HCs. (Wranik, BJ. *et al.*, *J. Biol. Chem.* (2012), 287:43331-9).

[0276] In some embodiments, the multi-specific binding protein is in the Cov-X-Body form. In bispecific CovX-Bodies, two different peptides are joined together using a branched azetidinone linker and fused to the scaffold antibody under mild conditions in a site-specific manner. Whereas the pharmacophores are responsible for functional activities, the antibody scaffold imparts long half-life and Ig-like distribution. The pharmacophores can be chemically optimized or replaced with other pharmacophores to generate optimized or unique bispecific antibodies. (Doppalapudi VR *et al.*, *PNAS* (2010), 107(52);22611-22616).

[0277] In some embodiments, the multi-specific binding protein is in an Oasc-Fab heterodimeric form that includes Fab binding to target 1, and scFab binding to target 2 fused to Fc. Heterodimerization is ensured by mutations in the Fc.

[0278] In some embodiments, the multi-specific binding protein is in a DuetMab form, 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 LC and HC pairing.

[0279] In some embodiments, the multi-specific binding protein is in a CrossmAb form, 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.

[0280] In some embodiments, the multi-specific binding protein is in a Fit-Ig form, 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.

[0281] Additional formats of the multi-specific binding proteins can be devised by combining various formats of CD33 binding-fragments described herein.

[0282] In certain embodiments of the present disclosure, the third component for the multi-specific binding proteins is an antibody constant region. In certain embodiments, each of the two immunoglobulin heavy chains of the antibody constant region includes a constant

region with an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to human IgG1 constant region. In certain embodiments, 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.

[0283] In certain embodiments of the present disclosure, the NKG2D-antigen binding site comprises:

(1) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:81 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:82 [ADI-29379];

(2) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:83 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:84 [ADI-29463];

(3) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:85 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:86 [ADI-27744];

(4) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:87 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:88 [ADI-27749];

(5) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:191 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:88 [A49MI]; or

(6) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:89 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:90 [ADI-29378].

[0284] In certain embodiments of the present disclosure, the NKG2D-antigen binding site comprises:

(1) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:124 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:125 [ADI-27705];

(2) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:129 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:130 [ADI-27724];

(3) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:131 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:132 [ADI-27740];

(4) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:133 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:134 [ADI-27741];

(5) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID

NO:135 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:136 [ADI-27743];

(6) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:137 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:138 [ADI-28153];

(7) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:139 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:140 [ADI-28226 (C26)];

(8) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:141 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:142;

(9) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:143 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:144;

(10) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:145 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:146;

(11) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:147 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:148;

(12) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:149 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:150;

(13) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:151 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:152;

(14) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:153 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:154;

(15) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:155 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:156;

(16) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:157 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:158;

(17) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:159 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:160;

(18) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:161 and a light chain variable domain comprising an amino acid sequence at least 90%

(*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:162;

(19) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:163 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:164;

(20) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:165 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:166;

(21) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:167 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:168;

(22) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:175 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:176;

(23) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:583 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:584; or

(24) a heavy chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:585 and a light chain variable domain comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a SEQ ID NO:580.

[0285] Table 2 lists peptide sequences of heavy chain variable domains and light chain variable domains that, in combination, can bind to NKG2D. Unless indicated otherwise, the

CDR sequences provided in Table 2 are determined under Kabat. The NKG2D-binding domains can vary in their binding affinity to NKG2D, nevertheless, they all activate human NKG2D and NK cells.

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
ADI-29379 (E79)	QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMHWVRQAPGQGLEWMGI INPSGGSTSYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGAPNY GDTTHDYYYMDVWGKGTTVTVSS [SEQ ID NO:81] CDR1: YTFTSYYMH [SEQ ID NO:93] (non-Kabat) or SYYMH [SEQ ID NO:566] CDR2: IINPSGGSTSYAQKFQG [SEQ ID NO:94] CDR3: ARGAPNYGDTTHDYYYMDV [SEQ ID NO:95] (non-Kabat) or GAPNYGDTTHDYYYMDV [SEQ ID NO:567]	EIVMTQSPATLSVSPGERATLS CRASQSVSSNLAWYQQKPGQA PRLLIYGASTRATGIPARFSGSG SGTEFTLTISSLQSEDFAVYYCQ QYDDWPFTFGGGTKVEIK [SEQ ID NO:82] CDR1: RASQSVSSNLA [SEQ ID NO:96] CDR2: GASTRAT [SEQ ID NO:97] CDR3: QQYDDWPFT [SEQ ID NO:98]
ADI-29463 (F63)	QVQLVQSGAEVKKPGASVKVSCKAS GYTFTGYYMHWVRQAPGQGLEWMG WINPNSGGTNYAQKFQGRVTMTRDT SISTAYMELSRLRSDDTAVYYCARDT GEYYDTDDHGMDVWGQGTTVTVSS [SEQ ID NO:83] CDR1: YTFTGYYMH [SEQ ID NO:99] (non-Kabat) or GYYMH [SEQ ID NO:568] CDR2: WINPNSGGTNYAQKFQG	EIVLTQSPGTLSLSPGERATLSC RASQSVSSNLAWYQQKPGQAP RLLIYGASTRATGIPARFSGSGS GTEFTLTISSLQSEDFAVYYCQ QDDYWPPTFGGGTKVEIK [SEQ ID NO:84] CDR1: RASQSVSSNLA [SEQ ID NO:102] CDR2: GASTRAT [SEQ ID NO:103]

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	[SEQ ID NO:100] CDR3: ARDTGEYYDTDDHGMDV [SEQ ID NO:101] (non-Kabat) or DTGEYYDTDDHGMDV [SEQ ID NO:569]	CDR3: QQDDYWPPT [SEQ ID NO:104]
ADI-27744 (A44)	EVQLLESGGGLVQPGGSLRLSCAASG FTFSSYAMSWVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAKDGGYY DSGAGDYWGQGTLVTVSS [SEQ ID NO:85] CDR1: FTFSSYAMS [SEQ ID NO:105] (non-Kabat) or SYAMS [SEQ ID NO:570] CDR2: AISGSGGSTYYADSVKG [SEQ ID NO:106] CDR3: AKDGGYYDSGAGDY [SEQ ID NO:107] (non-Kabat) or DGGYYDSGAGDY [SEQ ID NO:571]	DIQMTQSPSSVSASVGDRVTIT CRASQGIDSWLAWYQQKPGK APKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYC QQGVSYPRTFGGGTKVEIK [SEQ ID NO:86] CDR1: RASQGIDSWLA [SEQ ID NO:108] CDR2: AASSLQS [SEQ ID NO:109] CDR3: QQGVSYPRT [SEQ ID NO:110]
ADI-27749 (A49)	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAPMGA AAGWFDPWGQGTLVTVSS [SEQ ID NO:87] CDR1: FTFSSYSMN [SEQ ID NO:111] or SYSMN [SEQ ID NO:192]	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK [SEQ ID NO:88] CDR1: RASQGISSWLA [SEQ ID NO:114]

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	CDR2: SISSSSSYIYYADSVKG [SEQ ID NO:112] CDR3: (non-Kabat) ARGAPMGAAAGWFDP [SEQ ID NO:113] or GAPMGAAAGWFDP [SEQ ID NO:193]	CDR2: AASSLQS [SEQ ID NO:115] CDR3: QQGVSFPRT [SEQ ID NO:116]
A49MI	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAP**I**GA AAGWFDPWGQGTLVTVSS [SEQ ID NO:191] CDR1: (non-Kabat) FTFSSYSMN [SEQ ID NO:111] or SYSMN [SEQ ID NO:192] CDR2: SISSSSSYIYYADSVKG [SEQ ID NO:112] CDR3: (non-Kabat) ARGAP**I**GAAAGWFDP [SEQ ID NO:194] or GAP**I**GAAAGWFDP [SEQ ID NO:195]	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK [SEQ ID NO:88] CDR1: RASQGISSWLA [SEQ ID NO:114] CDR2: AASSLQS [SEQ ID NO:115] CDR3: QQGVSFPRT [SEQ ID NO:116]
A49MQ	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAP**QG**A AAGWFDPWGQGTLVTVSS (SEQ ID NO:586) CDR1 (non-Kabat) (SEQ ID NO:111) - FTFSSYSMN or CDR1 (SEQ ID NO:192) - SYSMN	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK (SEQ ID NO:88) CDR1 (SEQ ID NO:114) - RASQGISSWLA CDR2 (SEQ ID NO:115) -

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	CDR2 (SEQ ID NO:112) - SISSSSSYIYYADSVKG CDR3 (non-Kabat) (SEQ ID NO:587) - ARGAP**Q**GAAAGWFDP or CDR3 (SEQ ID NO:588) - GAP**Q**GAAAGWFDP	AASSLQS CDR3 (SEQ ID NO:116) - QQGVSFPRT
A49ML	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAP**L**GA AAGWFDPWGQGTLVTVSS (SEQ ID NO:589) CDR1 (non-Kabat) (SEQ ID NO:111) - FTFSSYSMN or CDR1 (SEQ ID NO:192) - SYSMN CDR2 (SEQ ID NO:112) - SISSSSSYIYYADSVKG CDR3 (non-Kabat) (SEQ ID NO:590) - ARGAP**L**GAAAGWFDP or CDR3 (SEQ ID NO:591) - GAP**L**GAAAGWFDP	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK (SEQ ID NO:88) CDR1 (SEQ ID NO:114) - RASQGISSWLA CDR2 (SEQ ID NO:115) - AASSLQS CDR3 (SEQ ID NO:116) - QQGVSFPRT
A49MF	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAP**F**GA AAGWFDPWGQGTLVTVSS (SEQ ID NO:592) CDR1 (non-Kabat) (SEQ ID NO:111) - FTFSSYSMN or CDR1 (SEQ ID NO:192) - SYSMN CDR2 (SEQ ID NO:112) - SISSSSSYIYYADSVKG CDR3 (non-Kabat) (SEQ ID NO:593) - ARGAP**F**GAAAGWFDP or CDR3 (SEQ ID NO:594) - GAP**F**GAAAGWFDP	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK [SEQ ID NO:88] CDR1: RASQGISSWLA [SEQ ID NO:114] CDR2: AASSLQS [SEQ ID NO:115] CDR3: QQGVSFPRT [SEQ ID NO:116]
A49MV	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS	DIQMTQSPSSVSASVGDRVTIT

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAP**V**GA AAGWFDPWGQGTLVTVSS (SEQ ID NO:595) CDR1 (non-Kabat) (SEQ ID NO:111) - FTFSSYSMN or CDR1 (SEQ ID NO:192) - SYSMN CDR2 (SEQ ID NO:112) - SISSSSSYIYYADSVKG CDR3 (non-Kabat) (SEQ ID NO:596) - ARGAP**V**GAAAGWFDP or CDR3 (SEQ ID NO:597) - GAP**V**GAAAGWFDP	CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK [SEQ ID NO:88] CDR1: RASQGISSWLA [SEQ ID NO:114] CDR2: AASSLQS [SEQ ID NO:115] CDR3: QQGVSFPRT [SEQ ID NO:116]
A49-consensus	EVQLVESGGGLVKPGGSLRLSCAASG FTFSSYSMNWVRQAPGKGLEWVSSIS SSSSYIYYADSVKGRFTISRDNAKNSL YLQMNSLRAEDTAVYYCARGAP**X**GA AAGWFDPWGQGTLVTVSS, wherein X is M, L, I, V, Q, or F (SEQ ID NO:91) CDR1 (non-Kabat) (SEQ ID NO:111) - FTFSSYSMN or CDR1 (SEQ ID NO:192) - SYSMN CDR2 (SEQ ID NO:112) - SISSSSSYIYYADSVKG CDR3 (non-Kabat) (SEQ ID NO:92) - ARGAP**X**GAAAGWFDP or CDR3 (SEQ ID NO:123) – GAP**X**GAAAGWFDP, wherein X is M, L, I, V, Q, or F	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQ QGVSFPRTFGGGTKVEIK [SEQ ID NO:88] CDR1: RASQGISSWLA [SEQ ID NO:114] CDR2: AASSLQS [SEQ ID NO:115] CDR3: QQGVSFPRT [SEQ ID NO:116]
ADI-29378 (E78)	QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMHWVRQAPGQGLEWMGI INPSGGSTSYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCAREGAGF	EIVLTQSPATLSLSPGERATLSC RASQSVSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGS GTDFTLTISSLEPEDFAVYYCQ

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	AYGMDYYYMDVWGKGTTVTVSS [SEQ ID NO:89] CDR1: YTFTSYYMH [SEQ ID NO:117] (non-Kabat) or SYYMH [SEQ ID NO:572] CDR2: IINPSGGSTSYAQKFQG [SEQ ID NO:118] CDR3: AREGAGFAYGMDYYYMDV [SEQ ID NO:119] (non-Kabat) or EGAGFAYGMDYYYMDV [SEQ ID NO:573]	QSDNWPFTFGGGTKVEIK [SEQ ID NO:90] CDR1: RASQSVSSYLA [SEQ ID NO:120] CDR2: DASNRAT [SEQ ID NO:121] CDR3: QQSDNWPFT [SEQ ID NO:122]
ADI-27705	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:124] CDR1: GSFSGYYWS [SEQ ID NO:126] (non-Kabat) or GYYWS [SEQ ID NO:574] CDR2: EIDHSGSTNYNPSLKS [SEQ ID NO:127] CDR3: ARARGPWSFDP [SEQ ID NO:128] (non-Kabat) or ARGPWSFDP [SEQ ID NO:575]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYNSYPITFGGGTKVEIK [SEQ ID NO:125]
ADI-27724	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS	EIVLTQSPGTLSLSPGERATLSC RASQSVSSSYLAWYQQKPGQA PRLLIYGASSRATGIPDRFSGSG SGTDFTLTISRLEPEDFAVYYC QQYGSSPITFGGGTKVEIK

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	[SEQ ID NO:129]	[SEQ ID NO:130]
ADI-27740 (A40)	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:131]	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYHSFYTFGGGTKVEIK [SEQ ID NO:132]
ADI-27741	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:133]	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QSNSYYTFGGGTKVEIK [SEQ ID NO:134]
ADI-27743	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:135]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYNSYPTFGGGTKVEIK [SEQ ID NO:136]
ADI-28153	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWG FDPWGQGTLVTVSS [SEQ ID NO:137]	ELQMTQSPSSLSASVGDRVTIT CRTSQSISSYLNWYQQKPGQPP KLLIYWASTRESGVPDRFSGSG SGTDFTLTISSLQPEDSATYYCQ QSYDIPYTFGQGTKLEIK [SEQ ID NO:138]
ADI-28226 (C26)	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:139]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYGSFPITFGGGTKVEIK [SEQ ID NO:140]

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
ADI-28154	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:141]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTDFTLTISSLQPDDFATYYC QQSKEVPWTFGQGTKVEIK [SEQ ID NO:142]
ADI-29399	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:143]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYNSFPTFGGGTKVEIK [SEQ ID NO:144]
ADI-29401	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:145]	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYDIYPTFGGGTKVEIK [SEQ ID NO:146]
ADI-29403	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:147]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYDSYPTFGGGTKVEIK [SEQ ID NO:148]
ADI-29405	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:149]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYGSFPTFGGGTKVEIK [SEQ ID NO:150]
ADI-	QVQLQQWGAGLLKPSETLSLTCAVY	DIQMTQSPSTLSASVGDRVTIT

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
29407	GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:151]	CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYQSFPTFGGGTKVEIK [SEQ ID NO:152]
ADI-29419	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:153]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYSSFSTFGGGTKVEIK [SEQ ID NO:154]
ADI-29421	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:155]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYESYSTFGGGTKVEIK [SEQ ID NO:156]
ADI-29424	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:157]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYDSFITFGGGTKVEIK [SEQ ID NO:158]
ADI-29425	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:159]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYQSYPTFGGGTKVEIK [SEQ ID NO:160]
ADI-29426	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGKA

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
	DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:161]	PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYHSFPTFGGGTKVEIK [SEQ ID NO:162]
ADI-29429	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:163]	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYELYSYTFGGGTKVEIK [SEQ ID NO:164]
ADI-29447 (F47)	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:165]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCQ QYDTFITFGGGTKVEIK [SEQ ID NO:166]
ADI-27727	QVQLVQSGAEVKKPGSSVKVSCKAS GGTFSSYAISWVRQAPGQGLEWMGGI IPIFGTANYAQKFQGRVTITADESTST AYMELSSLRSEDTAVYYCARGDSSIR HAYYYYGMDVWGQGTTVTVSS [SEQ ID NO:167] CDR1: GTFSSYAIS [SEQ ID NO:169] (non-Kabat) or SYAIS [SEQ ID NO:576] CDR2: GIIPIFGTANYAQKFQG [SEQ ID NO:170] CDR3: ARGDSSIRHAYYYYGMDV [SEQ ID NO:171] (non-Kabat) or GDSSIRHAYYYYGMDV [SEQ ID NO:577]	DIVMTQSPDSLAVSLGERATIN CKSSQSVLYSSNNKNYLAWYQ QKPGQPPKLLIYWASTRESGVP DRFSGSGSGTDFTLTISSLQAED VAVYYCQQYYSTPITFGGGTK VEIK [SEQ ID NO:168] CDR1: KSSQSVLYSSNNKNYLA [SEQ ID NO:172] CDR2: WASTRES [SEQ ID NO:173] CDR3: QQYYSTPIT [SEQ ID NO:174]

Table 2

Clones	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
ADI-29443 (F43)	QLQLQESGPGLVKPSETLSLTCTVSGG SISSSSYYWGWIRQPPGKGLEWIGSIY YSGSTYYNPSLKSRVTISVDTSKNQFS LKLSSVTAADTAVYYCARGSDRFHPY FDYWGQGTLVTVSS [SEQ ID NO:175] CDR1: GSISSSSYYWG [SEQ ID NO:177] (non-Kabat) or SSSYYWG [SEQ ID NO:578] CDR2: SIYYSGSTYYNPSLKS [SEQ ID NO:178] CDR3: ARGSDRFHPYFDY [SEQ ID NO:179] (non-Kabat) or GSDRFHPYFDY [SEQ ID NO:579]	EIVLTQSPATLSLSPGERATLSC RASQSVSRYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGS GTDFTLTISSLEPEDFAVYYCQ QFDTWPPTFGGGTKVEIK [SEQ ID NO:176] CDR1: RASQSVSRYLA [SEQ ID NO:180] CDR2: DASNRAT [SEQ ID NO:581] CDR3: QQFDTWPPT [SEQ ID NO:582]
ADI-29404 (F04)	QVQLQQWGAGLLKPSETLSLTCAVY GGSFSGYYWSWIRQPPGKGLEWIGEI DHSGSTNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARARGPWSF DPWGQGTLVTVSS [SEQ ID NO:583]	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGKA PKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFATYYCE QYDSYPTFGGGTKVEIK [SEQ ID NO:584]
ADI-28200	QVQLVQSGAEVKKPGSSVKVSCKAS GGTFSSYAISWVRQAPGQGLEWMGGI IPIFGTANYAQKFQGRVTITADESTST AYMELSSLRSEDTAVYYCARRGRKAS GSFYYYYGMDVWGQGTTVTVSS [SEQ ID NO:585]	DIVMTQSPDSLAVSLGERATIN CESSQSLLNSGNQKNYLTWYQ QKPGQPPKPLIYWASTRESGVP DRFSGSGSGTDFTLTISSLQAED VAVYYCQNDYSYPYTFGQGTK LEIK [SEQ ID NO:580]

[0286] The antibody molecule may have a heavy chain constant region chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE;

particularly, chosen from, *e.g.*, the (*e.g.*, human) heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In another embodiment, the antibody molecule has a light chain constant region chosen from, *e.g.*, the (*e.g.*, human) light chain constant regions of kappa or lambda. The constant region can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, and/or complement function). In one embodiment the antibody has effector function and can fix complement. In other embodiments the antibody does not recruit effector cells or fix complement. In another embodiment, the antibody has reduced or no ability to bind an Fc receptor. For example, it is an isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor, *e.g.*, it has a mutagenized or deleted Fc receptor binding region.

[0287] Within the Fc domain, CD16 binding is mediated by the hinge region and the CH2 domain. For example, within human IgG1, the interaction with CD16 is primarily focused on amino acid residues Asp 265 – Glu 269, Asn 297 – Thr 299, Ala 327 – Ile 332, Leu 234 – Ser 239, and carbohydrate residue N-acetyl-D-glucosamine in the CH2 domain (see, Sondermann *et al.*, Nature, 406 (6793):267-273). Based on the known domains, mutations can be selected to enhance or reduce the binding affinity to CD16, such as by using phage-displayed libraries or yeast surface-displayed cDNA libraries, or can be designed based on the known three-dimensional structure of the interaction.

[0288] In some embodiments, the antibody constant domain comprises a CH2 domain and a CH3 domain of an IgG antibody, for example, a human IgG1 antibody. In some embodiments, mutations are introduced in the antibody constant domain to enable heterdimerization with another antibody constant domain. For example, if the antibody constant domain is derived from the constant domain of a human IgG1, the antibody constant domain can comprise an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to amino acids 234-332 of a human IgG1 antibody, and differs at one or more positions selected from the group consisting of Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411, and K439. All the amino acid positions in an Fc domain or hinge region disclosed herein are numbered according to EU numbering.

[0289] The assembly of heterodimeric antibody heavy chains can be accomplished by expressing two different antibody heavy chain sequences in the same cell, which may lead to the assembly of homodimers of each antibody heavy chain as well as assembly of heterodimers. Promoting the preferential assembly of heterodimers can be accomplished by

incorporating different mutations in the CH3 domain of each antibody heavy chain constant region as shown in US13/494870, US16/028850, US11/533709, US12/875015, US13/289934, US14/773418, US12/811207, US13/866756, US14/647480, and US14/830336. For example, mutations can be made in the CH3 domain based on human IgG1 and incorporating distinct pairs of amino acid substitutions within a first polypeptide and a second polypeptide that allow these two chains to selectively heterodimerize with each other. The positions of amino acid substitutions illustrated below are all numbered according to the EU index as in Kabat.

[0290] In one scenario, an amino acid substitution in the first polypeptide replaces the original amino acid with a larger amino acid, selected from arginine (R), phenylalanine (F), tyrosine (Y) or tryptophan (W), and at least one amino acid substitution in the second polypeptide replaces the original amino acid(s) with a smaller amino acid(s), chosen from alanine (A), serine (S), threonine (T), or valine (V), such that the larger amino acid substitution (a protuberance) fits into the surface of the smaller amino acid substitutions (a cavity). For example, one polypeptide can incorporate a T366W substitution, and the other can incorporate three substitutions including T366S, L368A, and Y407V.

[0291] An antibody heavy chain variable domain of the invention can optionally be coupled to an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an antibody constant region, such as an IgG constant region including hinge, CH2 and CH3 domains with or without CH1 domain. In some embodiments, the amino acid sequence of the constant region is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to a human antibody constant region, such as an human IgG1 constant region, an IgG2 constant region, IgG3 constant region, or IgG4 constant region. In some other embodiments, the amino acid sequence of the constant region is at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an antibody constant region from another mammal, such as rabbit, dog, cat, mouse, or horse. One or more mutations can be incorporated into the constant region as compared to human IgG1 constant region, for example at Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411 and/or K439. Exemplary substitutions include, for example, Q347E, Q347R, Y349S, Y349K, Y349T, Y349D, Y349E, Y349C, T350V, L351K, L351D, L351Y, S354C, E356K, E357Q, E357L, E357W, K360E, K360W, Q362E, S364K, S364E, S364H, S364D, T366V, T366I, T366L, T366M, T366K, T366W, T366S, L368E, L368A, L368D, K370S, N390D, N390E, K392L, K392M, K392V, K392F, K392D, K392E,

T394F, T394W, D399R, D399K, D399V, S400K, S400R, D401K, F405A, F405T, Y407A, Y407I , Y407V, K409F, K409W, K409D, T411D, T411E, K439D, and K439E.

[0292] In certain embodiments, mutations that can be incorporated into the CH1 of a human IgG1 constant region may be at amino acid V125, F126, P127, T135, T139, A140, F170, P171, and/or V173. In certain embodiments, mutations that can be incorporated into the Cκ of a human IgG1 constant region may be at amino acid E123, F116, S176, V163, S174, and/or T164.

[0293] Alternatively, amino acid substitutions could be selected from the following sets of substitutions shown in Table 3.

Table 3

	First Polypeptide	**Second Polypeptide**
Set 1	S364E/F405A	Y349K/T394F
Set 2	S364H/D401K	Y349T/T411E
Set 3	S364H/T394F	Y349T/F405A
Set 4	S364E/T394F	Y349K/F405A
Set 5	S364E/T411E	Y349K/D401K
Set 6	S364D/T394F	Y349K/F405A
Set 7	S364H/F405A	Y349T/T394F
Set 8	S364K/E357Q	L368D/K370S
Set 9	L368D/K370S	S364K
Set 10	L368E/K370S	S364K
Set 11	K360E/Q362E	D401K
Set 12	L368D/K370S	S364K/E357L
Set 13	K370S	S364K/E357Q
Set 14	F405L	K409R
Set 15	K409R	F405L

[0294] Alternatively, amino acid substitutions could be selected from the following sets of substitutions shown in Table 4.

Table 4		
	First Polypeptide	**Second Polypeptide**
Set 1	K409W	D399V/F405T
Set 2	Y349S	E357W
Set 3	K360E	Q347R
Set 4	K360E/K409W	Q347R/D399V/F405T
Set 5	Q347E/K360E/K409W	Q347R/D399V/F405T
Set 6	Y349S/K409W	E357W/D399V/F405T

[0295] Alternatively, amino acid substitutions could be selected from the following set of substitutions shown in Table 5.

Table 5		
	First Polypeptide	**Second Polypeptide**
Set 1	T366K/L351K	L351D/L368E
Set 2	T366K/L351K	L351D/Y349E
Set 3	T366K/L351K	L351D/Y349D
Set 4	T366K/L351K	L351D/Y349E/L368E
Set 5	T366K/L351K	L351D/Y349D/L368E
Set 6	E356K/D399K	K392D/K409D

[0296] Alternatively, at least one amino acid substitution in each polypeptide chain could be selected from Table 6.

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Table 6	
First Polypeptide	**Second Polypeptide**
L351Y, D399R, D399K, S400K, S400R, Y407A, Y407I, Y407V	T366V, T366I, T366L, T366M, N390D, N390E, K392L, K392M, K392V, K392F K392D, K392E, K409F, K409W, T411D and T411E

[0297] Alternatively, at least one amino acid substitutions could be selected from the following set of substitutions in Table 7, where the position(s) indicated in the First Polypeptide column is replaced by any known negatively-charged amino acid, and the

position(s) indicated in the Second Polypeptide Column is replaced by any known positively-charged amino acid.

Table 7	
First Polypeptide	**Second Polypeptide**
K392, K370, K409, or K439	D399, E356, or E357

[0298] Alternatively, at least one amino acid substitutions could be selected from the following set of in Table 8, where the position(s) indicated in the First Polypeptide column is replaced by any known positively-charged amino acid, and the position(s) indicated in the Second Polypeptide Column is replaced by any known negatively-charged amino acid.

Table 8	
First Polypeptide	**Second Polypeptide**
D399, E356, or E357	K409, K439, K370, or K392

[0299] Alternatively, amino acid substitutions could be selected from the following set of in Table 9.

Table 9	
First Polypeptide	**Second Polypeptide**
T350V, L351Y, F405A, and Y407V	T350V, T366L, K392L, and T394W

[0300] Alternatively, or in addition, the structural stability of heterodimeric heavy chains within the multi-specific binding proteins can be increased by introducing S354C on either of the first or second polypeptide chain, and Y349C on the opposing polypeptide chain, which forms an artificial disulfide bridge within the interface of the two polypeptides.

[0301] 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 at position T366, 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 at one or more positions selected from the group consisting of T366, L368 and Y407.

[0302] 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 at one or more positions selected from the group consisting of T366, L368 and Y407, 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 at position T366.

[0303] 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 at one or more positions selected from the group consisting of E357, K360, Q362, S364, L368, K370, T394, D401, F405, and T411 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 at one or more positions selected from the group consisting of Y349, E357, S364, L368, K370, T394, D401, F405 and T411.

[0304] 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 at one or more positions selected from the group consisting of Y349, E357, S364, L368, K370, T394, D401, F405 and T411 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 at one or more positions selected from the group consisting of E357, K360, Q362, S364, L368, K370, T394, D401, F405, and T411.

[0305] 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 at one or more positions selected from the group consisting of L351, D399, S400 and Y407 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 at one or more positions selected from the group consisting of T366, N390, K392, K409 and T411.

[0306] 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 at one or more positions selected from the group consisting of T366, N390, K392, K409 and T411 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 at one or more positions selected from the group consisting of L351, D399, S400 and Y407.

[0307] 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 at one or more positions selected from the group consisting of Q347, Y349, K360, and K409, 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 at one or more positions selected from the group consisting of Q347, E357, D399 and F405.

[0308] 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 at one or more positions selected from the group consisting of Q347, E357, D399 and F405, 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 at one or more positions selected from the group consisting of Y349, K360, Q347 and K409.

[0309] 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 at one or more positions selected from the group consisting of K370, K392, K409 and K439, 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 at one or more positions selected from the group consisting of D356, E357 and D399.

[0310] 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 at one or more positions selected from the group consisting of D356, E357 and D399, 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 at one or more positions selected from the group consisting of K370, K392, K409 and K439.

[0311] 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 at one or more positions selected from the group consisting of L351, E356, T366 and D399, 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 at one or more positions selected from the group consisting of Y349, L351, L368, K392 and K409.

[0312] 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 at one or more positions selected from the group consisting of Y349, L351, L368, K392 and K409, 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 at one or more positions selected from the group consisting of L351, E356, T366 and D399.

[0313] 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 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.

[0314] 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 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 an S354C substitution.

[0315] 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.

[0316] 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 O347R, 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.

[0317] 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 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.

[0318] 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.

[0319] 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.

[0320] 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, T366L, K392L, and T394W 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, L351Y, F405A, and Y407V substitutions.

[0321] Listed below are examples of CD33-binding F3'-TriNKETs comprising: a CD33-binding single-chain variable fragment (scFv) linked to an Fc domain via a hinge comprising Ala-Ser; and an NKG2D-binding Fab fragment ("A49," "A49MI, "A49MQ," "A49ML," "A49MF," or "A49MV") comprising a heavy chain portion comprising an heavy chain variable domain (SEQ ID NO:87 or SEQ ID NO:191) and a CH1 domain, and a light chain portion comprising a light chain variable domain (SEQ ID NO:88) and a light chain constant domain, wherein the heavy chain variable domain is connected to the CH1 domain, and the CH1 domain is connected to an Fc domain. The CDR sequences are underlined.

[0322] In each of the examples, the Fc domain linked to the CD33-binding scFv comprises Q347R, D399V, and F405T substitutions for forming a heterodimer with the Fc domain linked to the Fab comprising K360E and K409W substitutions. These substitutions in the Fc domains are bold-underlined in the sequences described below. Alternatively, in an exemplary embodiment, the Fc domain linked to the NKG2D-binding Fab fragment includes the mutations of Q347R, D399V, and F405T, and the Fc domain linked to the CD33-binding scFv comprises matching mutations K360E and K409W for forming a heterodimer.

[0323] Additionally, the Fc domain linked to the CD33-binding scFv comprises S354C substitution, and the Fc domain linked to the Fab comprises Y349C substitution, thereby stabilizing the interaction between the two Fc domains via a S-S bridge. These substitutions in the Fc domains are bold-italics-underlined in the sequences below.

[0324] Alternatively, in an exemplary embodiment, the Fc domain linked to the NKG2D-binding Fab fragment includes a S354C substitution in the CH3 domain, which forms a disulfide bond with a Y349C substitution on the Fc linked to the CD33-binding scFv.

[0325] A CD33-binding scFv of the present disclosure can include a heavy chain variable domain connected to a light chain variable domain with a $(G4S)_4$ linker. The scFv is linked to an Fc domain via a hinge comprising Ala-Ser (bolded-underlined). SEQ ID NOs:188, 198, and 206-223 are exemplary sequences of such CD33-binding scFv polypeptides. The V_L and V_H comprised within the scFv (*e.g.*, SEQ ID NOs:188, 198 or 206-223) contain $100V_L$ - $44V_H$ S-S bridge (resulting from G100C and G44C substitutions, respectively) (cysteine residues are in bold-italics-underlined in the sequences below). $(G4S)_4$ is the bold-underlined sequence GGGGSGGGGSGGGGSGGGGS [SEQ ID NO:186] in SEQ ID NOs:188, 198, and 206-243.

[0326] Exemplary sequences of CD33-binding scFvs linked to an Fc domain via a hinge comprising Ala-Ser are provided below.

Ab1 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYESFPTFG***C***GTKVEIK**GGGGSGGGGS**
GGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGK***C***L
EWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREG
GPYYDSSGYFVYYGMDVWGQGTTVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP***C***RDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:224]

Ab1 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGK***C***LEWVANIKQDGS
EKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVY
YGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDR
VTITCRASQSISSWLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTEFTLTISS
LQPDDFATYYCQQYESFPTFG***C***GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP***C***RDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:225]

Ab2 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQLESYPLTFG***C***GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK***C***

LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPL
NAGELDVWGQGTMVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG [SEQ ID NO:226]

Ab2 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK**C**LEWVANIKQDG
SEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ
GTMVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASQ
SISSWLAWYQQKPGKAPKLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATY
YCQQLESYPLTFG**C**GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:227]

H76 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG**C**GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK**C**
LEWVSAIVGSGESTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREG
GPYYDSSGYFVYYGMDVWGQGTTVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:197]

H76 scFv (HC-LC) -Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK**C**LEWVSAIVGSGE
STYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVY
YGMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDR
VTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISS
LQPDDFATYYCQQYDDLPTFG**C**GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:228]

H76 scFc (LC-HC)-Fc (K360E, K409W, and Y349C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG**C**GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK**C**
LEWVSAIVGSGESTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREG
GPYYDSSGYFVYYGMDVWGQGTTVTVSS**AS**TKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC

VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQV*C*TLPPSRDELT**E**NQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS**W**LTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG [SEQ ID NO:243]

Ab4 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSN
RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQDVALPITFG*C*GTKVEIK**GGG**
GSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHW
VRQAPGQ*C*LEWMGMINPSWGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT
AVYYCAREAADGFVGERYFDLWGRGTLVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP*C*RD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:229]

Ab4 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

QVQLVQSGAEVKKPGASVKVSCKASGYTFSDYYMHWVRQAPGQ*C*LEWMGMINPS
WGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREAADGFVGERYF
DLWGRGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**DIVMTQSPLSLPVTPGEPASISC
RSSQSLLYSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKIS
RVEAEDVGVYYCMQDVALPITFG*C*GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP*C*RDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:230]

I07 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFG*C*GTKVEIK**GGGGSGGG**
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPG
K*C*LEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
PLNAGELDVWGQGTMVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP*C*RDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:187]

I07 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGK*C*LEWVATIKQDG
SEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ
GTMVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASQ
SISSWLAWYQQKPGKAPKLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATY
YCQQSQSYPPITFG*C*GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP*C*RDELTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLVSDGSFTLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:231]

I07 scFc (LC-HC)-Fc (K360E, K409W, and Y349C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGCGTKVEIK**GGGGSGGG GSGGGGSGGGGS**EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPG KCLEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR PLNAGELDVWGQGTMVTVSS**AS**TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTENQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSWLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPG [SEQ ID NO:242]

Ab6 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGCGTKVEIK**GGGGSGGG GSGGGGSGGGGS**EVQLVESGGGLVQPGGSLRLSCAASGFTFPSYWMSWVRQAPGK CLEWVATIKRDGSEKGYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARP LNAGELDVWGQGTMVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:232]

Ab6 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVQPGGSLRLSCAASGFTFPSYWMSWVRQAPGKCLEWVATIKRDGS EKGYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQG TMVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRVTITCRASQSI SSWLAWYQQKPGKAPKLLIYEASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYY CQQSQSYPPITFG**C**GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPG [SEQ ID NO:233]

Ab7 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHSYPLTFG**C**GTKVEIK**GGGGSGG GGSGGGGSGGGGS**QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQA PGQCLEWMGIINPSRGSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC ARGAGYDDEDMDVWGKGTTVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQV

SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:234]

Ab7 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGTYYMHWVRQAPGQ***C***LEWMGIINPSR
GSTVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGAGYDDEDMDV
WGKGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSSVSASVGDRVTITCR
ASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPED
FATYYCQQAHSYPLTFG***C***GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP***C***RDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:235]

Ab8 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASNSISSWLAWYQQKPGKAPKLLIYEASSTKSGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG***C***GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMSWVRQAPGK***C***
LEWVSSISSSSEGIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGG
PYYDSSGYFVYYGMDVWGQGTTVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP***C***RDELTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:236]

Ab8 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAMSWVRQAPGK***C***LEWVSSISSSSEGI
YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGPYYDSSGYFVYY
GMDVWGQGTTVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSTLSASVGDRV
TITCRASNSISSWLAWYQQKPGKAPKLLIYEASSTKSGVPSRFSGSGSGTEFTLTISSL
QPDDFATYYCQQYDDLPTFG***C***GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP***C***RDELTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:237]

Ab9 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSSLSASVGDRVTITCRASQVIYSYLNWYQQKPGKAPKLLIYAASSLKSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYDTPLTFG***C***GTKVEIK**GGGGSGGG**
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK
CLEWVANINTDGSEVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARD
VGPGIAYQGHFDYWGQGTLVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP***C***RDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:238]

Ab9 scFv (HC-LC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK**C**LEWVANINTDGS
EVYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDVGPGIAYQGHFD
YWGQGTLVTVSS**GGGGSGGGGSGGGGSGGGGS**DIQMTQSPSSLSASVGDRVTITC
RASQVIYSYLNWYQQKPGKAPKLLIYAASSLKSGVPSRFSGSGSGTDFTLTISSLQPE
DFATYYCQQVYDTPLTFG**C**GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG [SEQ ID NO:239]

Ab10 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

EIVLTQSPATLSLSPGERATLSCRASHSVYSYLAWYQQKPGQAPRLLIYDASNRATGI
PARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYDNLPTFG**C**GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSQLQLQESGPGLVKPSETLSLTCTVSGGSISSTDYYWGWIRQPPGK**C**
LEWIGSIGYSGTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARETAHDV
HGMDVWGQGTTVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG [SEQ ID NO:240]

Ab10 scFv (HC-LC) -Fc (Q347R, D399V, F405T, and S354C substitutions)

QLQLQESGPGLVKPSETLSLTCTVSGGSISSTDYYWGWIRQPPGK**C**LEWIGSIGYSGT
YYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARETAHDVHGMDVWGQG
TTVTVSS**GGGGSGGGGSGGGGSGGGGS**EIVLTQSPATLSLSPGERATLSCRASHSV
YSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYY
CQQYDNLPTFG**C**GTKVEIK**AS**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG [SEQ ID NO:241]

[0327] A TriNKET of the present disclosure is A49-F3'-TriNKET-I07, comprising a first polypeptide chain, named "I07 scFv-Fc," which comprises a CD33-binding scFv linked to an Fc domain via an Ala-Ser linker; a second polypeptide chain, named "A49 VH-CH1-Fc," which comprises an NKG2D-targeting heavy chain; and a third polypeptide chain, named "A49 VL-CL," which comprises an NKG2D-targeting light chain. The amino acid sequence of I07 scFv-Fc comprises:

I07 scFv (LC-HC)-Fc (Q347R, D399V, F405T, and S354C substitutions)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFG**C**GTKVEIK**GGGGSGGG**
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPG

KCLEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
PLNAGELDVWGQGTMVTVSSASDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPRVYTLPPCRDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLVSDGSFTLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:187]

[0328] The amino acid sequence of the scFv portion of I07 scFv-Fc comprises:

I07 scFv

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGCGTKVEIK**GGGGSGGG**
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPG
KCLEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
PLNAGELDVWGQGTMVTVSS
[SEQ ID NO:188]

[0329] A49 VH-CH1-Fc comprises A49 VH [SEQ ID NO:87] linked to a CH1 domain and an Fc domain (including hinge, CH2, and CH3 domains). The amino acid sequence of A49 VH-CH1-Fc comprises:

A49 VH-CH1-Fc (K360E, K409W, and Y349C substitutions)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI
YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAPMGAAAGWFDPW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVCTLPPSRDELTENQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSWLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:189]

A49 VH-CH1-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI
YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAPMGAAAGWFDPW
GQGTLVTVSSASDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPRVYTLPPCRDELTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLVSDGSFTLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSL [SEQ ID NO:244]

[0330] A49 VL-CL comprises A49 VL [SEQ ID NO:88] linked to a light chain constant domain (CL). The amino acid sequence of A49 VL-CL comprises:

A49 VL-CL
DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGVSFPRTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
[SEQ ID NO:190]

[0331] Another TriNKET of the present disclosure is A49MI-F3'-TriNKET-I07, comprising a first polypeptide chain, named "I07 scFv-Fc," as described above [SEQ ID NO:187]; a second polypeptide chain, named "A49MI VH-CH1-Fc," that comprises an NKG2D-targeting heavy chain with an Fc domain; and a third polypeptide chain, named "A49 VL-CL," as described above [SEQ ID NO:190]. A49MI-F3'-TriNKET-I07 is identical to A49-F3'-TriNKET-I07 except for a substitution of I for M in CDR3 of the NKG2D-targeting VH. This substitution is bold-italic (and underlined because it is part of a CDR) in the sequence below. A49MI VH-CH1-Fc comprises A49MI VH [SEQ ID NO:191] linked to a CH1 domain and an Fc domain (including hinge, CH2, and CH3 domains). The amino acid sequence of A49MI VH-CH1-Fc comprises:

A49MI VH-CH1-Fc (K360E, K409W, and Y349C substitutions)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI
YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAP***I***GAAAGWFDPWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQV***C***TLPPSRDELT***E***NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYS***W***LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:196]

A49MI VH-CH1-Fc (Q347R, D399V, F405T, and S354C substitutions)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI
YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAP***I***GAAAGWFDPWG
QGTLVTVSSASDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREP***R***VYTLPP***C***RDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVL***V***SDGSF***T***LYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSL [SEQ ID NO:245]

[0332] Another TriNKET of the present disclosure is A49-F3'-TriNKET-I07(si), comprising a first polypeptide chain, named "I07 scFv-Fc(si)," which comprises a CD33-binding scFv linked to a silent Fc domain via an Ala-Ser linker; a second polypeptide chain,

named "A49 VH-CH1-Fc(si)," which comprises an NKG2D-targeting heavy chain with a silent Fc domain; and a third polypeptide chain, named "A49 VL-CL," as described above [SEQ ID NO: 190]. A49-F3'-TriNKET-I07(si) is identical to A49-F3'-TriNKET-I07 except for L234A, L235A, and P329A substitutions in both Fc domains. These substitutions are bold-italic in the two sequences below. The amino acid sequence of I07 scFv-Fc(si) comprises:

I07 scFv-Fc(si)
DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFG***C***GTKVEIK**GGGGSGGG**
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPG
K***C***LEWVATIKQDGSEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
PLNAGELDVWGQGTMVTVSS**AS**DKTHTCPPCPAPE***AA***GGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKAL***G***APIEKTISKAKGQPREP**R**VYTLPP***C***RDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:204]

[0333] The amino acid sequence of the scFv portion of I07 scFv-Fc(si) is identical to that of the scFv portion of I07 scFv-Fc as described above [SEQ ID NO:188].

[0334] The amino acid sequence of A49 VH-CH1-Fc(si) comprises:

A49 VH-CH1-Fc(si)
EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI
YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAPMGAAAGWFDPW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPE***AA***GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL***G***APIE
KTISKAKGQPREPQV***C***TLPPSRDELT**E**NQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYS**W**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:205]

[0335] Another TriNKET of the present disclosure is A49-F3'-TriNKET-H76, comprising a first polypeptide chain, named "H76 scFv-Fc," that comprises a CD33-binding scFv linked to an Fc domain via an Ala-Ser linker; a second polypeptide chain, named "A49 VH-CH1-Fc," as described above [SEQ ID NO:189]; and a third polypeptide chain, named "A49 VL-CL," as described above [SEQ ID NO:190]. The amino acid sequence of H76 scFv-Fc comprises:

H76 scFv-Fc
DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG*C*GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK*C*
LEWVSAIVGSGESTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREG
GPYYDSSGYFVYYGMDVWGQGTTVTVSS**AS**DKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP*C*RDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:197]

[0336] The amino acid sequence of the scFv portion of H76 scFv-Fc comprises:

H76 scFv
DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYDDLPTFG*C*GTKVEIK**GGGGSGGGG**
SGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSKYTMSWVRQAPGK*C*
LEWVSAIVGSGESTYFADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREG
GPYYDSSGYFVYYGMDVWGQGTTVTVSS
[SEQ ID NO:198]

[0337] In other embodiments of the present disclosure, the CD33-binding scFv of the multi-specific binding protein (*e.g.*, TriNKET) comprises the heavy chain variable domain CDR1, CDR2, and CDR3, and light chain variable domain CDR1, CDR2, and CDR3, of any one of the antibodies provided in Table 1. In certain embodiments, the amino acid sequence of the heavy chain variable domain is identical to the VH sequence of an antibody in Table 1 except for a substitution of Cys at position 44, and the amino acid sequence of the light chain variable domain is identical to the VL sequence of the same antibody except for a substitution of Cys at position 100. In certain embodiments, the heavy chain variable domain is connected to the light chain variable domain with a $(G4S)_4$ linker. The heavy chain variable domain can be N-terminal to the light chain variable domain or C-terminal to the light chain variable domain. The scFv is linked to an Fc domain via a hinge comprising Ala-Ser.

[0338] The multi-specific binding proteins described above can be made using recombinant DNA technology well known to a skilled person in the art. For example, a first nucleic acid sequence encoding the first immunoglobulin heavy chain can be cloned into a first expression vector; a second nucleic acid sequence encoding the second immunoglobulin heavy chain can be cloned into a second expression vector; a third nucleic acid sequence encoding the first immunoglobulin light chain can be cloned into a third expression vector; a fourth nucleic acid sequence encoding the second immunoglobulin light chain can be cloned

into a fourth expression vector; the first, second, third and fourth expression vectors can be stably transfected together into host cells to produce the multimeric proteins.

[0339] To achieve the highest yield of the multi-specific binding proteins, different ratios of the first, second, third and fourth expression vectors can be explored to determine the optimal ratio for transfection into the host cells. After transfection, single clones can be isolated for cell bank generation using methods known in the art, such as limited dilution, ELISA, FACS, microscopy, or Clonepix.

[0340] Clones can be cultured under conditions suitable for bio-reactor scale-up and maintained expression of the multi-specific protein. The multi-specific binding proteins can be isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze-thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

[0341] In certain embodiments, the antibody binds CD33 with a K_D of 20 nM, 15 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM or lower, as measured using standard binding assays, for example, surface plasmon resonance or bio-layer interferometry. In certain embodiments the antibody binds EBI3 from a body fluid, tissue and/or cell of a subject.

[0342] Competition assays for determining whether an antibody binds to the same epitope as, or competes for binding with a disclosed antibody, *e.g.*, the Ab1 antibody, the Ab2 antibody, the Ab3 antibody, the Ab4 antibody, or the Ab5 antibody, are known in the art. Exemplary competition assays include immunoassays (*e.g.*, ELISA assays, RIA assays), surface plasmon resonance (*e.g.*, BIAcore analysis), bio-layer interferometry, and flow cytometry.

[0343] Typically, a competition assay involves the use of an antigen (*e.g.*, a human CD33 protein or fragment thereof) bound to a solid surface or expressed on a cell surface, a test CD33-binding antibody and a reference antibody. The reference antibody is labeled and the test antibody is unlabeled. Competitive inhibition is measured by determining the amount of labeled reference antibody bound to the solid surface or cells in the presence of the test antibody. Usually the test antibody is present in excess (*e.g.*, 1x, 5x, 10x, 20x or 100x). Antibodies identified by competition assay (*e.g.*, competing antibodies) include antibodies binding to the same epitope, or similar (*e.g.*, overlapping) epitopes, as the reference antibody, and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur.

[0344] A competition assay can be conducted in both directions to ensure that the presence of the label does not interfere or otherwise inhibit binding. For example, in the first direction the reference antibody is labeled and the test antibody is unlabeled, and in the second direction, the test antibody is labeled and the reference antibody is unlabeled.

[0345] A test antibody competes with the reference antibody for specific binding to the antigen if an excess of one antibody (*e.g.*, 1x, 5x, 10x, 20x or 100x) inhibits binding of the other antibody, *e.g.*, by at least 50%, 75%, 90%, 95% or 99% as measured in a competitive binding assay.

[0346] Two antibodies may be determined to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies may be determined to bind to overlapping epitopes if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0347] The antibodies disclosed herein may be further optimized (*e.g.*, affinity-matured) to improve biochemical characteristics including affinity and/or specificity, improve biophysical properties including aggregation, stability, precipitation and/or non-specific interactions, and/or to reduce immunogenicity. Affinity-maturation procedures are within ordinary skill in the art. For example, diversity can be introduced into an immunoglobulin heavy chain and/or an immunoglobulin light chain by DNA shuffling, chain shuffling, CDR shuffling, random mutagenesis and/or site-specific mutagenesis.

[0348] In certain embodiments, isolated human antibodies contain one or more somatic mutations. In these cases, antibodies can be modified to a human germline sequence to optimize the antibody (*e.g.*, by a process referred to as germlining).

[0349] Generally, an optimized antibody has at least the same, or substantially the same, affinity for the antigen as the non-optimized (or parental) antibody from which it was derived. Preferably, an optimized antibody has a higher affinity for the antigen when compared to the parental antibody.

[0350] If the antibody is for use as a therapeutic, it can be conjugated to an effector agent such as a small molecule toxin or a radionuclide using standard *in vitro* conjugation chemistries. If the effector agent is a polypeptide, the antibody can be chemically conjugated to the effector or joined to the effector as a fusion protein. Construction of fusion proteins is within ordinary skill in the art.

[0351] The antibody can be conjugated to an effector moiety such as a small molecule toxin or a radionuclide using standard *in vitro* conjugation chemistries. If the effector moiety

is a polypeptide, the antibody can be chemically conjugated to the effector or joined to the effector as a fusion protein. Construction of fusion proteins is within ordinary skill in the art.

[0352] In certain embodiments, the protein (*e.g.*, multi-specific binding protein) of the present disclosure is not substantially internalized by a CD33-expressing cell. A low level of internalization may improve the pharmacokinetics of the protein, thereby reducing the dose required to engage CD33-expressing target cells with effector cells (*e.g.*, NK cells). Internalization can be measured by any method known in the art, *e.g.*, the methods described in Examples 5 and 10 of the present disclosure. For example, in certain embodiments, internalization of the protein (*e.g.*, multi-specific binding protein) by EOL-1 cells is lower than 25%, 30%, 35%, 40%, 45%, or 50% after a two-hour incubation, as assessed by the methods disclosed herein. In certain embodiments, internalization of the protein (*e.g.*, multi-specific binding protein) by EOL-1 cells is lower than 25%, 30%, 35%, 40%, 45%, or 50% after a 24-hour incubation, as assessed by the methods disclosed herein. In certain embodiments, internalization of the protein (*e.g.*, multi-specific binding protein) by Molm-13 cells is lower than 25%, 30%, 35%, 40%, 45%, or 50% after a two-hour incubation, as assessed by the methods disclosed herein.

[0353] KHYG-1 cells express surface NKG2D, but do not express CD16. In certain embodiments, TriNKET mediated killings of Molm-13 and THP-1 cells are dependent upon NKG2D-mediated activation of the KHYG-1 effector cells. In certain embodiments, TriNKETs of the present disclosure mediate KHYG-1 effector cell killing of Molm-13 (FIG. 15A), EOL-1 (FIG. 16), and THP-1 (FIG. 17A) human AML target cell lines.

[0354] In certain embodiments, TriNKETs of the present disclosure mediate cytotoxicity of rested human NK cells against Molm-13 or THP-1 human AML cells. FIG. 15B and 38A show that TriNKETs of the present disclosure mediate rested human NK cell killing of Molm-13 human AML cells. The rested human NK effector cell (E) to target cancer cell (T) ratio (E:T) was 10:1 in FIG. 15B and 5:1 in FIG. 38A. The E:T ratio may reflect differences in the maximal % lysis.

[0355] In certain embodiments, TriNKETs of the present disclosure mediate rested human NK cell killing of EOL-1 human AML cells. FIG. 38B shows that TriNKETs mediate rested human NK cell killing of EOL-1 cells at an E:T of 5:1. In certain embodiments, TriNKETs of the present disclosure mediate rested human NK cell killing of THP-1 target cells, which express the high-affinity FcγRI. FIGs. 17B, 38C, and 38D show that TriNKETs mediate rested human NK cell killing of THP-1 human AML cells using an E:T of 5:1.

[0356] In certain embodiments, TriNKETs of the present disclosure mediate human $CD8^+$ T cell killing of Molm-13 target cells. FIGs. 40A-40B show that TriNKETs mediate human $CD8^+$ T cell killing of Molm-13 cells at an E:T of 50:1.

A protein comprising an antigen-binding site that competes with the CD33-binding sites described herein

[0357] In one aspect, the present invention provides a protein that includes an antigen-binding site that competes with the CD33-binding sites described herein to bind to CD33. In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:1 and an antibody light chain having the amino acid sequence of SEQ ID NO:2.

[0358] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:3 and an antibody light chain having the amino acid sequence of SEQ ID NO:4.

[0359] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:5 and an antibody light chain having the amino acid sequence of SEQ ID NO:6.

[0360] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:7 and an antibody light chain having the amino acid sequence of SEQ ID NO:8.

[0361] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:9 and an antibody light chain having the amino acid sequence of SEQ ID NO:10.

[0362] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:11 and an antibody light chain having the amino acid sequence of SEQ ID NO:12.

[0363] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an

antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:13 and an antibody light chain having the amino acid sequence of SEQ ID NO:14.

[0364] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:15 and an antibody light chain having the amino acid sequence of SEQ ID NO:16.

[0365] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:17 and an antibody light chain having the amino acid sequence of SEQ ID NO:18.

[0366] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody heavy chain having the amino acid sequence of SEQ ID NO:19 and an antibody light chain having the amino acid sequence of SEQ ID NO:20.

[0367] In some embodiments, an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:4.

[0368] In some embodiments, an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6.

[0369] In some embodiments, an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8.

[0370] In some embodiments an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:10.

[0371] In some embodiments an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:12.

[0372] In some embodiments an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14.

[0373] In some embodiments an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%,

60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:16.

[0374] In some embodiments an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:18.

[0375] In some embodiments an antigen-binding site of the protein that competes with the CD33-binding sites includes a heavy chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19 and a light chain variable domain having an amino acid sequence at least at least 50% (*e.g.*, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:20.

[0376] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antigen-binding site that binds a tumor-associated antigen.

[0377] In certain embodiments, the present invention provides a protein that includes an antigen-binding site that competes for binding to human and cynomolgus CD33 with an antibody that includes an antibody constant region or a portion thereof capable of binding CD16.

CAR T cells, CD33/CD3-directed bispecific T-cell engagers, immunocytokines, antibody-drug conjugates, and immunotoxins

[0378] Another aspect of the present disclosure provides a molecule or complex comprising an antigen-binding site that binds CD33 as disclosed herein. Exemplary molecules or complexes include but are not limited to chimeric antigen receptors (CARs), T-cell engagers (*e.g.*, CD33/CD3-directed bispecific T-cell engagers), immunocytokines, antibody-drug conjugates, and immunotoxins.

[0379] Any antigen-binding site that binds CD33 as disclosed herein can be used, including but not limited to the antigen-binding site that binds CD33 as disclosed in Section I. Antigen-Binding Site. In certain embodiments, the amino acid sequence(s) of the antigen-

binding site that binds CD33 are provided in Table 1. In certain embodiments, the antigen-binding site that binds CD33 is an scFv. In certain embodiments, the scFv comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an amino acid sequence selected from SEQ ID NO:188, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, and SEQ ID NO:484. In certain embodiments, the scFv comprises an amino acid sequence selected from SEQ ID NO:188, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, and SEQ ID NO:484.

[0380] In certain embodiments, the antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:181, 46, and 182, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:48, 49, and 50, respectively. In certain embodiments, the antigen-binding site comprises a heavy chain variable domain with an amino acid sequence at

least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9; and a light chain variable domain with an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:10. In certain embodiments, the antigen-binding site comprises an scFv comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:188.

[0381] In other embodiments of any one of the foregoing aspects in this subsection, the antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:183, 34, and 184, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:36, 185, and 38, respectively. In certain embodiments, the antigen-binding site comprises a heavy chain variable domain with an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5; and a light chain variable domain with an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6. In certain embodiments, the antigen-binding site comprises an scFv comprising an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:198.

Chimeric antigen receptors (CARs)

[0382] In certain embodiments, the present disclosure provides a CD33-targeting CAR comprising an antigen-binding site that binds CD33 as disclosed herein (*see, e.g.,* Table 1). The CD33-targeting CAR can comprise an Fab fragment or an scFv.

[0383] The term "chimeric antigen receptor" or alternatively a "CAR" refers to a recombinant polypeptide construct comprising at least an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule (also referred to herein as a "primary signaling domain").

[0384] Accordingly, in certain embodiments, the CAR comprises an extracellular antigen-binding site that binds CD33 as disclosed herein, a transmembrane domain, and an intracellular signaling domain comprising a primary signaling domain. In certain embodiments, the CAR further comprises one or more functional signaling domains derived

from at least one costimulatory molecule (also referred to as a "costimulatory signaling domain").

[0385] In one embodiment, the CAR comprises a chimeric fusion protein comprising a CD33-binding domain (*e.g.*, CD33-binding scFv domain) comprising a heavy chain variable domain and a light chain variable domain listed in Table 1 as an extracellular antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising a primary signaling domain. In one embodiment, the CAR comprises a chimeric fusion protein comprising a CD33-binding domain (*e.g.*, CD33-binding scFv domain) comprising a heavy chain variable domain and a light chain variable domain listed in Table 1 as an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain comprising a costimulatory signaling domain and a primary signaling domain. In one aspect, the CAR comprises a chimeric fusion protein comprising a CD33-binding domain (*e.g.*, CD33-binding scFv domain) comprising a heavy chain variable domain and a light chain variable domain listed in Table 1 as an extracellular antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising two costimulatory signaling domains and a primary signaling domain. In one embodiment, the CAR comprises a chimeric fusion protein comprising a CD33-binding domain comprising a heavy chain variable domain and a light chain variable domain listed in Table 1 as an extracellular antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising at least two costimulatory signaling domains and a primary signaling domain.

[0386] With respect to the transmembrane domain, in various embodiments, the CAR is designed to comprise a transmembrane domain that is fused to the extracellular domain of the CAR. In one embodiment, the transmembrane domain is one that naturally is associated with one of the domains in the CAR. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex. In another embodiment, the transmembrane domain is capable of homodimerization with another CAR on the CAR T cell surface. In another embodiment, the amino acid sequence of the transmembrane domain may be modified or substituted so as to minimize interactions with the binding domains of the native binding partner present in the same CAR T cell.

[0387] The transmembrane domain may be derived from any naturally occurring membrane-bound or transmembrane protein. In one embodiment, the transmembrane region is capable of signaling to the intracellular domain(s) whenever the CAR has bound to a target.

In some embodiments, the transmembrane domain comprises the transmembrane region(s) of one or more proteins selected from the group consisting of TCR α chain, TCR β chain, TCR ζ chain, CD28, CD3ε, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, and CD154. In some embodiments, the transmembrane domain comprises the transmembrane region(s) of one or more proteins selected from the group consisting of KIRDS2, OX40, CD2, CD27, LFA-1 (CD11a, CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, IL2Rβ, IL2Rγ, IL7Rα, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKG2D, and NKG2C.

[0388] The extracellular CD33-binding domain (*e.g.*, CD33-binding scFv domain) domain can be connected to the transmembrane domain by a hinge region. A variety of hinges can be employed, including but not limited to the human Ig (immunoglobulin) hinge (*e.g.*, an IgG4 hinge, an IgD hinge), a Gly-Ser linker, a $(G_4S)_4$ linker, a KIR2DS2 hinge, and a CD8α hinge.

[0389] The intracellular signaling domain of the CAR disclosed herein is responsible for activation of at least one of the specialized functions of the immune cell (*e.g.*, cytolytic activity or helper activity, including the secretion of cytokines, of a T cell) in which the CAR has been placed in. Thus, as used herein, the term "intracellular signaling domain" refers to the portion of a protein which transduces an effector function signal and directs the cell to perform a specialized function. While usually the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

[0390] The intracellular signaling domain of the CAR comprises a primary signaling domain (*i.e.*, a functional signaling domain derived from a stimulatory molecule) and one or more costimulatory signaling domains (*i.e.*, functional signaling domains derived from at least one costimulatory molecule).

[0391] As used herein, the term "stimulatory molecule" refers to a molecule expressed by an immune cell, *e.g.*, a T cell, an NK cell, or a B cell, that provide the cytoplasmic signaling sequence(s) that regulate activation of the immune cell in a stimulatory way for at least some aspect of the immune cell signaling pathway. In one embodiment, the signal is a primary signal that is initiated by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with a peptide, and which leads to mediation of a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like.

[0392] Primary signaling domains that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs. Examples of ITAM containing cytoplasmic signaling sequences that are of particular use in the present disclosure include those derived from CD3 zeta, common FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, and DAP12. In one embodiment, the primary signaling domain in any one or more CARs disclosed herein comprises a cytoplasmic signaling sequence derived from CD3-zeta.

[0393] In some embodiments, the primary signaling domain is a functional signaling domain of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD66d, 4-1BB, and/or CD3-zeta. In an embodiment, the intracellular signaling domain comprises a functional signaling domain of CD3 zeta, common FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, and/or DAP12. In a particular embodiment, the primary signaling domain is a functional signaling domain of the zeta chain associated with the T cell receptor complex.

[0394] As used herein, the term "costimulatory molecule" refers to a cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. A costimulatory molecule is a cell surface molecule other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18), CD2, CD7, CD258 (LIGHT), NKG2C, B7-H3, and a ligand that specifically binds with CD83, and the like. Further examples of such costimulatory molecules include CD5, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a,

ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, and a ligand that specifically binds with CD83. In some embodiments, the costimulatory signaling domain of the CAR is a functional signaling domain of a costimulatory molecule described herein, e.g., OX40, CD27, CD28, CD30, CD40, PD-1, CD2, CD7, CD258, NKG2C, B7-H3, a ligand that binds to CD83, ICAM-1, LFA-1 (CD11a/CD18), ICOS and 4-1BB (CD137), or any combination thereof.

[0395] As used herein, the term "signaling domain" refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

[0396] The cytoplasmic signaling sequences within the cytoplasmic signaling portion of the CAR disclosed herein may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example, between 2 and 10 amino acids in length may form the linkage.

[0397] Another aspect of the present disclosure provides a nucleic acid encoding a CD33-targeting CAR disclosed herein. The nucleic acid is useful for expressing the CAR in an effector cell (*e.g.*, T cell) by introducing the nucleic acid to the cell.

[0398] Exemplary nucleic acid sequences encoding the extracellular portions of the CARs are disclosed herein, *e.g.*, as SEQ ID NOs:246-265. Modifications may be made in the sequence to create an equivalent or improved variant of the nucleic acid sequences, for example, by changing one or more of the codons according to the codon degeneracy table. A DNA codon degeneracy table is provided in Table 10.

Table 10. Amino Acid Codons

Amino Acids	One letter code	Three letter code	Codons
Alanine	A	Ala	GCA GCC GCG GCU
Cysteine	C	Cys	UGC UGU
Aspartic acid	D	Asp	GAC GAU

Glutamic acid	E	Glu	GAA GAG
Phenylalanine	F	Phe	UUC UUU
Glycine	G	Gly	GGA GGC GGG GGU
Histidine	H	His	CAC CAU
Isoleucine	I	Iso	AUA AUC AUU
Lysine	K	Lys	AAA AAG
Leucine	L	Leu	UUA UUG CUA CUC CUG CUU
Methionine	M	Met	AUG
Asparagine	N	Asn	AAC AAU
Proline	P	Pro	CCA CCC CCG CCU
Glutamine	Q	Gln	CAA CAG
Arginine	R	Arg	AGA AGG CGA CGC CGG CGU
Serine	S	Ser	AGC AGU UCA UCC UCG UCU
Threonine	T	Thr	ACA ACC ACG ACU
Valine	V	Val	GUA GUC GUG GUU
Tryptophan	W	Trp	UGG
Tyrosine	Y	Tyr	UAC UAU

[0399] In certain embodiments, the nucleic acid is a DNA molecule (*e.g.*, a cDNA molecule). In certain embodiments, the nucleic acid further comprises an expression control sequence (*e.g.*, promoter and/or enhancer) operably linked to the CAR coding sequence. In certain embodiments, the present disclosure provides a vector comprising the nucleic acid. The vector can be a viral vector (*e.g.*, AAV vector, lentiviral vector, or adenoviral vector) or a non-viral vector (*e.g.*, plasmid).

[0400] In certain embodiments, the nucleic acid is an RNA molecule (*e.g.*, an mRNA molecule). A method for generating mRNA for use in transfection can involve *in vitro* transcription of a template with specially designed primers, followed by polyA addition, to produce an RNA construct containing 3' and 5' untranslated sequences, a 5' cap and/or Internal Ribosome Entry Site (IRES), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases in length. The RNA molecule can be further modified to increase translational efficiency and/or stability, *e.g.*, as disclosed in U.S. Patent Nos. 8,278,036; 8,883,506, and 8,716,465. RNA molecules so produced can efficiently transfect different kinds of cells.

[0401] In one embodiment, the nucleic acid encodes an amino acid sequence comprising a signal peptide at the amino-terminus of the CAR. Such signal peptide can facilitate the cell surface localization of the CAR when it is expressed in an effector cell, and is cleaved from the CAR during cellular processing. In one embodiment, the nucleic acid encodes an amino

acid sequence comprising a signal peptide at the N-terminus of the extracellular CD33-binding domain (*e.g.*, CD33-binding scFv domain).

[0402] RNA or DNA can be introduced into target cells using any of a number of different methods, for instance, commercially available methods which include, but are not limited to, electroporation, cationic liposome mediated transfection using lipofection, polymer encapsulation, peptide mediated transfection, or biolistic particle delivery systems such as "gene guns" (see, for example, Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001)).

[0403] Another aspect of the present disclosure provides an immune effector cell expressing the CD33-targeting CAR. Also provided is an immune effector cell comprising the nucleic acid encoding the CD33-targeting CAR. The immune effector cells include but are not limited to T cells and NK cells. In certain embodiments, the T cell is selected from a $CD8^+$ T cell, a $CD4^+$ T cell, and an NKT cell. The T cell or NK cell can be a primary cell or a cell line.

[0404] The immune effector cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors, by methods known in the art. The immune effector cells can also be differentiated *in vitro* from a pluripotent or multipotent cell (*e.g.*, a hematopoietic stem cell). In some embodiments, the present disclosure provides a pluripotent or multipotent cell (*e.g.*, a hematopoietic stem cell) expressing the CD33-targeting CAR or comprising a nucleic acid disclosed herein.

[0405] In certain embodiments, the immune effector cells are isolated and/or purified. For example, regulatory T cells can be removed from a T cell population using a CD25-binding ligand. Effector cells expressing a checkpoint protein (*e.g.*, PD-1, LAG-3, or TIM-3) can be removed by similar methods. In certain embodiments, the effector cells are isolated by a positive selection step. For example, a population of T cells can be isolated by incubation with anti-CD3/anti-CD28-conjugated beads. Other cell surface markers, such as IFN-7, TNF-α, IL-17A, IL-2, IL-3, IL-4, GM-CSF, IL-10, IL-13, granzyme B, and perforin, can also be used for positive selection.

[0406] Immune effector cells may be activated and expanded generally using methods known in the art, *e.g.*, as described in U.S. Patent Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publications Nos. 2006/0121005 and 2016/0340406. For example, in certain embodiments, T

cells can be expanded and/or activated by contact with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. The cells can be expanded in culture for a period of several hours (*e.g.*, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 18, 21 hours) to about 14 days (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days). In one embodiment, the cells are expanded for a period of 4 to 9 days. Multiple cycles of stimulation may be desirable for prolonged cell culture (*e.g.*, culture for a period of 60 days or more). In certain embodiments, the cell culture comprises serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, TNF-α, or a combination thereof. Other additives for the growth of cells known to the skilled person, *e.g.*, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol, can also be included in the cell culture. In certain embodiments, the immune effector cell of the present disclosure is a cell obtained from *in vitro* expansion.

[0407] Further embodiments of the CD33-targeting CAR (*e.g.*, regulatable CAR), nucleic acid encoding the CAR, and effector cells expressing the CAR or comprising the nucleic acid are provided in U.S. Patent Nos. 7,446,190 and 9,181,527, U.S. Patent Application Publication Nos. 2016/0340406 and 2017/0049819, and International Patent Application Publication No. WO2018/140725.

CD33/CD3-directed bispecific T-cell engagers

[0408] In certain embodiments, the present disclosure provides a CD33/CD3-directed bispecific T-cell engager comprising an antigen-binding site that binds CD33 disclosed herein. In certain embodiments, the CD33/CD3-directed bispecific T-cell engager comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:187. In certain embodiments, the CD33/CD3-directed bispecific T-cell engager comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:197.

[0409] In certain embodiments, the CD33/CD3-directed bispecific T-cell engager further comprises an antigen-binding site that binds CD3. Exemplary antigen-binding sites that bind CD3 are disclosed in International Patent Application Publication Nos. WO2014/051433 and WO2017/097723.

[0410] Another aspect of the present disclosure provides a nucleic acid encoding at least one polypeptide of the CD33/CD3-directed bispecific T-cell engager, wherein the polypeptide comprises an antigen binding site that binds CD33. In certain embodiments, the nucleic acid further comprises a nucleotide sequence encoding a signal peptide that, when

expressed, is at the N-terminus of one or more of the polypeptides of the CD33/CD3-directed bispecific T-cell engager. Also provided is a vector (*e.g.*, a viral vector) comprising the nucleic acid, a producer cell comprising the nucleic acid or vector, and a producer cell expressing the CD33/CD3-directed bispecific T-cell engager.

Immunocytokines

[0411] In certain embodiments, the present disclosure provides an immunocytokine comprising an antigen-binding site that binds CD33 disclosed herein and a cytokine. Any cytokine (*e.g.*, pro-inflammatory cytokines) known in the art can be used, including but not limited to IL-2, IL-4, IL-10, IL-12, IL-15, TNF, IFNα, IFNγ, and GM-CSF. More exemplary cytokines are disclosed in U.S. Patent No. 9,567,399. In certain embodiments, the antigen-binding site is connected to the cytokine by chemical conjugation (*e.g.*, covalent or noncovalent chemical conjugation). In certain embodiments, the antigen-binding site is connected to the cytokine by fusion of polypeptide. The immunocytokine can further comprise an Fc domain connected to the antigen-binding site that binds CD33. In certain embodiments, the immunocytokine comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:187. In certain embodiments, the immunocytokine comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:197. In certain embodiments, the cytokine is connected to the Fc domain directly or via a linker.

[0412] Another aspect of the present disclosure provides a nucleic acid encoding at least one polypeptide of the immunocytokine, wherein the polypeptide comprises an antigen binding site that binds CD33. In certain embodiments, the nucleic acid further comprises a nucleotide sequence encoding a signal peptide that, when expressed, is at the N-terminus of one or more of the polypeptides of the immunocytokine. Also provided is a vector (*e.g.*, a viral vector) comprising the nucleic acid, a producer cell comprising the nucleic acid or vector, and a producer cell expressing the immunocytokine.

Antibody-drug conjugates

[0413] In certain embodiments, the present disclosure provides an antibody-drug conjugate comprising an antigen-binding site that binds CD33 disclosed herein and a cytotoxic drug moiety. Exemplary cytotoxic drug moieties are disclosed in International Patent Application Publication Nos. WO2014/160160 and WO2015/143382. In certain

embodiments, the cytotoxic drug moiety is selected from auristatin, N-acetyl-γ calicheamicin, maytansinoid, pyrrolobenzodiazepine, and SN-38. The antigen-binding site can be connected to the cytotoxic drug moiety by chemical conjugation (*e.g.*, covalent or noncovalent chemical conjugation). In certain embodiments, the antibody-drug conjugate further comprises an Fc domain connected to the antigen-binding site that binds CD33. In certain embodiments, the antibody-drug conjugate comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:187. In certain embodiments, the antibody-drug conjugate comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:197. In certain embodiments, the cytotoxic drug moiety is connected to the Fc domain directly or via a linker.

Immunotoxins

[0414] In certain embodiments, the present disclosure provides an immunotoxin comprising an antigen-binding site that binds CD33 disclosed herein and a cytotoxic peptide moiety. Any cytotoxic peptide moiety known in the art can be used, including but not limited to ricin, *Diphtheria* toxin, and *Pseudomonas* exotoxin A. More exemplary cytotoxic peptides are disclosed in International Patent Application Publication Nos. WO2012/154530 and WO2014/164680. In certain embodiments, the cytotoxic peptide moiety is connected to the protein by chemical conjugation (*e.g.*, covalent or noncovalent chemical conjugation). In certain embodiments, the cytotoxic peptide moiety is connected to the protein by fusion of polypeptide. The immunotoxin can further comprise an Fc domain connected to the antigen-binding site that binds CD33. In certain embodiments, the immunotoxin comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:187. In certain embodiments, the immunotoxin comprises an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:197. In certain embodiments, the cytotoxic peptide moiety is connected to the Fc domain directly or via a linker.

[0415] Another aspect of the present disclosure provides a nucleic acid encoding at least one polypeptide of the immunotoxin, wherein the polypeptide comprises an antigen binding site that binds CD33. In certain embodiments, the nucleic acid further comprises a nucleotide sequence encoding a signal peptide that, when expressed, is at the N-terminus of one or more of the polypeptides of the immunotoxin. Also provided is a vector (*e.g.*, a viral vector)

comprising the nucleic acid, a producer cell comprising the nucleic acid or vector, and a producer cell expressing the immunotoxin.

III. Therapeutic Compositions and Their Use

[0416] The invention provides methods for treating cancer using a multi-specific binding protein described herein and/or a pharmaceutical composition described herein. The methods may be used to treat a variety of cancers which express CD33 by administering to a patient in need thereof a therapeutically effective amount of a multi-specific binding protein described herein.

[0417] The therapeutic method can be characterized according to the cancer to be treated. For example, in certain embodiments, the cancers are AML, myelodysplastic syndromes, chronic myelomonocytic leukemia, myeloid blast crisis of chronic myeloid leukemia, and ALLs.

[0418] For example, in certain embodiments, the cancer is a solid tumor. In certain other embodiments, the cancer is brain cancer, bladder cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, leukemia, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, stomach cancer, testicular cancer, or uterine cancer. In yet other embodiments, the cancer is a vascularized tumor, squamous cell carcinoma, adenocarcinoma, small cell carcinoma, melanoma, glioma, neuroblastoma, sarcoma (*e.g.*, an angiosarcoma or chondrosarcoma), larynx cancer, parotid cancer, bilary tract cancer, thyroid cancer, acral lentiginous melanoma, actinic keratoses, acute lymphocytic leukemia, acute myeloid leukemia, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, anal canal cancer, anal cancer, anorectum cancer, astrocytic tumor, bartholin gland carcinoma, basal cell carcinoma, biliary cancer, bone cancer, bone marrow cancer, bronchial cancer, bronchial gland carcinoma, carcinoid, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, chronic lymphocytic leukemia, chronic myeloid leukemia, clear cell carcinoma, connective tissue cancer, cystadenoma, digestive system cancer, duodenum cancer, endocrine system cancer, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, endothelial cell cancer, ependymal cancer, epithelial cell cancer, Ewing's sarcoma, eye and orbit cancer, female genital cancer, focal nodular hyperplasia, gallbladder cancer, gastric antrum cancer, gastric fundus cancer, gastrinoma, glioblastoma, glucagonoma, heart cancer, hemangiblastomas,

hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatobiliary cancer, hepatocellular carcinoma, Hodgkin's disease, ileum cancer, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, intrahepatic bile duct cancer, invasive squamous cell carcinoma, jejunum cancer, joint cancer, Kaposi's sarcoma, pelvic cancer, large cell carcinoma, large intestine cancer, leiomyosarcoma, lentigo maligna melanomas, lymphoma, male genital cancer, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, meningeal cancer, mesothelial cancer, metastatic carcinoma, mouth cancer, mucoepidermoid carcinoma, multiple myeloma, muscle cancer, nasal tract cancer, nervous system cancer, neuroepithelial adenocarcinoma nodular melanoma, non-epithelial skin cancer, non-Hodgkin's lymphoma, oat cell carcinoma, oligodendroglial cancer, oral cavity cancer, osteosarcoma, papillary serous adenocarcinoma, penile cancer, pharynx cancer, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, rectal cancer, renal cell carcinoma, respiratory system cancer, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, sinus cancer, skin cancer, small cell carcinoma, small intestine cancer, smooth muscle cancer, soft tissue cancer, somatostatin-secreting tumor, spine cancer, squamous cell carcinoma, striated muscle cancer, submesothelial cancer, superficial spreading melanoma, T cell leukemia, tongue cancer, undifferentiated carcinoma, ureter cancer, urethra cancer, urinary bladder cancer, urinary system cancer, uterine cervix cancer, uterine corpus cancer, uveal melanoma, vaginal cancer, verrucous carcinoma, VIPoma, vulva cancer, well differentiated carcinoma, or Wilms tumor.

[0419] In certain other embodiments, the cancer is non-Hodgkin's lymphoma, such as a B-cell lymphoma or a T-cell lymphoma. In certain embodiments, the non-Hodgkin's lymphoma is a B-cell lymphoma, such as a diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia, or primary central nervous system (CNS) lymphoma. In certain other embodiments, the non-Hodgkin's lymphoma is a T-cell lymphoma, such as a precursor T-lymphoblastic lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, angioimmunoblastic T-cell lymphoma, extranodal natural killer/T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma, or peripheral T-cell lymphoma.

[0420] The cancer to be treated can be characterized according to the presence of a particular antigen expressed on the surface of the cancer cell. In certain embodiments, the cancer cell can express one or more of the following in addition to CD33: CD2, CD19, CD20, CD30, CD38, CD40, CD52, CD70, EGFR/ERBB1, IGF1R, HER3/ERBB3, HER4/ERBB4, MUC1, TROP2, cMET, SLAMF7, PSCA, MICA, MICB, TRAILR1, TRAILR2, MAGE-A3, B7.1, B7.2, CTLA4, and PD1.

[0421] In embodiments of the present invention, the cancer to be treated is selected from acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPNs), lymphoma, non-Hodgkin lymphomas, and classical Hodgkin lymphoma.

[0422] In some embodiments of the present invention, the cancer to be treated is AML. In some embodiments of the present invention, 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). In some embodiments of the present invention, the AML is characterized by expression of CLL-1 on the AML leukemia stem cells (LSCs). In some embodiments of the present invention, the LSCs in an AML subject further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96. In some embodiments of the present invention, the AML is characterized as a minimal residual disease (MRD). In some embodiments of the present invention, the MRD of AML 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)).

[0423] In certain embodiments of the present invention, the cancer is MDS 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).

[0424] It is contemplated that the multi-specific binding proteins and/or pharmaceutical compositions of the present disclosure can be used to treat a variety of cancers, not limited to

cancers in which the cancer cells express CD33. For example, in certain embodiments, the multi-specific binding proteins and/or pharmaceutical compositions disclosed herein can be used to treat cancers that are associated with CD33-expressing immune cells. CD33 is expressed on many myeloid lineages, and tumor-infiltrating myeloid cells (*e.g.*, tumor-associated macrophages) may contribute to cancer progression and metastasis. Therefore, the methods disclosed herein may be used to treat a variety of cancers in which CD33 is expressed, whether on cancer cells or on immune cells.

[0425] In certain embodiments, the multi-specific binding proteins and/or pharmaceutical compositions of the present disclosure can be used to treat cancers that express an Fc receptor with a higher binding affinity to Fc (*e.g.*, IgG1 Fc) than CD16. In certain embodiments, the Fc receptor is FcγRI. In certain embodiments, the Fc receptor is expressed on cancer cells and/or other cells in the tumor microenvironment.

[0426] In certain embodiments, the patient has effector cells (*e.g.*, NK cells) that express a CD16 variant with V158F substitution. In certain embodiments, the patient has a single nucleotide polymorphism (SNP) in the CD16 gene that causes V158F substitution. In certain embodiments, the patient has such an SNP in only one allele. In certain embodiments, the patient has such an SNP or SNPs in both alleles.

IV. Combination Therapy

[0427] Another aspect of the invention provides for combination therapy. Multi-specific binding proteins described herein be used in combination with additional therapeutic agents to treat the cancer.

[0428] Exemplary therapeutic agents that may be used as part of a combination therapy in treating cancer, include, for example, radiation, mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, luteinizing hormone

releasing factor and variations of the aforementioned agents that may exhibit differential binding to its cognate receptor, and increased or decreased serum half-life.

[0429] An additional class of agents that may be used as part of a combination therapy in treating cancer is immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors include agents that inhibit one or more of (i) cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), (ii) programmed cell death protein 1 (PD1), (iii) PDL1, (iv) LAG3, (v) B7-H3, (vi) B7-H4, and (vii) TIM3. The CTLA4 inhibitor ipilimumab has been approved by the United States Food and Drug Administration for treating melanoma.

[0430] Yet other agents that may be used as part of a combination therapy in treating cancer are monoclonal antibody agents that target non-checkpoint targets (*e.g.*, herceptin) and non-cytotoxic agents (*e.g.*, tyrosine-kinase inhibitors).

[0431] Yet other categories of anti-cancer agents include, for example: (i) an inhibitor selected from an ALK Inhibitor, an ATR Inhibitor, an A2A Antagonist, a Base Excision Repair Inhibitor, a Bcr-Abl Tyrosine Kinase Inhibitor, a Bruton's Tyrosine Kinase Inhibitor, a CDC7 Inhibitor, a CHK1 Inhibitor, a Cyclin-Dependent Kinase Inhibitor, a DNA-PK Inhibitor, an Inhibitor of both DNA-PK and mTOR, a DNMT1 Inhibitor, a DNMT1 Inhibitor plus 2-chloro-deoxyadenosine, an HDAC Inhibitor, a Hedgehog Signaling Pathway Inhibitor, an IDO Inhibitor, a JAK Inhibitor, a mTOR Inhibitor, a MEK Inhibitor, a MELK Inhibitor, a MTH1 Inhibitor, a PARP Inhibitor, a Phosphoinositide 3-Kinase Inhibitor, an Inhibitor of both PARP1 and DHODH, a Proteasome Inhibitor, a Topoisomerase-II Inhibitor, a Tyrosine Kinase Inhibitor, a VEGFR Inhibitor, and a WEE1 Inhibitor; (ii) an agonist of OX40, CD137, CD40, GITR, CD27, HVEM, TNFRSF25, or ICOS; and (iii) a cytokine selected from IL-12, IL-15, GM-CSF, and G-CSF.

[0432] Proteins of the invention can also be used as an adjunct to surgical removal of the primary lesion.

[0433] The amount of multi-specific binding protein and additional therapeutic agent and the relative timing of administration may be selected in order to achieve a desired combined therapeutic effect. For example, when administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. Further, for example, a multi-specific binding protein may be administered during a time

when the additional therapeutic agent(s) exerts its prophylactic or therapeutic effect, or *vice versa*.

V. Pharmaceutical Compositions

[0434] The present disclosure also features pharmaceutical compositions that contain a therapeutically effective amount of a protein described herein. The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, see, *e.g.*, Langer (Science 249:1527-1533, 1990).

[0435] In one aspect, the present disclosure provides a formulation of a protein, which contains a CD33-binding site described herein, and a pharmaceutically acceptable carrier.

[0436] In certain embodiments, the pharmaceutical composition includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:1, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:2. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:3, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:4. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:5, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:6. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:7, and a light chain variable domain having an amino acid sequence at least 90%

(*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:8. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:9, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:10. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:11, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:12. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:13, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:14. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:15, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:16. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:17, and a light chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:18. In certain embodiments, the formulation includes a protein that includes an antigen-binding site with a heavy chain variable domain having an amino acid sequence at least 90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:19, and a light chain variable domain having an amino acid sequence at least

90% (*e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the amino acid sequence of SEQ ID NO:20.

[0437] The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, *see, e.g.*, Langer (Science 249:1527-1533, 1990).

[0438] For example, this present disclosure could exist in an aqueous pharmaceutical formulation including a therapeutically effective amount of the protein in a buffered solution forming a formulation. Aqueous carriers can include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.* phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution. In certain embodiments, an aqueous formulation is prepared including the protein disclosed herein in a pH-buffered solution. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5. Ranges intermediate to the above recited pH's are also intended to be part of this disclosure. For example, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included. Examples of buffers that will control the pH within this range include acetate (*e.g.*, sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers. In certain embodiments, the buffer system includes citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, and/or sodium dihydrogen phosphate dihydrate. In certain embodiments, the buffer system includes about 1.3 mg/mL of citric acid (*e.g.*, 1.305 mg/mL), about 0.3 mg/mL of sodium citrate (*e.g.*, 0.305 mg/mL), about 1.5 mg/mL of disodium phosphate dihydrate (*e.g.* 1.53 mg/mL), about 0.9 mg/mL of sodium dihydrogen phosphate dihydrate (*e.g.*, 0.86), and about 6.2 mg/mL of sodium chloride (*e.g.*, 6.165 mg/mL). In certain embodiments, the buffer system includes 1-1.5 mg/mL of citric acid, 0.25 to 0.5 mg/mL of sodium citrate, 1.25 to 1.75 mg/ml of disodium phosphate dihydrate, 0.7 to 1.1 mg/mL of sodium dihydrogen phosphate dihydrate, and 6.0 to 6.4 mg/mL of sodium chloride. The pH of the liquid formulation may be set by addition of a pharmaceutically acceptable acid and/or base. In certain embodiments, the pharmaceutically acceptable acid may be hydrochloric acid. In certain embodiments, the base may be sodium hydroxide.

[0439] In some embodiments, the formulation include an aqueous carrier, which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation. Illustrative carriers include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.*, phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0440] A polyol, which acts as a tonicifier and may stabilize the antibody, may also be included in the formulation. The polyol is added to the formulation in an amount which may vary with respect to the desired isotonicity of the formulation. In certain embodiments, the aqueous formulation may be isotonic. The amount of polyol added may also be altered with respect to the molecular weight of the polyol. For example, a lower amount of a monosaccharide (*e.g.*, mannitol) may be added, compared to a disaccharide (such as trehalose). In certain embodiments, the polyol which may be used in the formulation as a tonicity agent is mannitol. In certain embodiments, the mannitol concentration may be about 5 to about 20 mg/mL. In certain embodiments, the concentration of mannitol may be about 7.5 to 15 mg/mL. In certain embodiments, the concentration of mannitol may be about 10-14 mg/mL. In certain embodiments, the concentration of mannitol may be about 12 mg/mL. In certain embodiments, the polyol sorbitol may be included in the formulation.

[0441] A detergent or surfactant may also be added to the formulation. Exemplary detergents include nonionic detergents such as polysorbates (*e.g.*, polysorbates 20, 80 etc.) or poloxamers (*e.g.*, poloxamer 188). The amount of detergent added is such that it reduces aggregation of the formulated antibody and/or minimizes the formation of particulates in the formulation and/or reduces adsorption. In certain embodiments, the formulation may include a surfactant which is a polysorbate. In certain embodiments, the formulation may contain the detergent polysorbate 80 or Tween 80. Tween 80 is a term used to describe polyoxyethylene (20) sorbitanmonooleate (see Fiedler, Lexikon der Hifsstoffe, Editio Cantor Verlag Aulendorf, 4th edi., 1996). In certain embodiments, the formulation may contain between about 0.1 mg/mL and about 10 mg/mL of polysorbate 80, or between about 0.5 mg/mL and about 5 mg/mL. In certain embodiments, about 0.1% polysorbate 80 may be added in the formulation.

[0442] In certain embodiments, the liquid formulation of the disclosure may be prepared as a 10 mg/mL concentration solution in combination with a sugar at stabilizing levels. In certain embodiments the liquid formulation may be prepared in an aqueous carrier. In certain embodiments, a stabilizer may be added in an amount no greater than that which may result in a viscosity undesirable or unsuitable for intravenous administration. In certain

embodiments, the sugar may be disaccharides, *e.g.*, sucrose. In certain embodiments, the liquid formulation may also include one or more of a buffering agent, a surfactant, and a preservative, which is added to the formulations herein to reduce bacterial action. The addition of a preservative may, for example, facilitate the production of a multi-use (multiple-dose) formulation.

[0443] In some embodiments, the present disclosure provides a formulation with an extended shelf life including the protein of the present disclosure, in combination with mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 80, water, and sodium hydroxide.

[0444] Deamidation is a common product variant of peptides and proteins that may occur during fermentation, harvest/cell clarification, purification, drug substance/drug product storage and during sample analysis. Deamidation is the loss of NH3 from a protein forming a succinimide intermediate that can undergo hydrolysis. The succinimide intermediate results in a 17 u mass decrease of the parent peptide. The subsequent hydrolysis results in an 18 u mass increase. Isolation of the succinimide intermediate is difficult due to instability under aqueous conditions. As such, deamidation is typically detectable as 1 u mass increase. Deamidation of an asparagine results in either aspartic or isoaspartic acid. The parameters affecting the rate of deamidation include pH, temperature, solvent dielectric constant, ionic strength, primary sequence, local polypeptide conformation and tertiary structure. The amino acid residues adjacent to Asn in the peptide chain affect deamidation rates. Gly and Ser following an Asn in protein sequences results in a higher susceptibility to deamidation. In certain embodiments, the liquid formulation of the present disclosure may be preserved under conditions of pH and humidity to prevent deamination of the protein product.

[0445] In some embodiment, the formulation is a lyophilized formulation. In certain embodiments, the formulation is freeze-dried (lyophilized) and contained in about 12-60 vials. In certain embodiments, the formulation is freeze-dried and 45 mg of the freeze-dried formulation may be contained in one vial. In certain embodiments, the about 40 mg – about 100 mg of freeze-dried formulation is contained in one vial. In certain embodiments, freeze dried formulation from 12, 27, or 45 vials are combined to obtained a therapeutic dose of the protein in the intravenous drug formulation. The formulation may be a liquid formulation. In some embodiments, a liquid formulation is stored as about 250 mg/vial to about 1000 mg/vial. In certain embodiments, the liquid formulation is stored as about 600 mg/vial. In certain embodiments, the liquid formulation is stored as about 250 mg/vial.

[0446] In some embodiments, the lyophilized formulation includes the proteins described herein and a lyoprotectant. The lyoprotectant may be sugar, *e.g.*, disaccharides. In certain embodiments, the lyoprotectant may be sucrose or maltose. The lyophilized formulation may also include one or more of a buffering agent, a surfactant, a bulking agent, and/or a preservative. The amount of sucrose or maltose useful for stabilization of the lyophilized drug product may be in a weight ratio of at least 1:2 protein to sucrose or maltose. In certain embodiments, the protein to sucrose or maltose weight ratio may be of from 1:2 to 1:5.

[0447] In certain embodiments, the pH of the formulation, prior to lyophilization, may be set by addition of a pharmaceutically acceptable acid and/or base. In certain embodiments the pharmaceutically acceptable acid may be hydrochloric acid. In certain embodiments, the pharmaceutically acceptable base may be sodium hydroxide. Before lyophilization, the pH of the solution containing the protein of the present disclosure may be adjusted between 6 to 8. In certain embodiments, the pH range for the lyophilized drug product may be from 7 to 8.

[0448] In certain embodiments, a "bulking agent" may be added. A "bulking agent" is a compound which adds mass to a lyophilized mixture and contributes to the physical structure of the lyophilized cake (*e.g.*, facilitates the production of an essentially uniform lyophilized cake which maintains an open pore structure). Illustrative bulking agents include mannitol, glycine, polyethylene glycol and sorbitol. The lyophilized formulations of the present invention may contain such bulking agents.

[0449] In certain embodiments, the lyophilized protein product is constituted with an aqueous carrier. The aqueous carrier of interest herein is one which is pharmaceutically acceptable (*e.g.*, safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation, after lyophilization. Illustrative diluents include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.*, phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution. In certain embodiments, the lyophilized drug product of the current disclosure is reconstituted with either Sterile Water for Injection, USP (SWFI) or 0.9% Sodium Chloride Injection, USP. During reconstitution, the lyophilized powder dissolves into a solution. In certain embodiments, the lyophilized protein product of the instant disclosure is constituted to about 4.5 mL water for injection and diluted with 0.9% saline solution (sodium chloride solution).

[0450] The protein compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as-is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous

carrier prior to administration. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents. The composition in solid form can also be packaged in a container for a flexible quantity.

[0451] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0452] The specific dose can be a uniform dose for each patient, for example, 50-5000 mg of protein. Alternatively, a patient's dose can be tailored to the approximate body weight or surface area of the patient. Other factors in determining the appropriate dosage can include the disease or condition to be treated or prevented, the severity of the disease, the route of administration, and the age, sex and medical condition of the patient. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those skilled in the art, especially in light of the dosage information and assays disclosed herein. The dosage can also be determined through the use of known assays for determining dosages used in conjunction with appropriate dose-response data. An individual patient's dosage can be adjusted as the progress of the disease is monitored. Blood levels of the targetable construct or complex in a patient can be measured to see if the dosage needs to be adjusted to reach or maintain an effective concentration. Pharmacogenomics may be used to determine which targetable constructs and/or complexes, and dosages thereof, are most likely to be effective for a given individual (Schmitz *et al.*, *Clinica. Chimica. Acta.* 308: 43-53, 2001; Steimer *et al.*, *Clinica. Chimica. Acta.* 308: 33-41, 2001).

[0453] In general, dosages based on body weight are from about 0.01 μg to about 100 mg per kg of body weight, such as about 0.01 μg to about 100 mg/kg of body weight, about 0.01 μg to about 50 mg/kg of body weight, about 0.01 μg to about 10 mg/kg of body weight, about 0.01 μg to about 1 mg/kg of body weight, about 0.01 μg to about 100 μg/kg of body weight, about 0.01 μg to about 50 μg/kg of body weight, about 0.01 μg to about 10 μg/kg of body weight, about 0.01 μg to about 1 μg/kg of body weight, about 0.01 μg to about 0.1 μg/kg of body weight, about 0.1 μg to about 100 mg/kg of body weight, about 0.1 μg to about 50 mg/kg of body weight, about 0.1 μg to about 10 mg/kg of body weight, about 0.1 μg to about 1 mg/kg of body weight, about 0.1 μg to about 100 μg/kg of body weight, about 0.1 μg to about 10 μg/kg of body weight, about 0.1 μg to about 1 μg/kg of body weight, about 1 μg to about 100 mg/kg of body weight, about 1 μg to about 50 mg/kg of body weight, about 1 μg to

about 10 mg/kg of body weight, about 1 μg to about 1 mg/kg of body weight, about 1 μg to about 100 μg/kg of body weight, about 1 μg to about 50 μg/kg of body weight, about 1 μg to about 10 μg/kg of body weight, about 10 μg to about 100 mg/kg of body weight, about 10 μg to about 50 mg/kg of body weight, about 10 μg to about 10 mg/kg of body weight, about 10 μg to about 1 mg/kg of body weight, about 10 μg to about 100 μg/kg of body weight, about 10 μg to about 50 μg/kg of body weight, about 50 μg to about 100 mg/kg of body weight, about 50μg to about 50 mg/kg of body weight, about 50 μg to about 10 mg/kg of body weight, about 50 μg to about 1 mg/kg of body weight, about 50 μg to about 100 μg/kg of body weight, about 100 μg to about 100 mg/kg of body weight, about 100 μg to about 50 mg/kg of body weight, about 100 μg to about 10 mg/kg of body weight, about 100 μg to about 1 mg/kg of body weight, about 1 mg to about 100 mg/kg of body weight, about 1 mg to about 50 mg/kg of body weight, about 1 mg to about 10 mg/kg of body weight, about 10 mg to about 100 mg/kg of body weight, about 10 mg to about 50 mg/kg of body weight, about 50 mg to about 100 mg/kg of body weight. Doses may be given once or more times daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the targetable construct or complex in bodily fluids or tissues. Administration of the present invention could be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, intracavitary, by perfusion through a catheter or by direct intralesional injection. This may be administered once or more times daily, once or more times weekly, once or more times monthly, and once or more times annually.

[0454] The description above describes multiple aspects and embodiments of the invention. The patent application specifically contemplates all combinations and permutations of the aspects and embodiments.

[0455] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0456] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components, or the element

or component can be selected from a group consisting of two or more of the recited elements or components.

[0457] Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without departing from the spirit and scope of the present invention, whether explicit or implicit herein. For example, where reference is made to a particular compound, that compound can be used in various embodiments of compositions of the present invention and/or in methods of the present invention, unless otherwise understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is intended and will be appreciated that embodiments may be variously combined or separated without parting from the present teachings and invention(s). For example, it will be appreciated that all features described and depicted herein can be applicable to all aspects of the invention(s) described and depicted herein.

[0458] It should be understood that the expression "at least one of" includes individually each of the recited objects after the expression and the various combinations of two or more of the recited objects unless otherwise understood from the context and use. The expression "and/or" in connection with three or more recited objects should be understood to have the same meaning unless otherwise understood from the context.

[0459] The use of the term "include," "includes," "including," "have," "has," "having," "contain," "contains," or "containing," including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional unrecited elements or steps, unless otherwise specifically stated or understood from the context.

[0460] Where the use of the term "about" is before a quantitative value, the present invention also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term "about" refers to a ±10% variation from the nominal value unless otherwise indicated or inferred.

[0461] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present invention remain operable. Moreover, two or more steps or actions may be conducted simultaneously.

[0462] The use of any and all examples, or exemplary language herein, for example, "such as" or "including," is intended merely to illustrate better the present invention and does not pose a limitation on the scope of the invention unless claimed. No language in the

specification should be construed as indicating any non-claimed element as essential to the practice of the present invention.

EXAMPLES

[0463] The following examples are merely illustrative and are not intended to limit the scope or content of the invention in any way.

Example 1. Kinetics and affinity of binding to different variants of CD33.

[0464] Kinetics and affinity of a series of Fab fragments of anti-CD33 antibodies with different CD33 variants (human CD33 ECD, cyno CD33 ECD, V-domain of human CD33, C-domain or human CD33 and selected CD33 SNPs) were assessed by surface plasmon resonance using Biacore 8K instrument (GE Healthcare). Anti-Fab antibody was immobilized on a CM5 chip using standard amine coupling chemistry. CD33 FABs were captured on the anti-Fab chip at a density of ~100 RU. Solutions containing different concentrations of soluble monomeric CD33 or its domains were injected over the captured FABs and control surfaces at 30 µl/min at 37 °C. Surfaces were regenerated between cycles by quick injection of 10 mM glycine, pH 1.8. To obtain kinetic rate constants double-referenced data were fit to a 1:1 interaction model using Biacore 8K Evaluation software (GE Healthcare). The equilibrium binding constant K_D was determined by the ratio of binding rate constants k_d/k_a.

Octet Platform-Based Kinetic and Affinity Analyis

[0465] ForteBio affinity measurements were performed on an Octet HTX generally as described in Estep *et al.*, High throughput solution-based measurement of antibody-antigen affinity and epitope binning. *Mabs* 5(2), 270-278 (2013). Briefly, ForteBio affinity measurements were performed by loading IgGs on-line onto AHC sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to 100 nM antigen for 3 minutes, and afterwards were transferred to assay buffer for 3 min for off-rate measurement. All kinetics were analyzed using the 1:1 binding model. The results are shown in Table 11.

Table 11. Kinetic parameters of human CD33 binding to IgG antibodies measured by BLI.

IgG ADI Name	K_D (M)	k_{on} (1/M/s)	k_{off} (1/s)
ADI-10154	3.70E-09	2.46E+05	8.97E-04
ADI-10155	5.30E-09	2.29E+05	1.21E-03
ADI-10157	4.20E-09	7.99E+04	3.36E-04

IgG ADI Name	K_D (M)	k_{on} (1/M/s)	k_{off} (1/s)
ADI-10158	2.60E-09	5.86E+05	1.55E-03
ADI-10159	5.80E-10	3.48E+05	2.00E-04
ADI-10160	5.10E-09	6.38E+05	3.25E-03
ADI-10161	3.70E-09	5.87E+05	2.17E-03
ADI-10163	6.80E-09	6.65E+05	4.53E-03
ADI-10164	4.30E-09	3.44E+05	1.48E-03
ADI-10165	4.00E-09	7.79E+05	3.11E-03
ADI-10167	3.90E-09	1.00E+06	3.93E-03
ADI-10168	1.00E-08	4.76E+05	4.78E-03
ADI-10173	9.70E-09	3.24E+05	3.14E-03
ADI-10177	3.60E-09	6.01E+05	2.14E-03
ADI-11776	2.94E-10	6.79E+05	2.00E-04
ADI-11801	4.57E-10	4.38E+05	2.00E-04
ADI-11802	4.53E-10	4.41E+05	2.00E-04
ADI-11807	3.07E-10	6.51E+05	2.00E-04
ADI-11809	3.13E-10	6.38E+05	2.00E-04
ADI-11812	1.91E-09	1.66E+05	3.15E-04
ADI-11815	1.44E-09	1.59E+05	2.29E-04
ADI-11819	2.43E-10	8.24E+05	2.00E-04
ADI-11825	5.40E-10	6.96E+05	3.76E-04
ADI-11826	3.93E-10	6.19E+05	2.43E-04
ADI-11828	8.10E-10	6.58E+05	5.33E-04
ADI-11830	1.20E-09	7.70E+05	9.23E-04
ADI-11835	2.81E-10	8.44E+05	2.37E-04
ADI-11839	2.45E-09	7.04E+05	1.72E-03
Lintuzumab	2.21E-09	4.31E+05	9.52E-04

Example 2. CD33 antibodies bind to human CD33 with high affinity and cross-react with cyno CD33.

[0466] Despite rather high homology between human and cyno CD33 (87% in the ECD), most of commercially available anti-CD33 antibodies, *e.g.,* lintuzumab, mylotarg, etc. lack cross-reactivity with cyno CD33. Figure 2 shows alignment of full length human and cyno CD33 highlighting the differences in the primary sequence in the ECD domain.

[0467] Affinity of 29 Fab fragments binding to human and cyno CD33 ECD were assayed by Biacore analysis. Eight out of 29 antibodies show cross-reactivity with cyno

CD33. Kinetic parameters of binding are given in Table 12. Data are compared to lintuzumab. Several antibodies show affinities >100 fold higher than lintuzumab.

[0468] Binding of the Fab fragments from CD33 monoclonal antibodies to the human CD33 extracellular domain (ECD) was measured by Biacore at 37 °C. The Biacore profile of ADI-10159 is shown in FIG. 3A; the Biacore profile of ADI-10177 is shown in FIG. 3B; the Biacore profile of ADI-11776 is shown in FIG. 3C; the Biacore profile of ADI-11801 in FIG. 3D; the Biacore profile of ADI-11807 is shown in FIG. 3E; the Biacore profile of ADI-11809 is shown in FIG. 3F; the Biacore profile of ADI-11815 is shown in FIG. 3G; the Biacore profile of ADI-11819 FIG. 3H; the Biacore profile of ADI-11830 is shown in FIG. 3I; the Biacore profile of ADI-11835 is shown in FIG. 3J; and the Biacore profile of the Fab fragment from Lintuzumab is shown in FIG. FIG. 3K.

[0469] Binding of the Fab fragments from CD33 monoclonal antibodies to the cyno CD33 ECD was measured by Biacore at 37 °C. The Biacore profile of ADI-10159 is shown in FIG. 4A; the Biacore profile of ADI-10177 in FIG. 4B; the Biacore profile of ADI-11776 is shown in FIG. 4C; the Biacore profile of ADI11807 is shown in FIG. 4D; the Biacore profile of ADI-11809 is shown in FIG. 4E; the Biacore profile of ADI-11819 is shown in FIG. 4F; the Biacore profile of ADI-11830 is shown in FIG. 4G; and the Biacore profile of ADI-11835 is shown in FIG. 4H.

[0470] Binding of the Fab fragments from CD33 monoclonal antibodies to V domain and C domain of human CD33 was measured by Biacore at 37 °C. FIGs. 5A-5J represent binding to the V-domain; panels K-T represent binding to the C domain. Both FIGs. 5A and 5K are Biacore profiles of ADI-10159; both FIGs. 5B and 5L are Biacore profiles of ADI-10177; both FIGs. 5C and 5M are Biacore profiles of ADI-11776; both FIGs. 5D and 5N are Biacore profiles of ADI-11801; both FIGs. 5E and 5O are Biacore profiles of ADI-11807; both FIGs. 5F and 5P are Biacore profiles of ADI-11809; both FIGs. 5G and 5Q are Biacore profiles of ADI-11815; both FIGs. 5H and 5R are Biacore profiles of ADI-11819; both FIGs. 5I and 5S are Biacore profiles of ADI-11830; and FIGs. 5J and 5T are Biacore profiles of ADI-11835.

Table 12. Kinetic parameters of human CD33 ECD and cyno CD33 ECD binding to Fabs measured by SPR at 37 °C. No binding is defined as absence of signal at highest concentration of 100 nM.

Antibody	Human CD33			Cyno CD33		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-10159	4.29e5	1.95e-3	4.53	5.28e5	4.36e-2	74.9
ADI-10177	5.58e5	6.36e-3	11.4	3.53e5	7.54e-3	21.4
ADI-11776	1.6e6	1.24e-3	0.78	2.62e6	4.72e-3	1.81
ADI-11807	1.14e6	3.32e-4	0.29	9.98e5	1.51e-4	0.15
ADI-11809	1.02e6	1.23e-6	0.0012	1.06e6	1.26e-4	0.118
ADI-11819	2.84e6	5.65e-5	0.02	3.82e6	1.90e-2	4.96
ADI-11830	1.99e6	5.47e-3	2.75	1.34e6	3.64e-2	27.8
ADI-11835	2.6e6	1.43e-3	0.53	2.76e6	1.89e-2	6.86
ADI-11815	3.39e5	7.91e-5	0.23	No binding		
ADI-11801	7.56e5	4.17e-4	0.55	No binding		
ADI-10152	2.46e5	9.14e-3	37.2	No binding		
ADI-10154	1.92e5	8.33e-3	43.4	No binding		
ADI-10155	1.70e5	6.85e-3	40.2	No binding		
ADI-10157	2.82e6	7.60e-3	2.69	No binding		
ADI-10158	4.75e5	1.49e-2	3.14	No binding		
ADI-10160	6.37e5	2.69e-2	42.2	No binding		
ADI-10161	5.74e5	1.18e-2	20.6	No binding		
ADI-10163	5.15e5	2.75e-2	53.5	No binding		
ADI-10164	3.19e5	1.01e-2	31.5	No binding		
ADI-10165	5.91e5	1.88e-2	31.8	No binding		
ADI-10167	1.25e6	3.07e-2	24.4	No binding		
ADI-10168	3.75e5	1.75e-2	46.6	No binding		
ADI-10173	2.12e5	1.25e-2	58.8	No binding		
ADI-11802	4.9e5	1.54e-3	3.14	No binding		
ADI-11812	3.96e5	4.86e-4	1.23	No binding		
ADI-11825	2.13e6	3.8e-3	1.78	No binding		
ADI-11826	1.76e6	4.63e-3	2.63	No binding		

Antibody	Human CD33			Cyno CD33		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-11828	1.32e6	3.51e-3	2.67	1.03e6	5.48e-2	53.5
ADI-11839	8.74e5	1.62e-2	18.6	No binding		
Lintuzumab	7.35e5	1.22e-2	16.7	No binding		

Mapping of binding interface to individual domains of CD33

[0471] The binding interface between the Fab fragment of each CD33 antibody to CD33 was mapped. FIGs. 5A-5T show binding of Fab fragments of different CD33 antibodies to individual domains of human CD33 (V domain and C domain). No binding to C domain was observed for any antibody tested. ADI-11815 did not bind to either V or C domain, suggesting that it requires a unique conformational epitope.

[0472] Table 13 shows a comparison between kinetics of binding to full ECD of human CD33 and a V domain. ADI-10159, ADI-11176, ADI-11807, ADI-11830, ADI-11835, ADI-11801, ADI-10155, ADI-11802, ADI-11825, ADI-11826, ADI-11828, and ADI-11839 show similar kinetics suggesting that the epitope for these antibodies are located entirely in the V domain. Reduced binding to V domain is observed for ADI-10177, ADI-11809 ADI-11819, ADI-10157, ADI-10158, and ADI-10164, suggesting that these antibodies bind to a conformational epitope, partially located in the V domain.

[0473] Kinetics of binding to the C domain of human CD33 was also measured with ADI-10152, ADI-10154, ADI-10155, ADI-10157, ADI-10158, ADI-10160, ADI-10161, ADI-10163, ADI-10164, ADI-10165, ADI-10167, ADI-10168, ADI-10173, ADI-11802, ADI-11812, ADI-11825, ADI-11826, ADI-11828, and ADI-11839. None of these antibodies bound the C domain of human CD33.

Table 13. Biacore analysis of FABs binding to recombinant full-length ECD and V domain of human CD33 performed at 37 °C. Asterisk indicates antibodies that bind to a conformational epitope partially located in V domain.

Antibody	Human CD33 V domain			Human CD33		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-10159	9.05e5	5.0e-3	5.56	4.29e5	1.95e-3	4.53
ADI-10177*	1.56e6	8.57e-2	54.8	5.58e5	6.36e-3	11.4
ADI-11776	4.52e6	1.43e-2	0.33	1.6e6	1.24e-3	0.78

Antibody	Human CD33 V domain			Human CD33		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-11807	3.07e6	8.47e-4	0.28	1.14e6	3.32e-4	0.29
ADI-11809*	2.6e6	7.69e-4	0.3	1.02e6	1.23e-6	0.0012
ADI-11819	6.75e6	9.16e-4	0.14	2.84e6	5.65e-5	0.02
ADI-11830	6.67e6	2.99e-2	4.5	1.99e6	5.47e-3	2.75
ADI-11835	7.6e6	8.68e-3	1.14	2.6e6	1.43e-3	0.53
ADI-11815	No binding			3.39e5	7.91e-5	0.23
ADI-11801	1.8e6	1.25e-3	0.69	7.56e5	4.17e-4	0.55
ADI-10152	4.88e5	4.09e-2	100	2.46e5	9.14e-3	37.2
ADI-10154	1.52e6	3.35e-1	220	1.92e5	8.33e-3	43.4
ADI-10155	5.48e5	4.67e-2	85.2	1.70e5	6.85e-3	40.2
ADI-10157*	1.12e5	1.51e-2	134	2.82e6	7.60e-3	2.69
ADI-10158*	1.04e6	1.33e-1	127	4.75e5	1.49e-2	3.14
ADI-10160	1.59e6	3.27e-1	206	6.37e5	2.69e-2	42.2
ADI-10161	1.29e6	1.24e-1	95.8	5.74e5	1.18e-2	20.6
ADI-10163	No binding			5.15e5	2.75e-2	53.5
ADI-10164	1.29e6	3.7e-1	286	3.19e5	1.01e-2	31.5
ADI-10165	No binding			5.91e5	1.88e-2	31.8
ADI-10167	No binding			1.25e6	3.07e-2	24.4
ADI-10168	No binding			3.75e5	1.75e-2	46.6
ADI-10173	No binding			2.12e5	1.25e-2	58.8
ADI-11802	1.34e6	4.35e-3	3.2	4.9e5	1.54e-3	3.14
ADI-11812	No binding			3.96e5	4.86e-4	1.23
ADI-11825	4.93e6	1.95e-2	3.95	2.13e6	3.8e-3	1.78
ADI-11826	5.12e6	2.25e-3	4.38	1.76e6	4.63e-3	2.63
ADI-11828	3.37e6	2.13e-2	6.3	1.32e6	3.51e-3	2.67
ADI-11839	9.19e6	4.1e-1	44.6	8.74e5	1.62e-2	18.6

Antibodies recognize CD33 independent of its glycosylation status.

[0474] The ability of anti-CD33 antibodies to recognize glycosylated CD33 was assayed. Table 14 shows that antibodies recognize V domain independent of its glycosylation status. Human CD33 is heavily glycosylated with 2 glycosylation sites located in the V domain.

Differences in the glycosylation level of CD33 in different cells have been reported in the literature. Glycosylation can potentially disturb antibody binding to the target. In some samples, the V domain was deglycosylated by PNGase before testing. De-glycosylation status was confirmed by a shift on SDS-PAGE and MS. All antibodies tested in Table 14 bound to deglycosylated V CD33 similarly to the fully glycosylated version except for ADI-10163, ADI-10165, ADI-10167, and ADI-10173.

Table 14. Biacore analysis of FABs binding to fully glycosylated vs deglycosylated V domain performed at 37 °C.

Antibody	Deglycosylated V domain			V domain		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-10159	9.78e5	1.2e-2	12.3	9.05e5	5.0e-3	5.56
ADI-10177	1.88e6	7.01e-2	38.2	1.56e6	8.57e-2	54.8
ADI-11776	4.85e6	1.36e-3	0.28	4.52e6	1.43e-2	0.33
ADI-11807	3.9e6	7.45e-4	0.19	3.07e6	8.47e-4	0.28
ADI-11809	3.4e6	7.11e-4	0.21	2.6e6	7.69e-4	0.3
ADI-11819	9.15e6	1.03e-3	0.11	6.75e6	9.16e-4	0.14
ADI-11830	6.8e6	2.69e-2	3.95	6.67e6	2.99e-2	4.5
ADI-11835	7.94e6	7.79e-3	0.98	7.6e6	8.68e-3	1.14
ADI-11801	2.1e6	1.15e-3	0.55	1.8e6	1.25e-3	0.69
ADI-10152	1.05e5	7.7e-2	76.8	4.88e5	4.09e-2	100
ADI-10154	3.13e5	6.55e-2	209	1.52e6	3.35e-1	220
ADI-10155	1.25e6	1.32e-1	105	5.48e5	4.67e-2	85.2
ADI-10157	4.11e5	2.61e-2	63.8	1.12e5	1.51e-2	134
ADI-10158	2.63e6	2.31e-1	88.1	1.04e6	1.33e-1	127
ADI-10160	1.7e6	2.25e-1	133	1.59e6	3.27e-1	206
ADI-10161	2.29e6	1.96e-1	85.6	1.29e6	1.24e-1	95.8
ADI-10163	1.68e6	2.56e-1	152	No binding		
ADI-10164	8.11e5	1.16e-1	143	1.29e6	3.7e-1	286
ADI-10165	1.3e6	2.03e-1	156	No binding		
ADI-10167	1.66e6	1.28e-1	77.8	No binding		
ADI-10168	No binding			No binding		
ADI-10173	6.74e5	1.31e-1	200	No binding		

Antibody	Deglycosylated V domain			V domain		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-11802	1.57e6	4.17e-3	2.65	1.34e6	4.35e-3	3.2
ADI-11812	No binding			No binding		
ADI-11825	5.78e6	1.8e-2	3.11	4.93e6	1.95e-2	3.95
ADI-11826	5.37e6	1.98e-2	3.69	5.12e6	2.25e-3	4.38
ADI-11828	3.588e6	1.89e-2	4.87	3.37e6	2.13e-2	6.3
ADI-11839	1.65e6	1.16e-1	70.3	9.19e6	4.1e-1	44.6

CD33 antibodies bind to the R69G SNP of CD33.

[0475] The ability of anti-CD33 antibodies to recognize the R69G mutation in CD33 was assayed. Although several SNPs have been described for CD33, R69G is particularly prominent, occurring in 39-42% of the population. Table 15 shows antibodies binding to human CD33 containing the R69G mutation.

Table 15. Biacore analysis of FABs binding to CD33 R69G.

Antibody	Human CD33 R69G			Human CD33		
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)
ADI-10159	4.26e5	2.43e-3	5.68	4.29e5	1.95e-3	4.53
ADI-10177	2.3e5	2.01e-3	87.4	5.58e5	6.36e-3	11.4
ADI-11776	1.98e6	4.26e-4	0.22	1.6e6	1.24e-3	0.78
ADI-11807	5.97e5	2.59e-4	0.43	1.14e6	3.32e-4	0.29
ADI-11809	8.15e5	1.79e-4	0.22	1.02e6	1.23e-6	0.0012
ADI-11819	2.78e6	2.44e-4	0.09	2.84e6	5.65e-5	0.02
ADI-11830	2.27e6	6.63e-3	2.94	1.99e6	5.47e-3	2.75
ADI-11835	3.07e6	2.05e-3	0.67	2.6e6	1.43e-3	0.53
ADI-11815	3.00e5	1.3e-3	4.34	3.39e5	7.91e-5	0.23
ADI-11801	No binding			7.56e5	4.17e-4	0.55
ADI-10152	2.88e5	2.18e-2	75.8	2.46e5	9.14e-3	37.2
ADI-10154	1.53e5	2.83e-2	186	1.92e5	8.33e-3	43.4
ADI-10155	2.33e5	1.05e-2	45.0	1.70e5	6.85e-3	40.2
ADI-10157	1.56e6	2.87e-2	17.8	2.82e6	7.60e-3	2.69
ADI-10158	5.30e5	3.31e-2	62.3	4.75e5	1.49e-2	3.14

ADI-10160	8.36e5	5.33e-2	63.7	6.37e5	2.69e-2	42.2
ADI-10161	6.29e5	3.07e-2	48.9	5.74e5	1.18e-2	20.6
ADI-10163	5.59e5	5.9e-2	106	5.15e5	2.75e-2	53.5
ADI-10164	3.08e5	3.5e-2	113	3.19e5	1.01e-2	31.5
ADI-10165	6.9e5	5.02e-2	72.7	5.91e5	1.88e-2	31.8
ADI-10167	1.22e6	8.74e-2	71.6	1.25e6	3.07e-2	24.4
ADI-10168	4.85e5	3.07e-2	63.5	3.75e5	1.75e-2	46.6
ADI-10173	No binding			2.12e5	1.25e-2	58.8
ADI-11802	No binding			4.9e5	1.54e-3	3.14
ADI-11812	3.38e5	2.28e-3	6.74	3.96e5	4.86e-4	1.23
ADI-11825	1.86e6	6.95e-3	3.74	2.13e6	3.8e-3	1.78
ADI-11826	1.89e6	7.23e-3	3.83	1.76e6	4.63e-3	2.63
ADI-11828	1.16e6	7.00e-3	6.03	1.32e6	3.51e-3	2.67
ADI-11839	No binding			8.74e5	1.62e-2	18.6

CD33 antibodies bind to the S128N SNP of CD33

[0476] The ability of anti-CD33 antibodies to recognize the S128N mutation in CD33 was assayed. Table 16 shows antibodies binding to human CD33 containing the S128N mutation. The binding affinity of ADI-10152, ADI-10154, ADI-10157, ADI-10158, ADI-10163, ADI-10164, ADI-10165, ADI-10167, ADI-10168, and ADI-10173 to human CD33 was impaired by the S128N SNP.

Table 16. Biacore analysis of FABs binding to CD33 S128N.

Antibody	**Human CD33 S128N**			**Human CD33**		
	k_a **(1/Ms)**	k_d **(1/s)**	K_D **(nM)**	k_a **(1/Ms)**	k_d **(1/s)**	K_D **(nM)**
ADI-10152	2.74e5	3.39e-2	124	2.46e5	9.14e-3	37.2
ADI-10154	1.93e5	5.39e-2	279	1.92e5	8.33e-3	43.4
ADI-10155	1.87e5	1.59e-2	85	1.70e5	6.85e-3	40.2
ADI-10157	5.65e4	9.24e-3	163	2.82e6	7.60e-3	2.69
ADI-10158	5.73e5	4.17e-2	72.8	4.75e5	1.49e-2	3.14
ADI-10160	7.86e5	6.73e-2	85.7	6.37e5	2.69e-2	42.2
ADI-10161	6.05e5	3.85e-2	63.6	5.74e5	1.18e-2	20.6
ADI-10163	5.07e5	7.48e-2	147	5.15e5	2.75e-2	53.5

ADI-10164	1.93e5	5.39e-2	279	3.19e5	1.01e-2	31.5
ADI-10165	6.41e5	5.82e-2	90.7	5.91e5	1.88e-2	31.8
ADI-10167	1.28e6	1.27e-1	98.6	1.25e6	3.07e-2	24.4
ADI-10168	4.04e5	4.69e-2	116	3.75e5	1.75e-2	46.6
ADI-10173	1.83e5	3.42e-2	187	2.12e5	1.25e-2	58.8
ADI-11802	6.62e5	5.90e-4	0.809	4.9e5	1.54e-3	3.14
ADI-11812	5.56e5	1.12e-3	2.01	3.96e5	4.86e-4	1.23
ADI-11825	2.10e6	6.49e-3	3.09	2.13e6	3.8e-3	1.78
ADI-11826	2.17e6	5.74e-3	2.65	1.76e6	4.63e-3	2.63
ADI-11828	1.37e6	7.42e-3	5.41	1.32e6	3.51e-3	2.67
ADI-11839	9.63e5	2.84e-2	29.5	8.74e5	1.62e-2	18.6

ADI-11815 recognizes a unique conformational epitope.

[0477] The binding epitope of the CD33-binding domain of ADI-11815 was assayed. FIG. 6 and Table 17 demonstrate that ADI-11815 has a unique conformational epitope. This antibody binds to the full-length ECD of human CD33, but not to individual domains and does not cross-block with lintuzumab.

Table 17. Kinetic parameters of ADI-11815 Fab binding to different domains and SNP R69G of human CD33.

	hCD33			V domain			C domain			hCD33 R69G SNP			Cross-blocking with lintuzumab
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)	
ADI-11815	3.39e5	7.91e-5	0.23	No binding			No binding			3.00e5	1.3e-3	4.34	No

ADI-11801 binds to a unique epitope that includes R69.

[0478] The binding epitope of CD33-binding domain including ADI-11815 was assayed. FIG. 7 and Table 18 demonstrate the epitope on CD33 that ADI-11801 recognize. Its binding to the human CD33 ECD is abrogated by R69G mutation.

Table 18. Kinetics of ADI-11801 Fab binding to different domains of CD33 and SNP R69G.

	hCD33			V domain			C domain			hCD33 R69G SNP			Cross-blocking with lintuzumab
	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)	k_a (1/Ms)	k_d (1/s)	K_D (nM)	
ADI-11801	7.56e5	4.17e-4	0.55	1.80e6	1.25e-3	0.69	No binding			No binding			No

Example 3: Assessment of TriNKET binding to cell expressing human NKG2D

[0479] The ability of TriNKETs that include an NKG2D-binding domain and a CD33-binding domain to bind to NKG2D was assayed. EL4 cells transduced with human NKG2D and human KHYG-1 cells were used to test binding to cell-expressed human NKG2D. TriNKETs were diluted to the top concentration, and then diluted serially. The mAb or TriNKET dilutions were used to stain cells, and binding of the TriNKET or mAb was detected using a fluorophore-conjugated anti-human IgG secondary antibody. Cells were analyzed by flow cytometry, binding MFI was normalized to secondary antibody controls to obtain fold over background values.

[0480] FIGs. 10A-10B show binding of CD33-targeting TriNKETs to human NKG2D expressed on EL4 (top) or KHYG-1 (bottom) cells. FOB binding signal was similar on both EL4-hNKG2D cells and KHYG-1 cells, the ranking of binding between clones was also maintain on the two cell lines. FIG. 10A shows binding of CD33-targeting TriNKETs to human NKG2D expressed on EL4 cells. FIG. 10B shows binding of CD33-targeting TriNKETs to human NKG2D expressed on KHYG-1 cells. FOB binding signal was similar on both EL4-hNKG2D cells and KHYG-1 cells, the ranking of binding between clones was also maintain on the two cell lines.

Example 4: Assessment of TriNKET or mAb binding to cell expressed human cancer antigens

[0481] The ability of TriNKETs that include an NKG2D-binding domain and a CD33-binding domain to bind to CD33 was assayed. The Molm-13, human AML cell line, was used to assess binding of monoclonal antibodies to CD33 expressed on the cell surface. mAbs were diluted to 2 μg/mL, and mAb dilutions were used to stain cells. Bound antibody was detected using a fluorophore conjugated anti-human IgG secondary antibody. Cells were analyzed by flow cytometry, binding to cell-expressed CD33 was compared to isotype stained and unstained cell populations.

[0482] Human cancer cell lines expressing CD33 were used to assess tumor antigen binding of TriNKETs derived from different NKG2D-targeting clones. The human AML cell line Molm-13 was used to assess binding of TriNKETs to cell expressed CD33. TriNKETs were diluted, and were incubated with the respective cells. Binding of the TriNKET was detected using a fluorophore conjugated anti-human IgG secondary antibody. Cells were analyzed by flow cytometry, binding MFI to cell expressed CD33 was normalized to secondary antibody controls to obtain fold over background values.

[0483] The ability of CD33 TriNKETs to bind CD33 expressed on Molm-13 cells was tested. FIG. 8 shows binding of TriNKETs targeting CD33 to Molm- shows binding MFI of six anti-CD33 antibodies to CD33 expressed on Molm-13 cells. All six antibodies bound to cell-expressed CD33. Five of the six antibodies show higher MFI binding signal compared to Lintuzumab.

[0484] The ability of CD33 TriNKETs to induce rested NK cell-mediated killing of Molm-13 AML cells was tested. Four different CD33-targeting domains were used with five NKG2D-targeting domains to make a total of 20 different TriNKETs. Regardless of the NKG2D-targeting domain used in the TriNKET, binding to CD33 was conserved for a single CD33-targeting domain.

Example 5: Assessment of TriNKET or mAb internalization

[0485] Internalization of TriNKETs after binding to CD33 on cell surface was assayed. The Molm-13, human AML cell line, was used to assess internalization of monoclonal antibodies bound to CD33 expressed on the cell surface. Monoclonal antibodies were diluted to 2 μg/mL, and mAb dilutions were used to stain cells. Following surface staining of CD33 samples were split, half the sample was placed at 37 ^{o}C overnight to facilitate internalization, with the other half of the sample bound antibody was detected using a fluorophore conjugated anti-human IgG secondary antibody. Cells were fixed after staining with the secondary antibody, and were stored at 4 ^{o}C overnight for analysis on the following day. After 24 hours at 37 ^{o}C samples were removed from the incubator, and bound antibody on the surface of the cells was detected using a fluorophore conjugated anti-human IgG secondary antibody. Samples were fixed and all samples were analyzed on the same day. Internalization of antibodies was calculated as follows: % internalization = (1-(sample MFI 24hours/baseline MFI)) * 100%.

[0486] FIG. 9 shows internalization of anti-CD33 antibodies bound to the surface of Molm-13 cells after 24 hours. All the anti-CD33 antibodies showed similar internalization after 24 hours. Lintuzumab showed slightly higher internalization compare to other anti-CD33 antibodies.

Example 6: Activation of primary NK cells by TriNKETs

[0487] The ability of TriNKETs that include an NKG2D-binding domain and a CD33-binding domain to activate primary NK cells was assayed. PBMCs were isolated from human peripheral blood buffy coats using density gradient centrifugation. Isolated PBMCs were washed and prepared for NK cell isolation. NK cells were isolated using a negative selection technique with magnetic beads, purity of isolated NK cells was typically >90% CD3-CD56+. Isolated NK cells were cultured in media containing 100 ng/mL IL-2 for activation or rested overnight without cytokine. IL-2-activated NK cells were used either 24-48 hours later; rested NK cells were always used the day after purification.

[0488] Human cancer cell lines expressing a cancer target of interest were harvested from culture, and cells were adjusted to $2x10^6$/mL. Monoclonal antibodies or TriNKETs targeting the cancer target of interest were diluted in culture media. Rested and/or activated NK cells were harvested from culture, cells were washed, and were resuspended at $2x10^6$/mL in culture media. IL-2, and fluorophore-conjugated anti-CD107a was added to the NK cells for the activation culture. Brefeldin-A and monensin were diluted into culture media to block protein transport out of the cell for intracellular cytokine staining. Into a 96-well plate 50 µl of tumor targets, mAbs/TriNKETs, BFA/monensin, and NK cells were added for a total culture volume of 200 µl. Plate was cultured for 4 hours before samples were prepared for FACS analysis.

[0489] Following the 4 hour activation culture, cells were prepared for analysis by flow cytometry using fluorophore-conjugated antibodies against CD3, CD56 and IFNγ. CD107a and IFNγ staining was analyzed in CD3-CD56+ populations to assess NK cell activation.

[0490] FIG. 12 shows TriNKET-mediated activation of rested human NK cells in co-culture with CD33-expressing THP-1 AML cells. Human NK cell activation was assessed using IFNγ production and CD107a degranulation as markers for activation. All TriNKETs and monoclonal antibodies activated human NK cells above the isotype control. Similar activity was observed for four different anti-CD33 antibodies. TriNKET activity was dependent upon the NKG2D-targeting clone, some clones provided better TriNKET mediated

activation than others. NKG2D clones provided similar activity with each of the anti-CD33 targeting domains.

Example 7: Primary human NK cell cytotoxicity assay

[0491] The ability of TriNKETs that include an NKG2D-binding domain and a CD33-binding domain to induce cytotoxicity of NK cells against CD33-expressing cells was assayed. PBMCs were isolated from human peripheral blood buffy coats using density gradient centrifugation. Isolated PBMCs were washed and prepared for NK cell isolation. NK cells were isolated using a negative selection technique with magnetic beads, purity of isolated NK cells was typically >90% CD3-CD56+. Isolated NK cells were cultured in media containing 100 ng/mL IL-2 or were rested overnight without cytokine. IL-2-activated or rested NK cells were used the following day in cytotoxicity assays.

[0492] KHYG-1 cells were maintained in 10% HI-FBS-RPMI-1640 with 10 ng/mL IL-2. The day before use as effector cells in killing assays KHYG-1 cells were harvest from culture, and cells were washed out of the IL-2-containing media. After washing KHYG-1 cells were resuspended in 10% HI-FBS-RPMI-1640, and were rested overnight without cytokine.

DELFIA cytotoxicity assay:

[0493] Human cancer cell lines expressing a target of interest were harvested from culture, cells were washed with HBS, and were resuspended in growth media at 10^6/mL for labeling with BATDA reagent (Perkin Elmer AD0116). Manufacturer instructions were followed for labeling of the target cells. After labeling cells were washed 3x with HBS, and were resuspended at 0.5-1.0x10^5/mL in culture media. To prepare the background wells an aliquot of the labeled cells was put aside, and the cells were spun out of the media. 100 µl of the media was carefully added to wells in triplicate to avoid disturbing the pelleted cells. 100 µl of BATDA labeled cells were added to each well of the 96-well plate. Wells were saved for spontaneous release from target cells, and wells were prepared for max lysis of target cells by addition of 1% Triton-X. Monoclonal antibodies or TriNKETs against the tumor target of interest were diluted in culture media and 50 µl of diluted mAb or TriNKET was added to each well. Rested and/or activated NK cells were harvested from culture, cells were washed, and were resuspended at 10^5-2.0x10^6/mL in culture media depending on the desired E:T ratio. 50 µl of NK cells was added to each well of the plate to make a total of 200 µl culture

volume. The plate was incubated at 37 °C with 5% CO2 for 2-3 hours before developing the assay.

[0494] After culturing for 2-3 hours, the plate was removed from the incubator and the cells were pelleted by centrifugation at 200g for 5 minutes. 20 µl of culture supernatant was transferred to a clean microplate provided from the manufacturer and 200 µl of room temperature europium solution was added to each well. The plate was protected from the light and incubated on a plate shaker at 250 rpm for 15 minutes. Plate was read using either Victor 3 or SpectraMax i3X instruments. % Specific lysis was calculated as follows: % Specific lysis = ((Experimental release – Spontaneous release) / (Maximum release – Spontaneous release)) * 100%.

[0495] FIG. 13 and FIG. 14 show human NK cell killing of Molm-13 (FIG. 13) and THP-1 (FIG. 14) AML target cells mediated by CD33-targeting TriNKETs. Human NK cell killing of Molm-13 AML target cells mediated by CD33-targeting TriNKETs was assayed (FIG. 13). Rested NK effector cells were used with Molm-13 target cells. Activated human NK effector cells gave higher background killing, compared to rested human NK effector cells. With NK effector cells, TriNKETs were able to increase lysis against Molm-13 AML target cells. Similar activity of each TriNKET was observed with rested and activated human NK cells, as well as with Molm-13 target cells.

[0496] Human NK cell killing of THP-1 AML target cells, mediated by CD33-targeting TriNKETs was assayed. Activated human NK effector cells were used with THP-1 cells (FIG. 14), which resulted in higher background killing, compared to rested human NK effector cells. With NK effector cells, TriNKETs were able to increase lysis against THP-1 AML target cells. Similar activity of each TriNKET was observed with rested and activated human NK cells, as well as with THP-1 target cells.

[0497] Thus, with NK effector cells TriNKETs were able to increase lysis against Molm-13 (FIG. 13) and THP-1 (FIG. 14) AML target cells. Similar activity of each TriNKET was observed with rested and activated human NK cells, as well as with Molm-13 (FIG. 13) and THP-1 (FIG. 14) target cells.

[0498] FIG. 15A, FIG. 16, and FIG. 17A show KHYG-1 effector cell killing of Molm-13 (FIG. 15A), EOL-1 (FIG. 16), and THP-1 (FIG. 17A) human AML target cells respectively. KHYG-1 cells were demonstrated to express surface NKG2D, but do not express CD16. Therefore, TriNKET mediated killing here is dependent upon NKG2D mediated activation of the KHYG-1 effector cells. TriNKETs were able to mediate KHYG-1 effector cell killing of

all three human AML target cell lines. Similar, TriNKET activity was demonstrated on all three target cell lines.

[0499] TriNKET mediated cytotoxicity of rested human NK cells was also tested. FIG. 15B and FIG. 17B show that TriNKETs also mediated cytotoxicity of rested human NK cells against Molm-13 (FIG. 15B) and THP-1 (FIG. 17B) human AML cells. FIG. 15B shows that TriNKETs mediated rested human NK cell killing of Molm-13 human AML cells. In FIG. 15B the rested human NK effector cell (E) to target cancer cell (T) ratio (E:T) was 10:1. The E:T ratio may reflect differences in the maximal % lysis.

[0500] TriNKETs also mediated rested human NK cell killing of THP-1 target cells, which express the high-affinity FcγRI. FIG. 17B shows that TriNKETs mediated rested human NK cell killing of THP-1 human AML cells, in which the E:T was 5:1.

Example 8: Assessment of TriNKET binding to cells expressing human NKG2D

[0501] I07 mAb was identified as a monoclonal antibody with high binding affinity to CD33. The heavy and light chain amino acid sequences of I07-F405L, an Fc variant of I07, are provided below. The I07-F405L mAb included a substitution of Leu for Phe at position 405 (under EU numbering) in the Fc CH3 domain. A Lys may be optionally included at the C-terminus of the heavy chain.

I07-F405L mAb heavy chain

EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGKGLEWVATIKQDG
SEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ
GTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:199]

I07-F405L mAb light chain

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYEASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSQSYPPITFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
[SEQ ID NO:200]

[0502] A49-F3'-TriNKET-I07, a TriNKET derivative of I07 mAb, is described in Section II – Multi-specific Binding Proteins. The amino acid sequences of this TriNKET are provided in SEQ ID NOs: 187, 189, and 190.

[0503] The ability of A49-F3'-TriNKET-I07 to bind to NKG2D was assessed using EL4 cells transduced with human NKG2D (EL4-hNKG2D). Briefly, A49-F3'-TriNKET-I07 and I07-F405L mAb were serially diluted. EL4-hNKG2D cells were incubated with the diluted TriNKET or mAb solutions. Binding of the TriNKET or mAb to the EL4 cells was detected using a fluorophore-conjugated anti-human IgG secondary antibody. The cells were analyzed by flow cytometry, and fold over background values were calculated by normalizing binding MFI to the MFI of a control group in which the cells were incubated with the secondary antibody only.

[0504] As shown in FIG. 35, I07-F405L mAb showed no binding to EL4-hNKG2D cells. A49-F3'-TriNKET-I07 demonstrated weak binding to EL4-hNKG2D cells, without reaching saturation even at the high concentrations of 100 μg/mL.

Example 9: Assessment of TriNKET binding to cells expressing human CD33

[0505] The ability of A49-F3'-TriNKET-I07 to bind to CD33 was assessed using human cancer cell lines expressing CD33. Briefly, human AML cell lines Mv4-11 and Molm-13, which expressed CD33, were incubated with serially diluted A49-F3'-TriNKET-I07 and I07-F405L mAb solutions. Binding of A49-F3'-TriNKET-I07 or I07-F405L mAb to the AML cells was detected using a fluorophore-conjugated anti-human IgG secondary antibody. The cells were analyzed by flow cytometry, and fold over background values were calculated by normalizing binding MFI to the MFI of a control group in which the cells were incubated with the secondary antibody only.

[0506] As shown in FIGs. 36A and 36B, A49-F3'-TriNKET-I07 exhibited a decrease in binding potency by three to four fold compared to I07-F405L mAb on both Molm-13 and Mv4-11 cells. A49-F3'-TriNKET-I07 was also found to bind to the cells with a higher maximum fold over background compared to I07-F405L mAb.

Example 10: Assessment of TriNKET internalization

[0507] Internalization of A49-F3'-TriNKET-I07 and I07-F405L mAb upon binding to CD33 was assessed using human AML cell lines EOL-1 and Molm-13, which expressed CD33 on the cell surface. Briefly, the cells were incubated with 2 μg/mL A49-F3'-TriNKET-I07 or I07-F405L mAb for 20 minutes at room temperature. The cell samples were then split into three portions. The first and second portions were placed at 37 °C for 2 hours and 24 hours, respectively, to allow antibody internalization. Then the cells were incubated with a fluorophore-conjugated anti-human IgG secondary antibody, and were fixed for flow

cytometry analysis. The third portion of the cell samples, used to set the baseline level, was incubated with the fluorophore-conjugated anti-human IgG secondary antibody without incubation at 37 °C. The cells were fixed after staining with the secondary antibody, and were stored at 4 °C for analysis on the following day (when the first half of the samples were ready). The amount of A49-F3'-TriNKET-I07 and I07-F405L mAb bound to the cell surface was analyzed by flow cytometry on the same day. Internalization of antibodies was calculated as: % internalization = (1-(MFI of 24-hour sample / MFI of baseline sample)) × 100%.

[0508] As shown in FIGs. 37A and 37B, internalization of A49-F3'-TriNKET-I07 and I07-F405L mAb after engagement of CD33 increased overtime on EOL-1 and Molm-13 cells. In both cells, I07-F405L mAb was internalized more rapidly and to a greater extent than A49-F3'-TriNKET-I07.

Example 11: Activation of primary NK cells by TriNKET

[0509] The ability of A49-F3'-TriNKET-I07 to elicit cytotoxicity of primary NK cells against human AML cells was assessed using the DELFIA cytotoxicity assay. Briefly, PBMCs were isolated from human peripheral blood buffy coats using density gradient centrifugation. The isolated PBMCs were washed, and NK cells were isolated using a negative selection technique with magnetic beads. The purity of the isolated NK cells was typically >90% $CD3^-CD56^+$. The isolated NK cells were rested without cytokine overnight.

[0510] On the following day, human AML cell lines Molm-13, THP-1, and EOL-1 were harvested from culture. The AML cells were washed with HBS, and were resuspended in growth media at 10^6 cells/mL for labeling with BATDA reagent (Perkin Elmer AD0116) following the manufacturer instructions. After labeling, the AML cells were washed three times with HBS, and were resuspended at $0.5\text{-}1.0\times10^5$ cells/mL in culture media. 100 µl of BATDA labeled cells were added to each well of a 96-well plate.

[0511] The tested TriNKET or mAb was diluted in culture media, and 50 µl of diluted TriNKET or mAb was added to each well. Rested NK cells were harvested from culture, washed, and resuspended at $10^5\text{-}2.0\times10^6$ cells/mL in culture media to attain a desired E:T ratio of 5:1. 50 µl of NK cells were added to each well of the plate to make a total of 200 µl culture volume in each well. The plate was incubated at 37C with 5%CO_2 for 2-3 hours.

[0512] After the culturing, the plate was removed from the incubator, and the cells were pelleted by centrifugation at 200×g for 5 minutes. 20 µl of culture supernatant was transferred to a clean microplate provided from the manufacturer. Supernatant from the labeled cells

incubated alone was used to measure spontaneous release of TDA. Supernatant from labeled cells incubated with 1% Triton-X was used to measure maximum lysis of the target cells. Supernatant from the labeled cells prior to the 2-3 hours of incubation was used to measure the background and for quality control purposes.

[0513] 200 µl of room temperature europium solution was added to each well containing culture supernatant. The plate was protected from light and incubated on a plate shaker at 250 rpm for 15 minutes. Fluorescence was measured using a Victor 3 or SpectraMax i3X instrument.

[0514] The fluorescent levels represented lysis of the target cells. The values of % specific lysis were calculated as: % specific lysis = ((Experimental release – Spontaneous release) / (Maximum release – Spontaneous release)) × 100%.

[0515] A49-F3'-TriNKET-I07 and several monoclonal antibodies were tested in this assay. The monoclonal antibodies include I07-F405L mAb, I07-DE mAb, lintuzumab-GA, and 280-31-01(mut)-DE. I07-DE mAb is a variant of I07 mAb, with S239D and I332E substitutions in the Fc to enhance ADCC activity (bold-underlined in the sequence below). The amino acid sequence of I07-DE heavy chain is shown below, optionally with a Lys at the C-terminus.

I07-DE mAb heavy chain

EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWMSWVRQAPGKGLEWVATIKQDG
SEKSYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARPLNAGELDVWGQ
GTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPELLGGP**D**VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP**E**EKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
[SEQ ID NO:201]

[0516] The light chain of I07-DE mAb is identical to that of I07-F405L mAb [SEQ ID NO:200].

[0517] 280-31-01(mut)-DE is a variant of antibody clone 280-31-01 (mut) disclosed in WO2012045752, with S239D and I332E substitutions in the Fc to enhance ADCC activity (bold-underlined in the sequence below). The amino acid sequences of 280-31-01(mut)-DE heavy chain and light chain are shown below, optionally with a Lys at the C-terminus of the heavy chain.

280-31-01(mut)-DE heavy chain

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSDYAISWVRQAPGQGLEWMGRIIPILGV
ADYAQKFQGRVTITADKSTRTAYMELSSLRSEDTAVYYCARNWADAFDIWGQGTM
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP
CPAPELLGGPDVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPEEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO:202)

280-31-01(mut)-DE light chain

DIQLTQSPSSLSASVGDRVTITCRASQGISSVLAWYQQKPGKAPKLLIYDASSLESGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQFDSSITFGQGTKLEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO:203)

[0518] An SNP in the CD16 gene can result in V158 or F158 variants of the human CD16 protein. CD16 with F158 is known to have reduced binding affinity of CD16 to Fc than CD16 with V158, thereby decreasing antibody-dependent cell-mediated cytotoxicity (ADCC). NK cells having CD16-F158 are therefore less responsive to CD16 stimulation than NK cells expressing CD16-V158. Indeed, as shown in FIG. 38A, I07-F405L mAb only led to a low level of killing of Molm-13 cells by NK cells that only expressed the low affinity CD16 variant ($CD16^{F/F}$). In comparison, A49-F3'-TriNKET-I07 mediated more potent NK cell killing with a higher specific lysis of Molm-13 cells, likely due to its additional ability to engage NK cells by NKG2D binding. Similarly, when incubated with NK cells that had this SNP in one allele ($CD16^{V/F}$), A49-F3'-TriNKET-I07 exhibited stronger activity in killing EOL-1 cells than I07-F405L mAb (FIG. 38B).

[0519] 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

[0520] 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.

[0521] 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.

[0522] 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, the isolated $CD8^+$ T cells had high purity, as more than 99% of them were positive of CD3, CD8, and NKG2D expression, and were negative of CD16 expression.

[0523] 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 10^6 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 0.5×10^5 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.

[0524] $CD8^+$ effector T cells were harvested from culture, washed, and resuspended at 5×10^6 cells/mL in culture media. 50 μl of $CD8^+$ T cells were added to each well of the plate to reach an E:T ratio of 50:1 and a total of culture volume of 200 μl. The plate was incubated at 37°C with 5% CO_2 for 3.5 hours. After incubation, the cells were pelleted by centrifugation at 500×g for 5 minutes. 20 μl of culture supernatant was transferred to a clean microplate provided from the manufacturer. Supernatant from the labeled cells incubated alone was used to measure spontaneous release of TDA. Supernatant from labeled cells incubated with 1% Triton-X was used to measure maximum lysis of the target cells.

[0525] 200 μl of room temperature europium solution was added to each well. The plate was protected from light and incubated on a plate shaker at 250rpm for 15 minutes. Fluorescence was measured using a SpectraMax i3X instrument.

[0526] The fluorescent levels represented lysis of the target cells. The values of % specific lysis were calculated as: % specific lysis = ((Experimental release – Spontaneous release) / (Maximum release – Spontaneous release)) × 100%.

[0527] As shown in FIGs. 40A and 40B, A49-F3'-TriNKET-I07 enhanced the cytotoxic activity of human primary $CD8^+$ T cells in a dose-dependent manner. A49-F3'-TriNKET-H76, a protein described in Section II – Multi-specific Binding Proteins (having polypeptides comprising the sequences of SEQ ID NOs: 197, 189, and 190), was also active under the conditions but exhibited less potency than A49-F3'-TriNKET-I07. Monoclonal antibody I07-F405L and a non-target TriNKET did not show this activity.

Example 13: Binding of TriNKET to monocytes

[0528] The expression of CD33 on blood cells is assessed by flow cytometry using the method described in Example 9. Briefly, human whole blood was incubated with A49-F3'-TriNKET-I07 or human IgG1 isotype control antibody conjugated to a fluorophore. Binding of A49-F3'-TriNKET-I07 or the isotype control antibody was detected by flow cytometry. To assess the binding levels on specific types of cells, fluorophore-conjugated antibodies that bind to surface markers of NK cells, $CD8^+$ T cells, $CD4^+$ T cells, B cells, and monocytes were added to the incubation, and the presence or absence of binding of these antibodies were used for gating when analyzing the flow cytometry data.

[0529] As shown in FIGs. 41A-41E, the binding of A49-F3'-TriNKET-I07 to NK cells was weak compared to a non-target human IgG1 isotype antibody control, whereas strong binding of the TriNKET to $CD33^+$ monocytes was observed.

Example 14: Long-term NK cell cytotoxicity mediated by TriNKET

[0530] NK cells have a natural ability to sense transformed or stressed cells and kill them, but do not kill healthy cells. We tested the ability of A49-F3'-TriNKET-I07 to preserve the natural selective NK cell cytotoxicity using Molm-13 AML cells and human primary monocytes as target cells. The Molm-13 cells were obtained from DSMZ cell bank. The human primary monocytes were isolated from human peripheral blood. Briefly, PBMCs were isolated from human peripheral blood buffy coats using density gradient centrifugation. Monocytes were isolated by negative selection. CD33 expression on human primary monocytes and Molm-13 AML cells were confirmed by flow cytometry analysis (FIGs. 42A-42B).

[0531] Human primary NK cells were isolated from human peripheral blood. Briefly, PBMCs were isolated from human peripheral blood buffy coats using density gradient centrifugation. NK cells were isolated by negative selection. To distinguish target cells from NK cells in the co-culture, the target cells were fluorescently labeled. Specifically, the isolated monocytes were labeled with IncuCyte CytoLight Rapid live-cell labeling reagent according manufacturer's recommendations. The Molm-13 cells were infected with lentivirus encoding nuclear GFP, and cells with stable expression were selected with puromycin.

[0532] Isolated NK cells and target cells were mixed at an E:T ratio of 10:1 in the presence of 20 nM A49-F3'-TriNKET-I07. Non-specific activation of NK cells in the co-cultures was conducted in parallel as a positive control group for AML cell killing. The mixture was added to an Ibidi μ-slide. Time-lapse images for the phase and green channels were collected every hour, with 3 images per sample, using an IncuCyte S3 instrument. The images were analyzed using the IncuCyte S3 software. Live target cells were detected by green fluorescence, and the number of green cells at each time point was normalized to the number of green cells at time 0 from the same sample.

[0533] As shown in FIGs. 43A and 43B, Molm-13 AML cells were able to proliferation in the presence of the NK cells alone, but target cell outgrowth was substantially inhibited by A49-F3'-TriNKET-I07. By contrast, A49-F3'-TriNKET-I07 did not mediate human NK cell killing of normal monocytes in the long-term co-culture. The activity of A49-F3'-TriNKET-I07 was similar to that of PMA+ionomycin, which also preserves the natural selectivity of NK cells. These results suggest that A49-F3'-TriNKET-I07 selectively compromised cancer cells, and potentially had a wide therapeutic window.

INCORPORATION BY REFERENCE

[0534] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0535] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and the range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A protein comprising:

(a) a first antigen-binding site comprising an Fab fragment that binds NKG2D;

(b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds CD33 comprising a heavy chain variable domain and a light chain variable domain; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16, wherein the scFv is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser or Gly-Ala-Ser.

2. The protein of claim 1, wherein the scFv is linked to the antibody Fc domain.

3. The protein of claim 1 or 2, wherein the heavy chain variable domain of the scFv forms a disulfide bridge with the light chain variable domain of the scFv.

4. The protein of claim 3, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

5. The protein of any one of claims 1-4, wherein the scFv is linked to the antibody Fc domain, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv, and is linked to the heavy chain variable domain of the scFv via a flexible linker $(GlyGlyGlyGlySer)_4$ $((G4S)_4)$, and the Fab is linked to the antibody Fc domain.

6. A protein according to any one of claims 2-4, wherein the heavy chain variable domain of the scFv is linked to the light chain variable domain of the scFv via a flexible linker.

7. The protein of claim 6, wherein the flexible linker comprises $(GlyGlyGlyGlySer)_4$ $((G4S)_4)$.

8. A protein according to any one of claims 2-4 or 6-7, wherein the heavy chain variable domain of the scFv is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv.

9. The protein of claim 8, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv.

10. A protein according to any one of claims 1 to 9, wherein the Fab fragment is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16 or the third antigen-binding site that binds CD16.

11. The protein of claim 10, wherein the heavy chain portion of the Fab fragment comprises a heavy chain variable domain and a CH1 domain, and wherein the heavy chain variable domain is linked to the CH1 domain.

12. A protein according to claim 10 or 11, wherein the Fab fragment is linked to the antibody Fc domain.

13. The protein according any one of claims 1-12, wherein the first antigen-binding site that binds NKG2D comprises:

(1) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 193, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(2) a heavy chain variable domain comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity-determining region 3 (CDR3) sequences represented by the amino acid sequences of SEQ ID NOs:93, 94, and 95, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:96, 97, and 98, respectively;

(3) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:99, 100, and 101, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:102, 103, and 104, respectively;

(4) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:105, 106, and 107, respectively;

and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:108, 109, and 110, respectively;

(5) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 195, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(6) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:117, 118, and 119, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:120, 121, and 122, respectively;

(7) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 588, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(8) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 591, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(9) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 594, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(10) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 597, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively; or

(11) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 123, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively.

14. The protein according any one of claims 1-13, wherein the first antigen-binding site that binds NKG2D comprises:

(1) a heavy chain variable domain comprising an amino acid sequence at least 90%

identical to SEQ ID NO:87 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(2) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:81 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:82;

(3) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:83 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:84;

(4) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:85 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:86;

(5) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:191 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(6) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:89 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:90;

(7) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:586 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(8) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:589 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(9) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:592 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(10) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:595 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88; or

(11) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:91 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88.

15. The protein according any one of claims 1-14, wherein the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising heavy chain CDR1 (CDRH1), heavy chain CDR2 (CDRH2), and heavy chain CDR3 (CDRH3), and a light chain variable domain comprising light chain CDR1 (CDRL1), light chain CDR2 (CDRL2), and light chain CDR3 (CDRL3), wherein the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 are set forth in SEQ ID NOs: 181, 46, 182, 48, 49, and 50; 434, 22, 435, 24, 25, and 26; 181, 28, 436, 30, 31, and 32; 183, 34, 184, 36, 185, and 38; 437, 40, 438, 42, 43, and 44; 181, 52, 439, 54, 55, and 56; 440, 58, 441, 60, 61, and 62; 442, 64, 443, 66, 67, and 68; 181, 70, 444, 72, 73, and 74; 445, 76, 446, 78, 79, and 80; 304, 305, 306, 307, 308, and 309; 310, 311, 312, 313, 314, and 315; 316, 317, 318, 319, 320, and 321; 322, 323, 324, 325, 326, and 327; 328, 329, 330, 331, 332, and 333; 334, 335, 336, 337, 338, and 339; 340, 341, 342, 343, 344, and 345; 346, 347, 348, 349, 350, and 351; 352, 353, 354, 355, 356, and 357; 358, 359, 360, 361, 362, and 363; 364, 365, 366, 367, 368, and 369; 370, 371, 372, 373, 374, and 375; 376, 377, 378, 379, 380, and 381; 382, 383, 384, 385, 386, and 387; 388, 389, 390, 391, 392, and 393; 394, 395, 396, 397, 398, and 399; 400, 401, 402, 403, 404, and 405; 406, 407, 408, 409, 410, and 411; 412, 413, 414, 415, 416, and 417; 422, 423, 424, 425, 426, and 427; or 428, 429, 430, 431, 432, and 433, respectively.

16. The protein according any one of claims 1-15, wherein the second antigen-binding site that binds CD33 comprises:

(a) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:9 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:10;

(b) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:1 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:2;

(c) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:3 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:4;

(d) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:5 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:6;

(e) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:7 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:8;

(f) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:11 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:12;

(g) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:13 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:14;

(h) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:15 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:16;

(i) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:17 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:18;

(j) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:19 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:20;

(k) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:266 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:267;

(l) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:268 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:269;

(m) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:270 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:271;

(n) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:272 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:273;

(o) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:274 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:275;

(p) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:276 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:277;

(q) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:278 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:279;

(r) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:280 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:281;

(s) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:282 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:283;

(t) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:284 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:285;

(u) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:286 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:287;

(v) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:288 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:289;

(w) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:290 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:291;

(x) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:292 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:293;

(y) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:294 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:295;

(z) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:296 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:297;

(aa) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:298 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:299;

(bb) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:300 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:301;

(cc) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:302 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:303;

(dd) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:418 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:419; or

(ee) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:420 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:421.

17. A protein according to any one of claims 1 to 16 comprising a sequence selected from SEQ ID NOs:188, 198, 206-223, and 447-488.

18. A protein according to any one of claims 2-16 comprising an scFv linked to an antibody Fc domain, wherein the scFv linked to the antibody Fc domain is represented by a sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243.

19. A protein according to any one of claims 2-16 comprising a sequence selected from SEQ ID NO:189, SEQ ID NO:196, SEQ ID NO:244, and SEQ ID NO:245.

20. A protein according to any one of claims 2-16 comprising a sequence at least 90% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, 206-223, and 447-488.

21. A protein according to any one of claims 2-16 comprising a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, 206-223, and 447-488.

22. A protein according to any one of claims 2-16 comprising a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NOs:188, 198, 206-223, and 447-488.

23. A protein according to any one of claims 2-16 comprising a sequence at least 90% identical to an amino acid sequence selected from SEQ ID NO:187,SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243.

24. A protein according to any one of claims 2-16 comprising a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243.

25. A protein according to any one of claims 2-16 comprising a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:187, SEQ ID NO:197, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, and SEQ ID NO:243.

26. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds CD33, comprising a heavy chain variable domain comprising an amino acid sequence at least 90% identical to a heavy chain variable domain listed in Table 1, and a light chain variable domain comprising an amino acid sequence at least 90% identical to a light chain variable domain listed in Table 1; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

27. The protein according to claim 26, wherein the first antigen-binding site that binds NKG2D comprises:

(1) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 193, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(2) a heavy chain variable domain comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity-determining region 3 (CDR3) sequences represented by the amino acid sequences of SEQ ID NOs:93, 94, and 95, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:96, 97, and 98, respectively;

(3) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:99, 100, and 101, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:102, 103, and 104, respectively;

(4) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:105, 106, and 107, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:108, 109, and 110, respectively;

(5) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 195, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(6) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:117, 118, and 119, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:120, 121, and 122, respectively;

(7) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 588, respectively;

and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(8) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 591, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(9) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 594, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively;

(10) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 597, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively; or

(11) a heavy chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:192, 112, and 123, respectively; and a light chain variable domain comprising CDR1, CDR2, and CDR3 sequences represented by the amino acid sequences of SEQ ID NOs:114, 115, and 116, respectively.

28. The protein according to any one of claims 26-27, wherein the first antigen-binding site that binds NKG2D comprises:

(1) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:87 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(2) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:81 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:82;

(3) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:83 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:84;

(4) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:85 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:86;

(5) a heavy chain variable domain comprising an amino acid sequence at least 90%

identical to SEQ ID NO:191 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(6) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:89 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:90;

(7) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:586 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(8) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:589 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(9) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:592 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88;

(10) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:595 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88; or

(11) a heavy chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:91 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:88.

29. The protein according to any one of claims 26-28, wherein the second antigen-binding site that binds CD33 comprises a heavy chain variable domain comprising heavy chain CDR1 (CDRH1), heavy chain CDR2 (CDRH2), and heavy chain CDR3 (CDRH3), and a light chain variable domain comprising light chain CDR1 (CDRL1), light chain CDR2 (CDRL2), and light chain CDR3 (CDRL3), wherein the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 are set forth in SEQ ID NOs: 181, 46, 182, 48, 49, and 50; 434, 22, 435, 24, 25, and 26; 181, 28, 436, 30, 31, and 32; 183, 34, 184, 36, 185, and 38; 437, 40, 438, 42, 43, and 44; 181, 52, 439, 54, 55, and 56; 440, 58, 441, 60, 61, and 62; 442, 64, 443, 66, 67, and 68; 181, 70, 444, 72, 73, and 74; 445, 76, 446, 78, 79, and 80; 304, 305, 306, 307, 308, and 309; 310, 311, 312, 313, 314, and 315; 316, 317, 318, 319, 320, and 321; 322, 323, 324, 325, 326, and 327; 328, 329, 330, 331, 332, and 333; 334, 335, 336, 337, 338, and 339; 340, 341, 342, 343, 344, and 345; 346, 347, 348, 349, 350, and 351; 352, 353, 354, 355, 356, and 357; 358, 359, 360, 361, 362, and 363; 364, 365, 366, 367, 368, and 369;

370, 371, 372, 373, 374, and 375; 376, 377, 378, 379, 380, and 381; 382, 383, 384, 385, 386, and 387; 388, 389, 390, 391, 392, and 393; 394, 395, 396, 397, 398, and 399; 400, 401, 402, 403, 404, and 405; 406, 407, 408, 409, 410, and 411; 412, 413, 414, 415, 416, and 417; 422, 423, 424, 425, 426, and 427; or 428, 429, 430, 431, 432, and 433, respectively.

30. A protein according to any one of claims 27-29, wherein the heavy chain variable domain and the light chain variable domain are present on the same polypeptide.

31. The protein according to any one of claims 27-30, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.

32. A protein according to any one of claims 1-31, wherein the protein binds to NKG2D with a K_D of 10 nM or weaker affinity, optionally wherein the K_D is measured by Biacore surface plasmon resonance (SPR) analysis.

33. A formulation comprising a protein of any one of claims 1-32, and a pharmaceutically acceptable carrier.

34. A method of treating a CD33-expressing cancer, the method comprising administering an effective amount of the protein according to any one of claims 1-32 or the formulation according to claim 33 to a subject in need thereof.

35. The method of claim 34, 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.

36. The method of claim 35, 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).

37. The method of claim 35 or 36, wherein the AML is characterized by expression of CLL-1 on the AML leukemia stem cells (LSCs).

38. The method of claim 37, wherein the LSCs further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96.

39. The method of any one of claims 35-37, wherein the AML is a minimal residual disease (MRD).

40. The method of claim 39, 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)).

41. The method of claim 35, 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).

42. The method of claim 35 or 41, wherein the MDS is a primary MDS or a secondary MDS.

43. The method of claim 35, wherein the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL).

44. The method of claim 35, wherein the MPN is selected from polycythaemia vera, essential thrombocythemia (ET), and myelofibrosis.

45. The method of claim 35, wherein the non-Hodgkin lymphoma is selected from B-cell lymphoma and T-cell lymphoma.

46. The method of claim 35, 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.

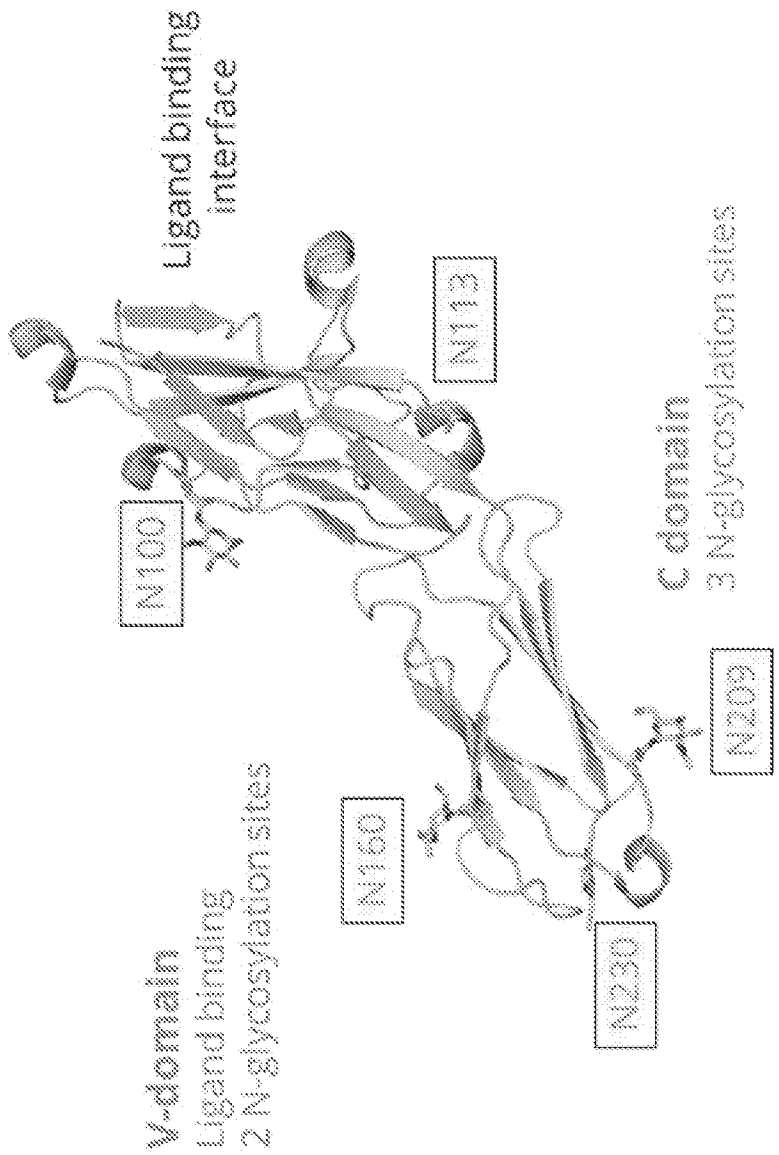

Ligand binding
interface
N100
N113
V-domain
Ligand binding
2 N-glycosylation sites
N160
C domain
3 N-glycosylation sites
N209
N230

FIG. 1

Features:
Query 1 DFNFWLQQESVTVQEGLCVLVPCTFFHPIPYYDKNSPVHGYWFREGAITSRD 70
Sbjct 1 D# L+VQESVTVQEGLCVLVPCTFFHP+PY+ +NSPVHGYWFREGAI+S D 89
Sbjct 1 DMRVRLEVQESVTVQEGLCVLVPCTFFHPVPYYHTRNSPVHGYWFREGAIVSLD
Query 71 SPVATMKLQQEVQEETQGRFRLLGDPSRMNCSLSIVDARRRDNGSYFFRMERGSTKYSYK 130
Sbjct 90 SPVATMKLQQEVQEETQGRFRLLGDPSRMNCSLSIVDARRRDNGSYFFRMERGSTKYSYK 149
Query 131 APDLSVHVTDLTHRPKILIPGTLEPGHSKNLTCSVSWACEQGTPPIFSWTAAPTSLGPR 190
Sbjct 150 APNLSVHVTDLTHRPRILIPGALDPDHSKNLTCSVPWACEQGTPPIFSWMAAPTSLGLR 209
Query 191 TTHSSVLIITPRPQDHGTNLTCQVKFPGAGVTTERTIQLNVTYVPQNPTTGIFPDDGSGK 250
Sbjct 210 TTHSSVLIITPRPQDHGTNLTCQVKFPGAGVTTERTIQLNVSYASQNPRTDIFLDDGSGK 269
Query 251 QETRAGVHGAIGGAGVTALLALCLCLIFFIVKTHRRKAARTAVGRNDTHPTTGSASPKH 310
Sbjct 270 Q---EVVQGAIGGAGVTVLLALCLCLIFFTVKTHRRKAARTAVGRIDTHPATGPTSSKH 325
Query 311 QKKSKLHGPTETSSCSGAAPTVEMDEELHYASLNFHGMNPSKDTSTEYSEVRTQ (SEQ ID NO:598)
Sbjct 326 QKKSKLHG TETS CSG TVEMDEELHYASLNFHGMNPS+DTSTEYSEVRTQ
Sbjct 326 QKKSKLHGATETSGCSGTTLTVEMDEELHYASLNFHGMNPSEDTSTEYSEVRTQ (SEQ ID NO:599)

FIG. 2

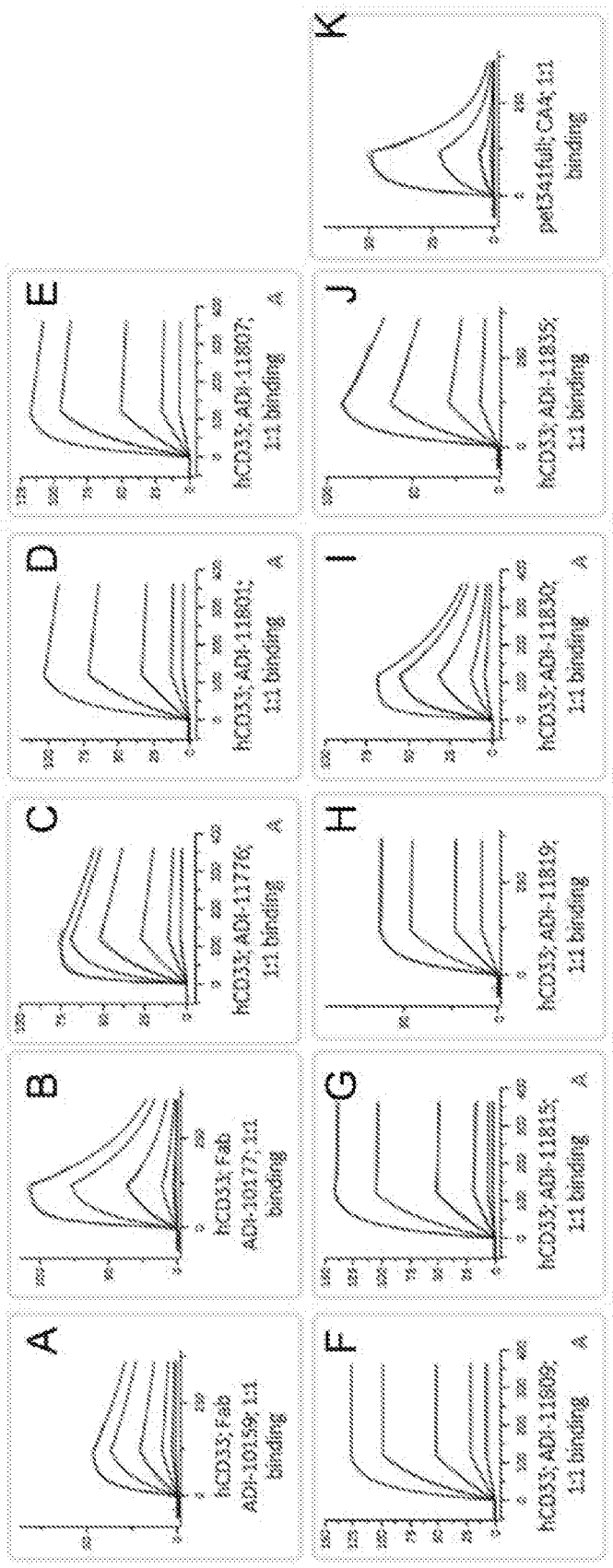

A
hCD33; Fab
ADI-101139; 1:1 binding
B
hCD33; Fab
ADI-101177; 1:1 binding
C
hCD33; ADI-11776; 1:1 binding
D
hCD33; ADI-11801; 1:1 binding
E
hCD33; ADI-11807; 1:1 binding
F
hCD33; ADI-11809; 1:1 binding
G
hCD33; ADI-11815; 1:1 binding
H
hCD33; ADI-11819; 1:1 binding
I
hCD33; ADI-11830; 1:1 binding
J
hCD33; ADI-11835; 1:1 binding
K
pdB41fab; CA4; 1:1 binding

FIG. 3

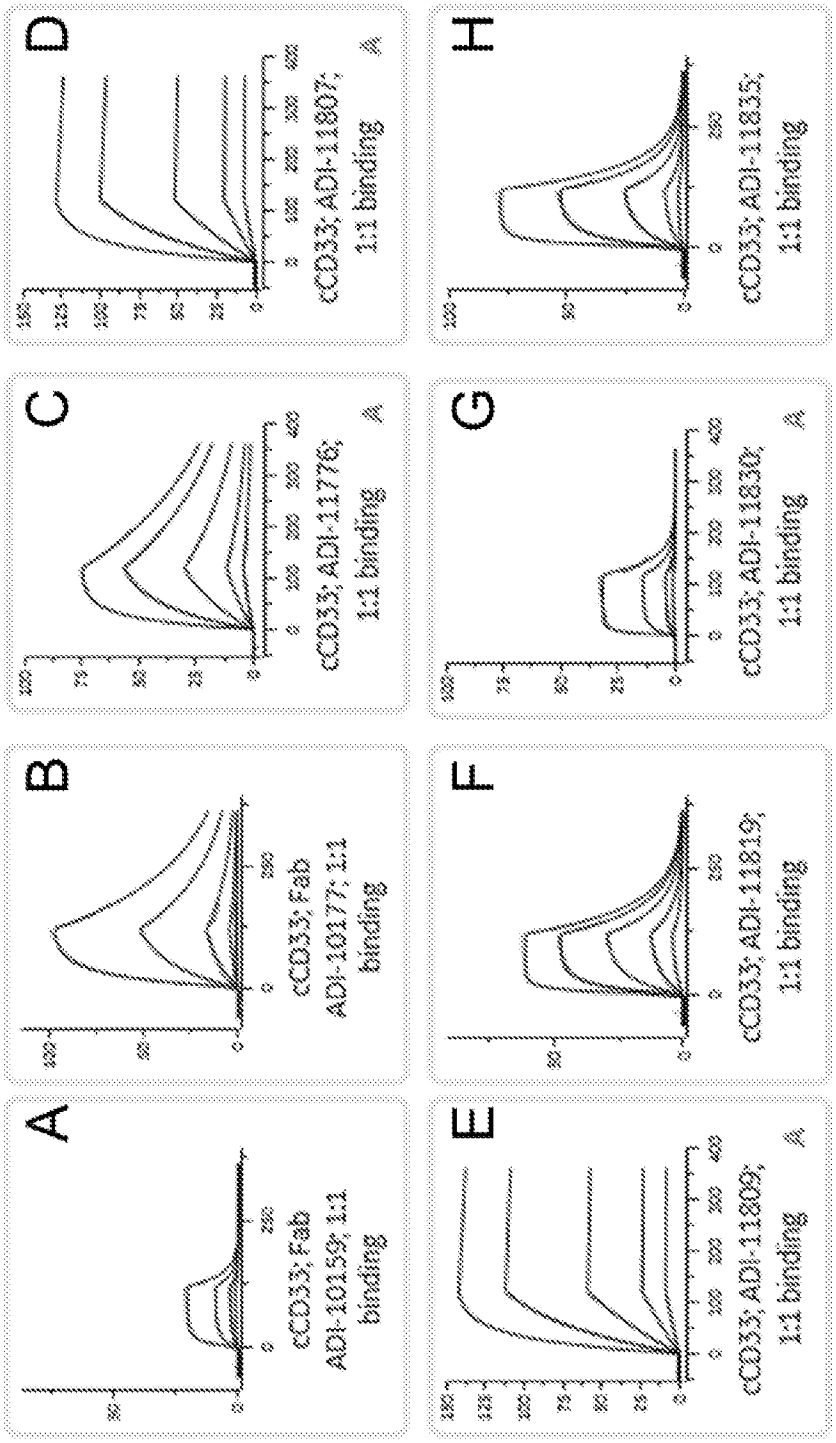

A
cCD33; Fab
ADI-10159; 1:1
binding
B
cCD33; Fab
ADI-10177; 1:1
binding
C
cCD33; ADI-11776;
1:1 binding
D
cCD33; ADI-11807;
1:1 binding
E
cCD33; ADI-11809;
1:1 binding
F
cCD33; ADI-11819;
1:1 binding
G
cCD33; ADI-11830;
1:1 binding
H
cCD33; ADI-11835;
1:1 binding

FIG. 4

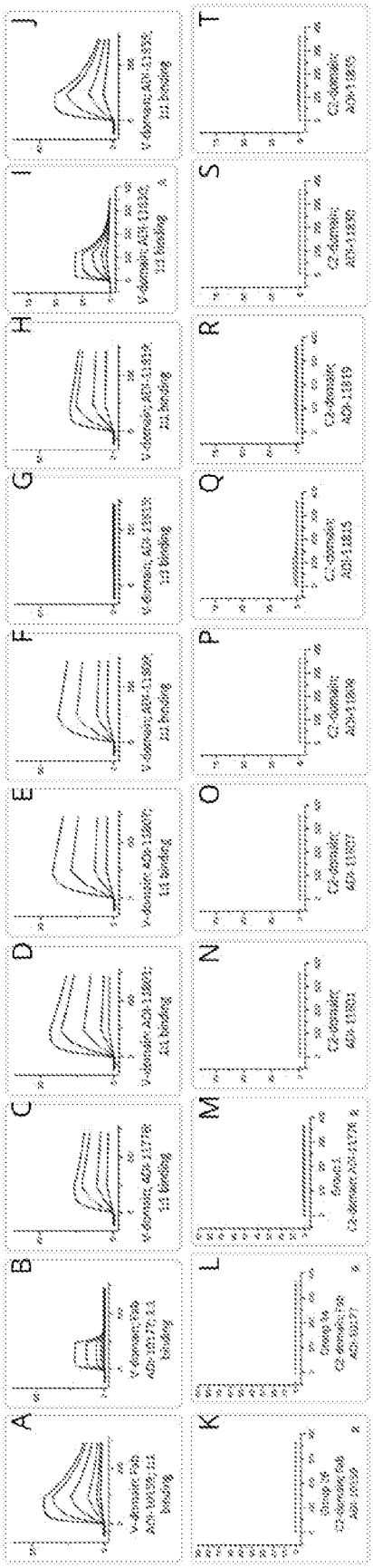


FIG. 5

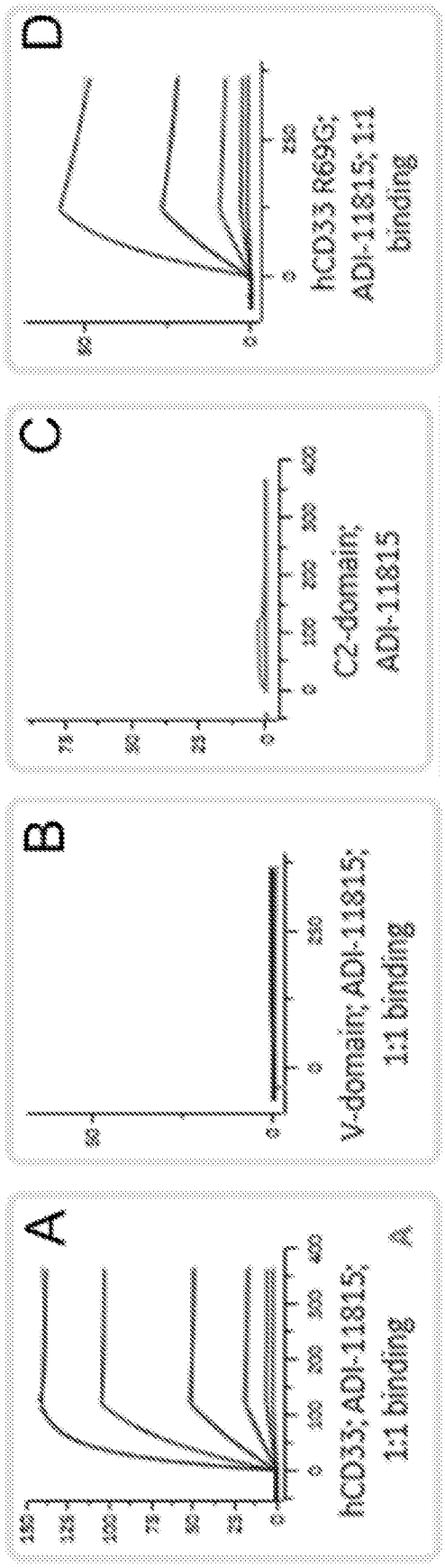

A
hCD33; ADI-11815;
1:1 binding
B
V-domain; ADI-11815;
1:1 binding
C
C2-domain;
ADI-11815
D
hCD33 R69G;
ADI-11815; 1:1
binding

FIG. 6

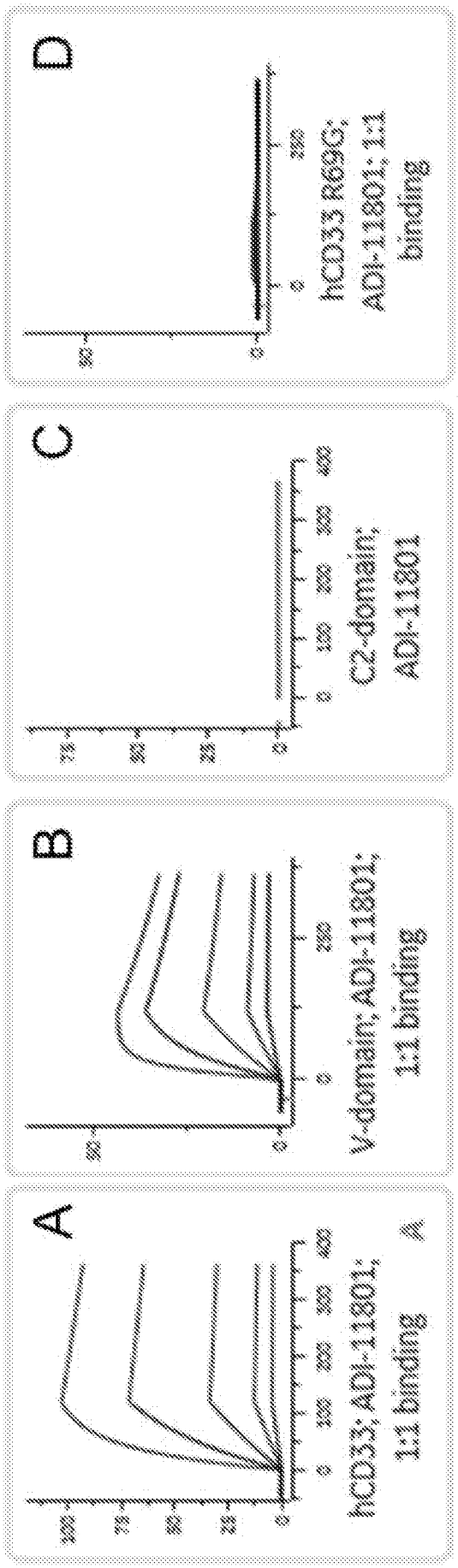

A
hCD33; ADI-11801;
1:1 binding
B
V-domain; ADI-11801;
1:1 binding
C
C2-domain;
ADI-11801
D
hCD33 R69G;
ADI-11801; 1:1
binding

FIG. 7

FIG. 8

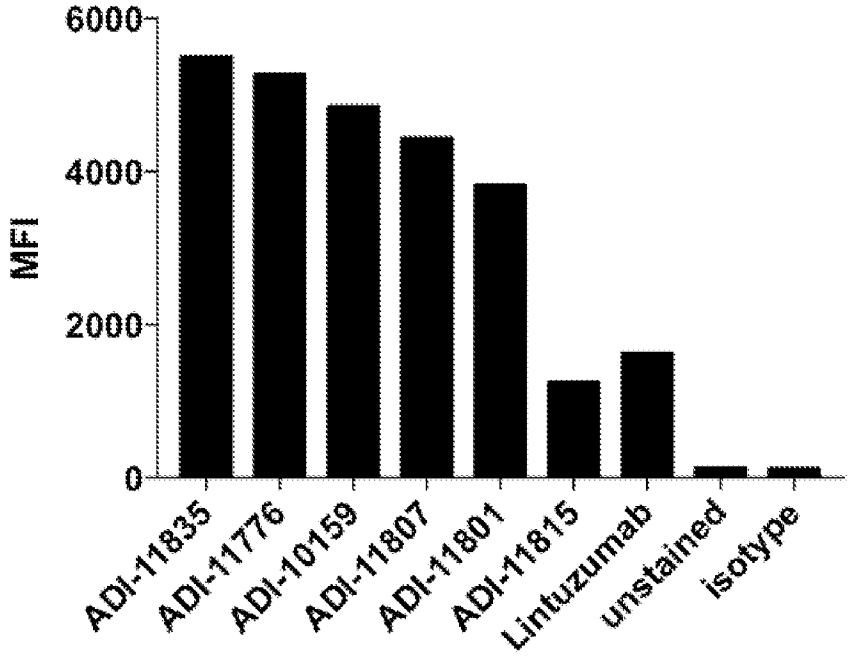

6000
4000
2000
0
MFI
ADI-11835
ADI-11776
ADI-10159
ADI-11807
ADI-11801
ADI-11815
Lintuzumab
unstained
isotype

FIG. 9

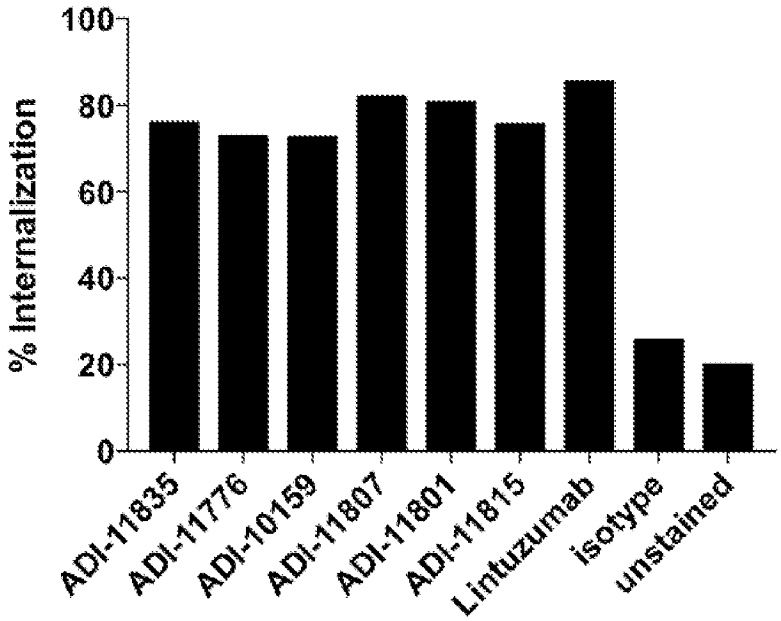

100
80
60
40
20
0
% Internalization
ADI-11835
ADI-11776
ADI-10159
ADI-11807
ADI-11801
ADI-11815
Lintuzumab
isotype
unstained

FIG. 10A

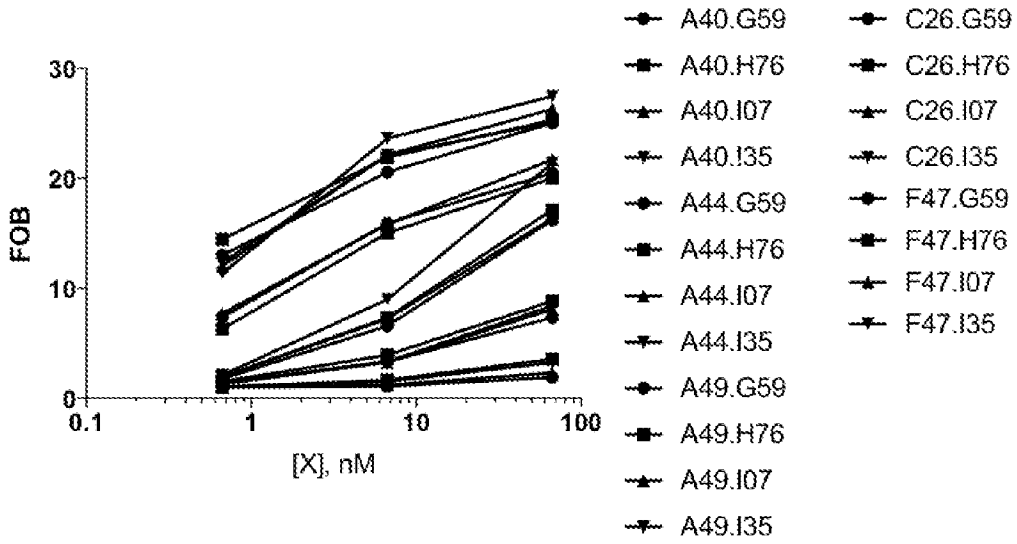


FIG. 10B

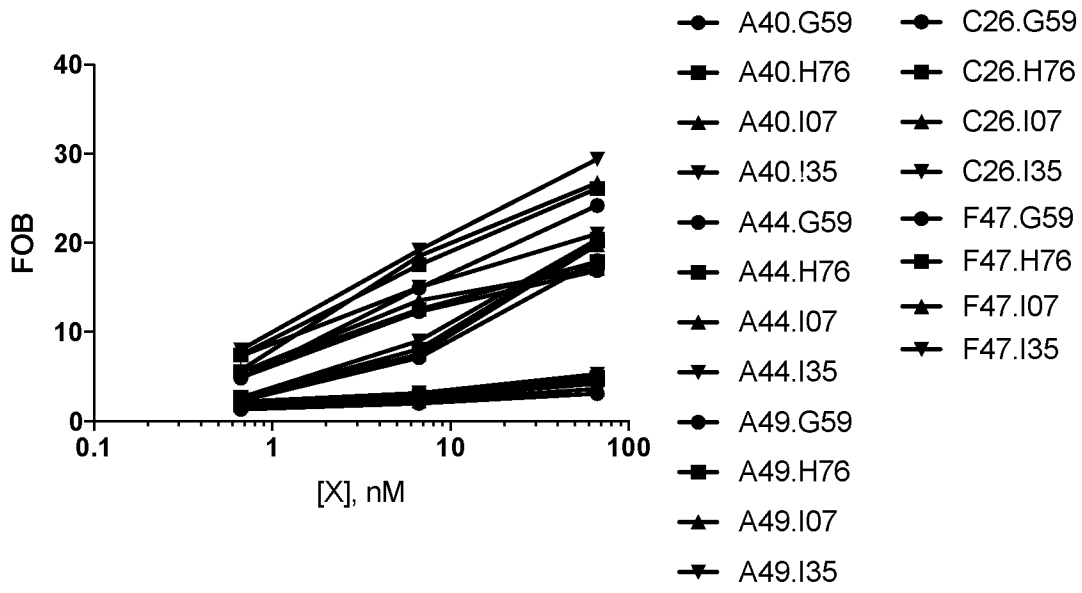


FIG. 11

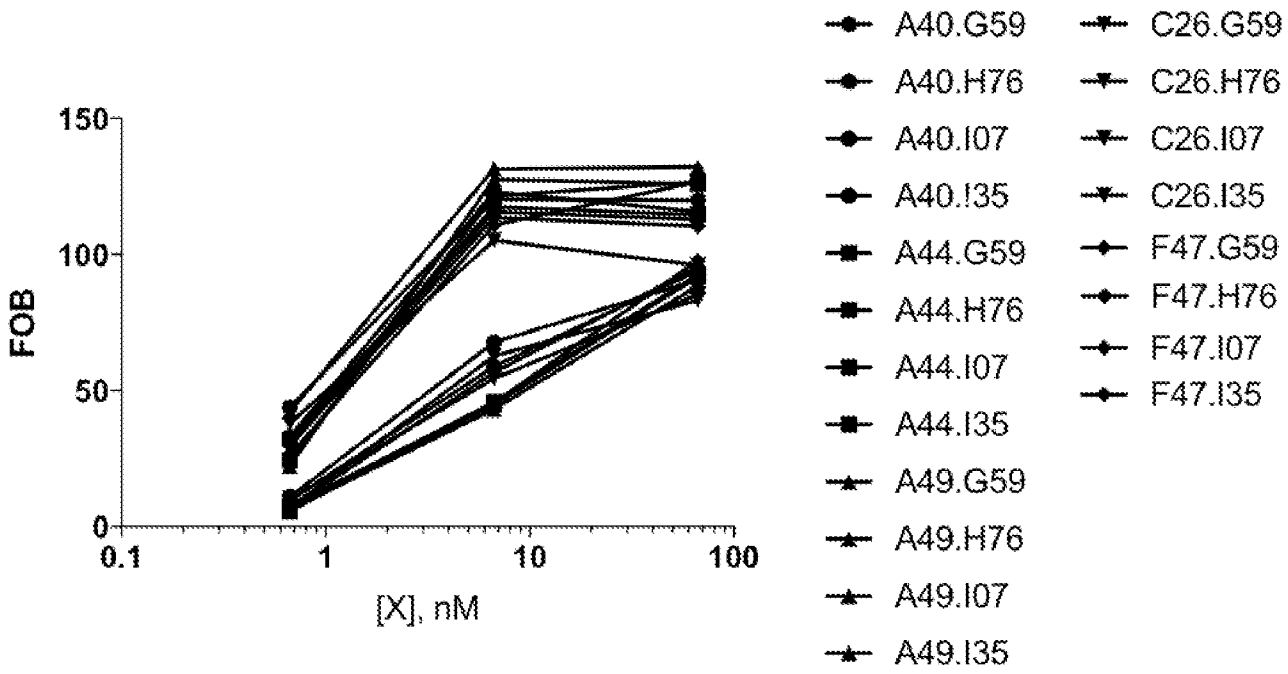

150
100
50
0
FOB
0.1
1
10
100
[X], nM
A40.G59
A40.H76
A40.I07
A40.I35
A44.G59
A44.H76
A44.I07
A44.I35
A49.G59
A49.H76
A49.I07
A49.I35
C26.G59
C26.H76
C26.I07
C26.I35
F47.G59
F47.H76
F47.I07
F47.I35

Fig. 12

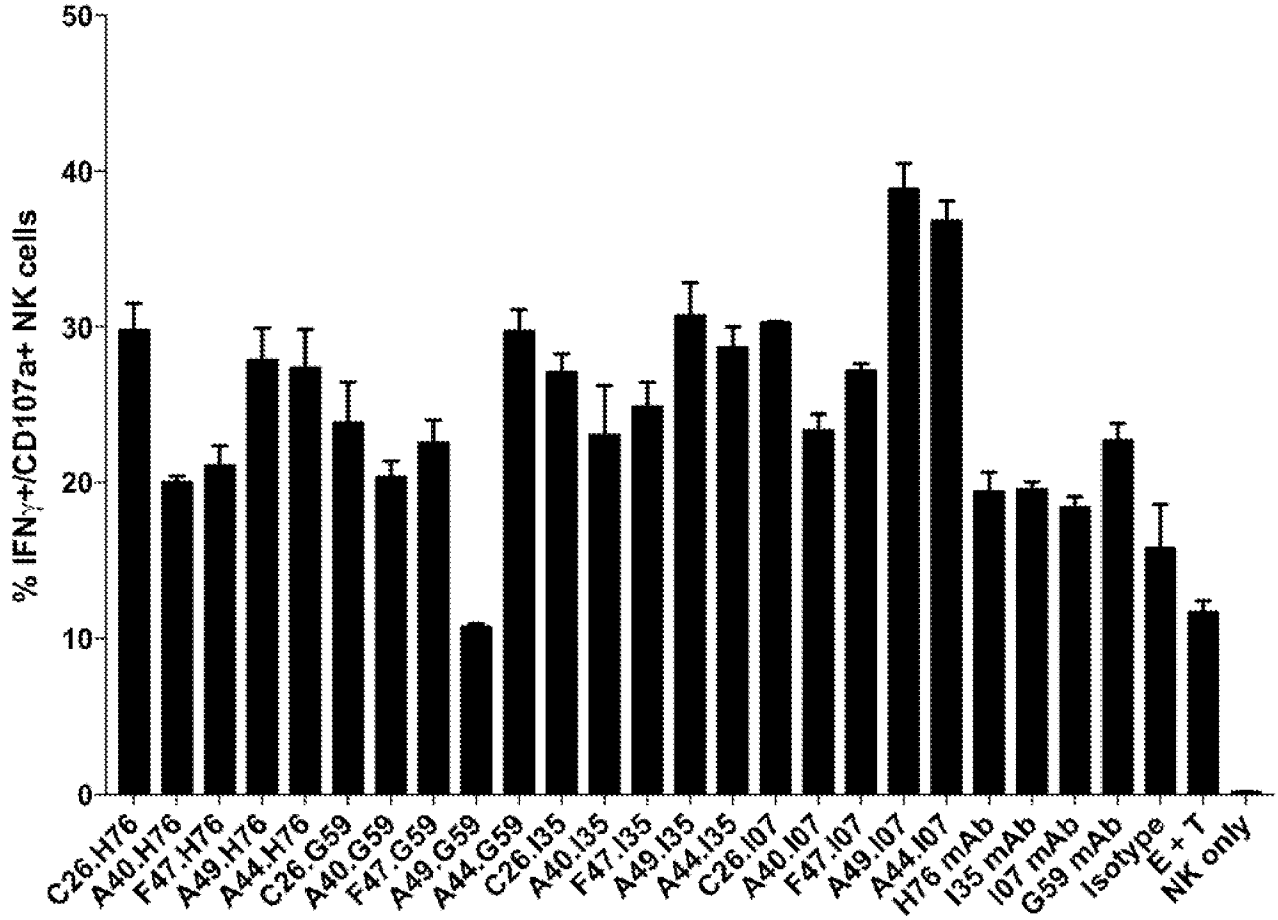

% IFNγ+/CD107a+ NK cells
50
40
30
20
10
0
C26.H76
A40.H76
F47.H76
A49.H76
A44.H76
C26.G59
A40.G59
F47.G59
A49.G59
A44.G59
C26.I35
A40.I35
F47.I35
A49.I35
A44.I35
C26.I07
A40.I07
F47.I07
A49.I07
A44.I07
H76 mAb
I35 mAb
I07 mAb
G59 mAb
Isotype
E + T
NK only

FIG. 13

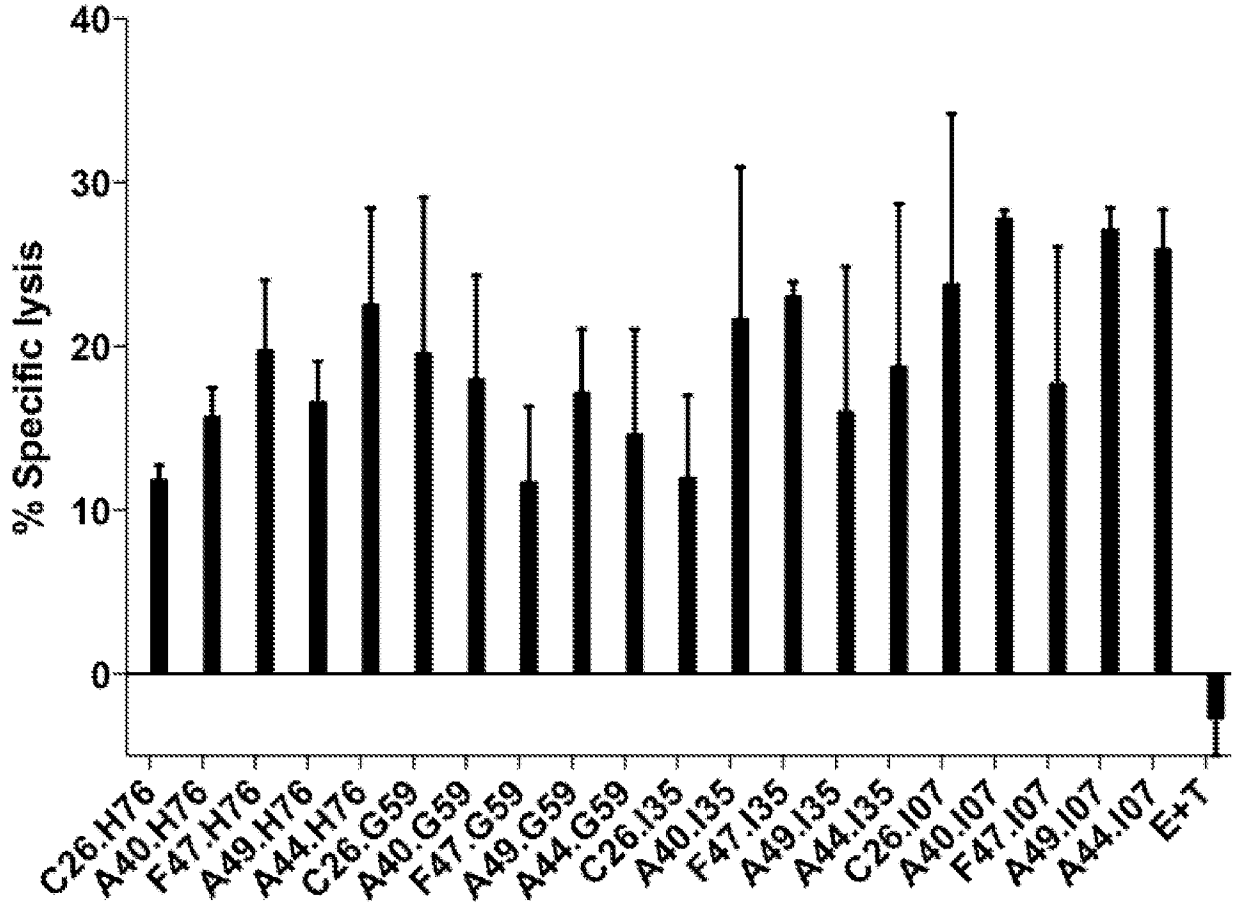

% Specific lysis
40
30
20
10
0
C26.H76
A40.H76
F47.H76
A49.H76
A44.H76
C26.G59
A40.G59
F47.G59
A49.G59
A44.G59
C26.I35
A40.I35
F47.I35
A49.I35
A44.I35
C26.I07
A40.I07
F47.I07
A49.I07
A44.I07
E+T

FIG. 14

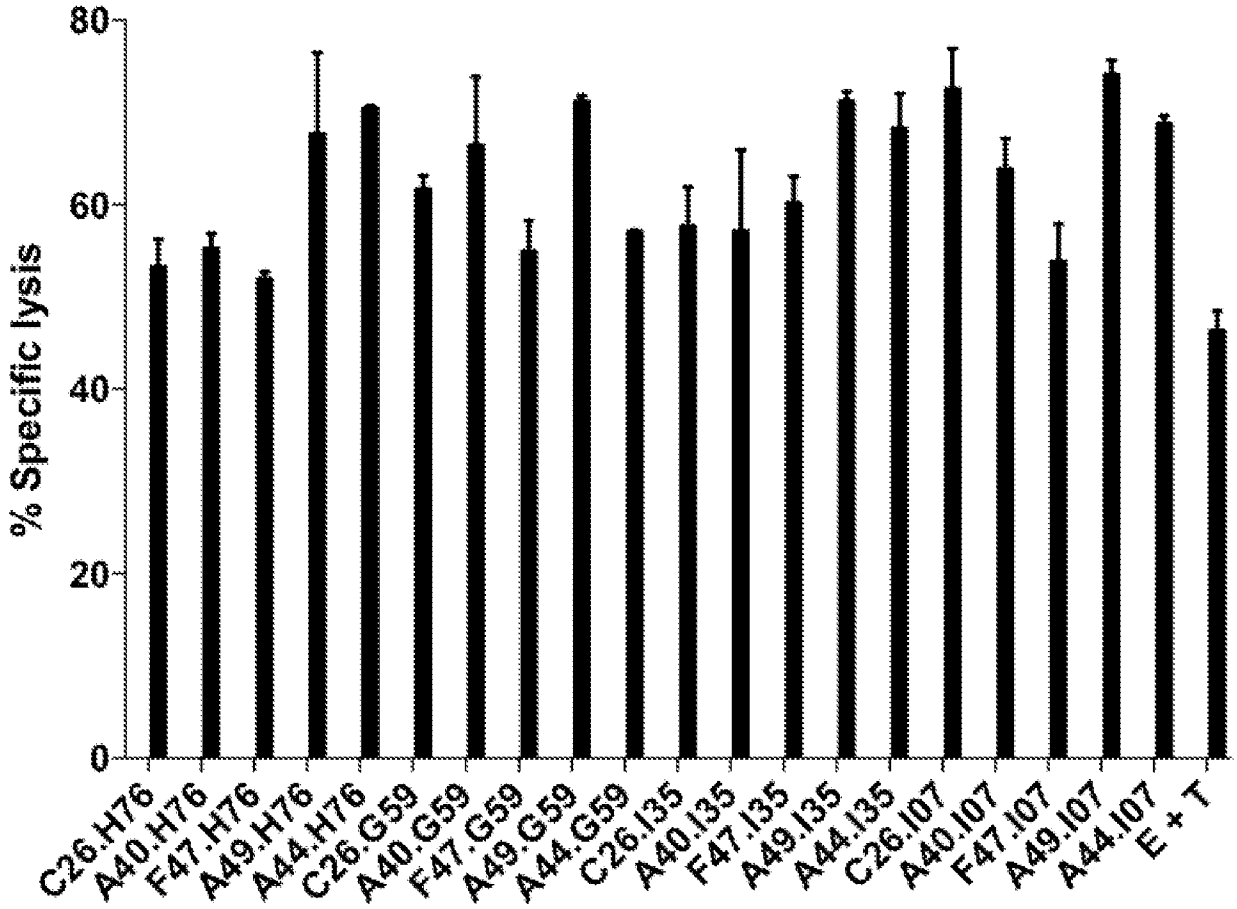

% Specific lysis
80
60
40
20
0
C26.H76
A40.H76
F47.H76
A49.H76
A44.H76
C26.G59
A40.G59
F47.G59
A49.G59
A44.G59
C26.I35
A40.I35
F47.I35
A49.I35
A44.I35
C26.I07
A40.I07
F47.I07
A49.I07
A44.I07
E + T

FIG. 15A

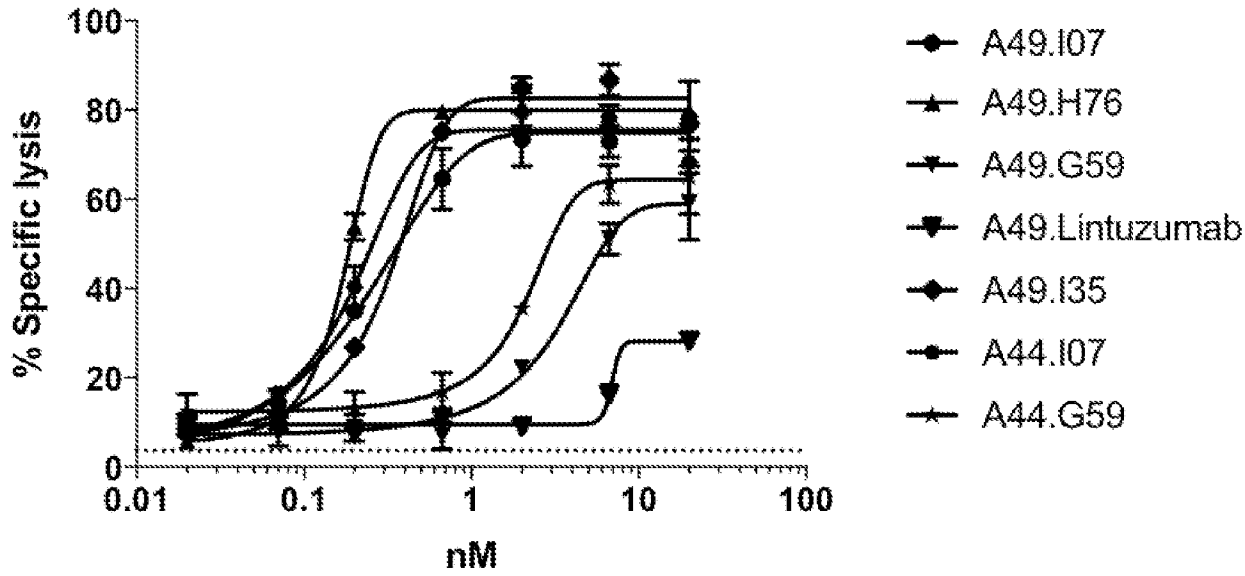


FIG. 15B

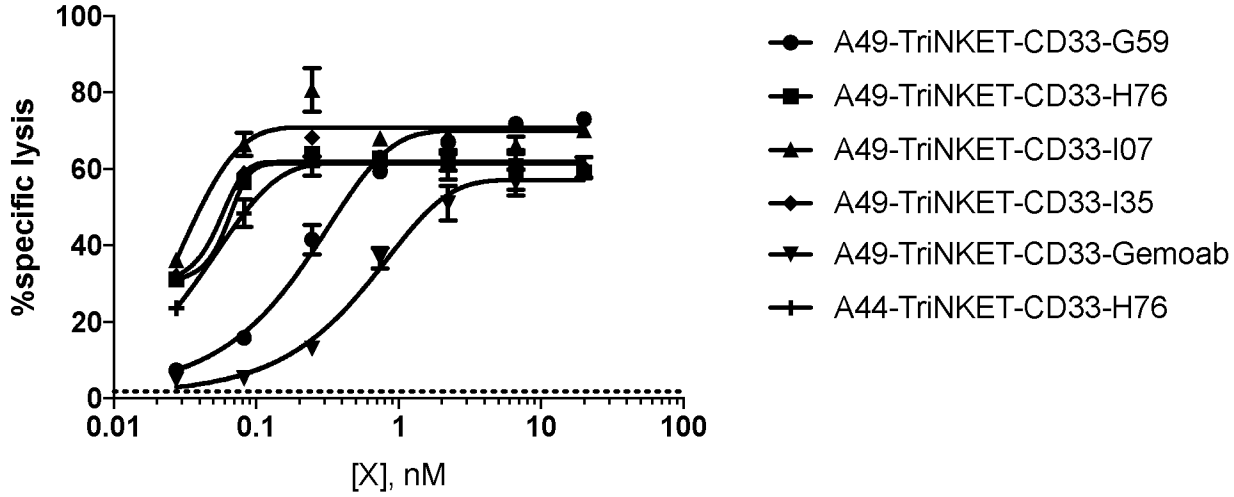


FIG. 16

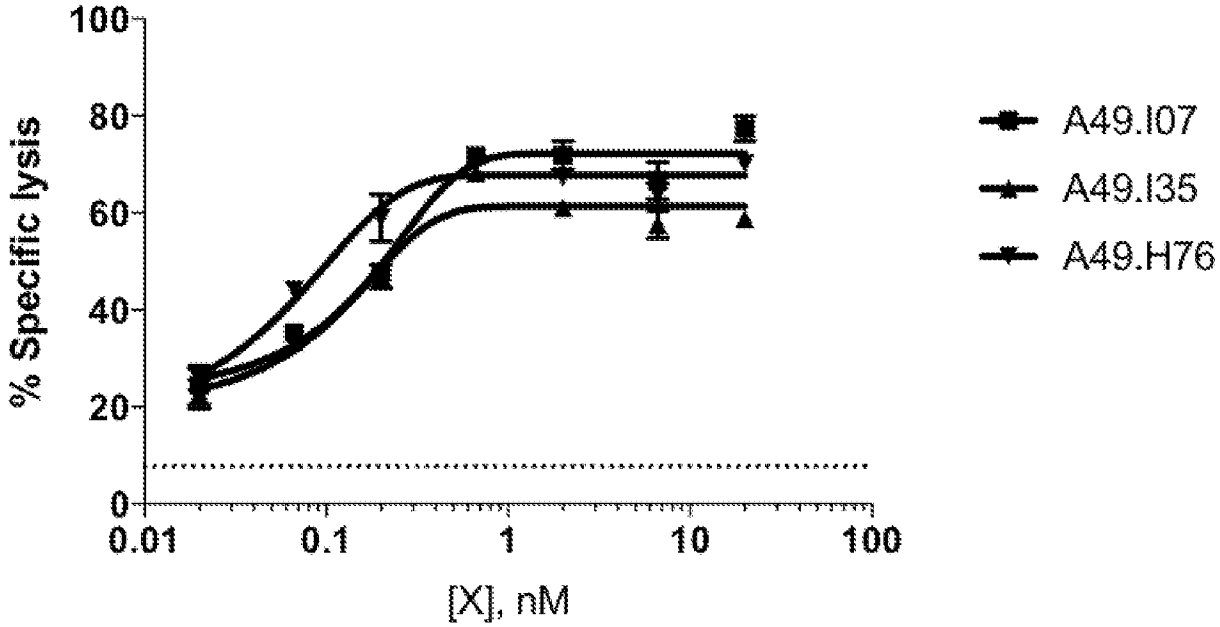

100
80
60
40
20
0
% Specific lysis
0.01
0.1
1
10
100
[X], nM
A49.I07
A49.I35
A49.H76

FIG. 17A

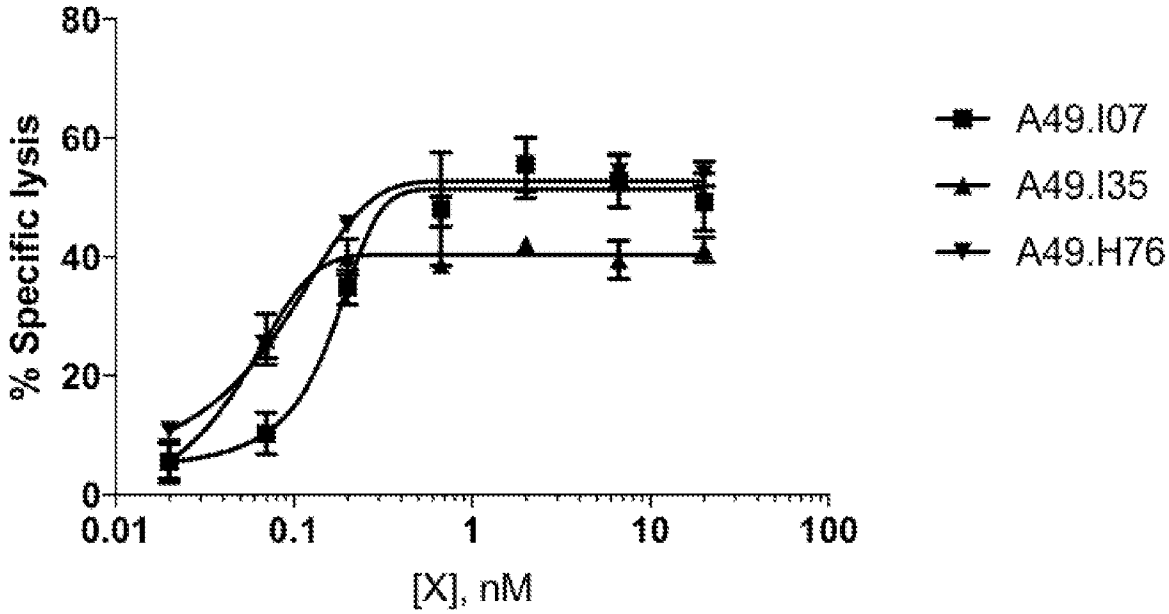


FIG. 17B

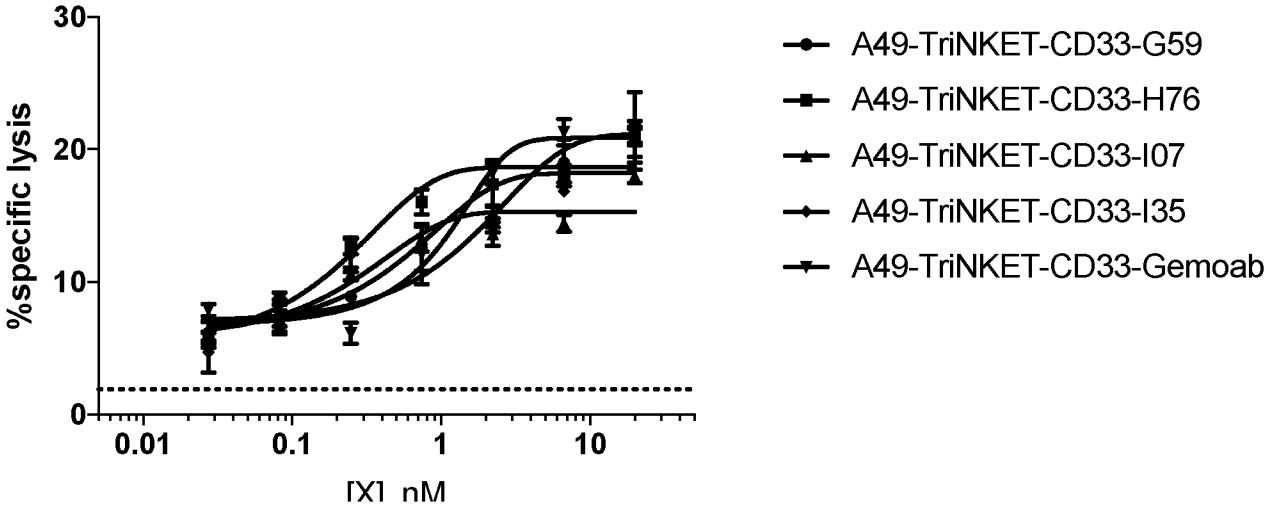


FIG. 18

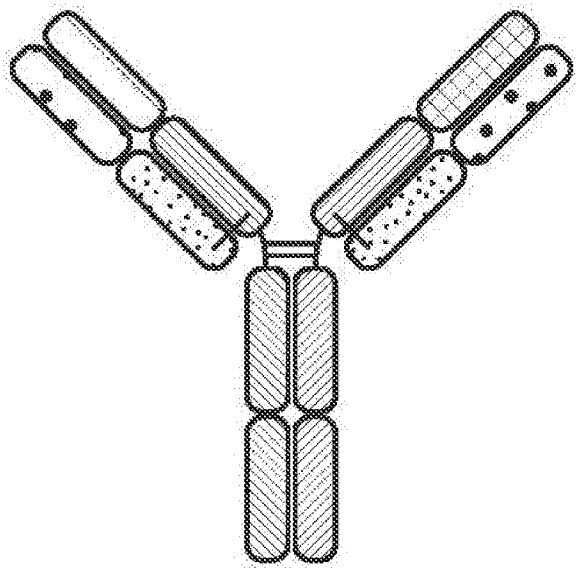


FIG. 19

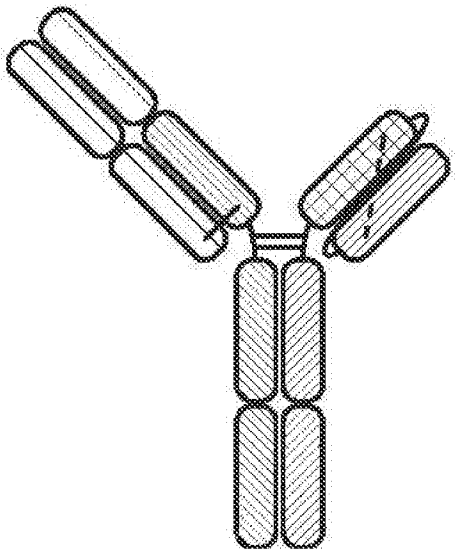


FIG. 20

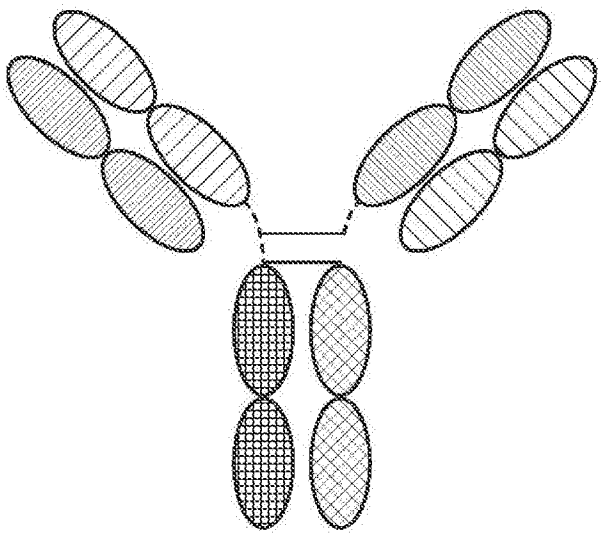


FIG. 21

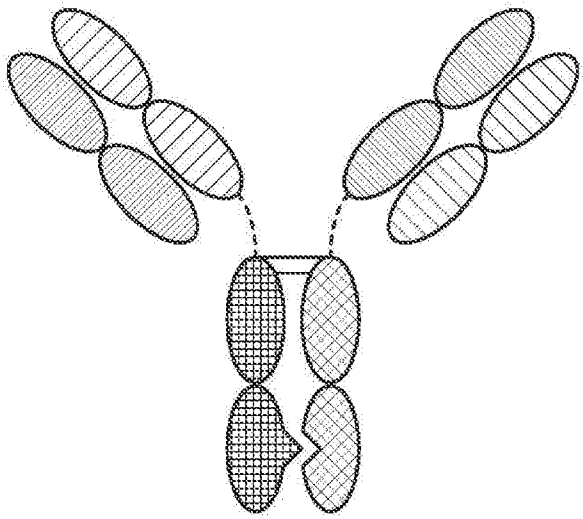


FIG. 22

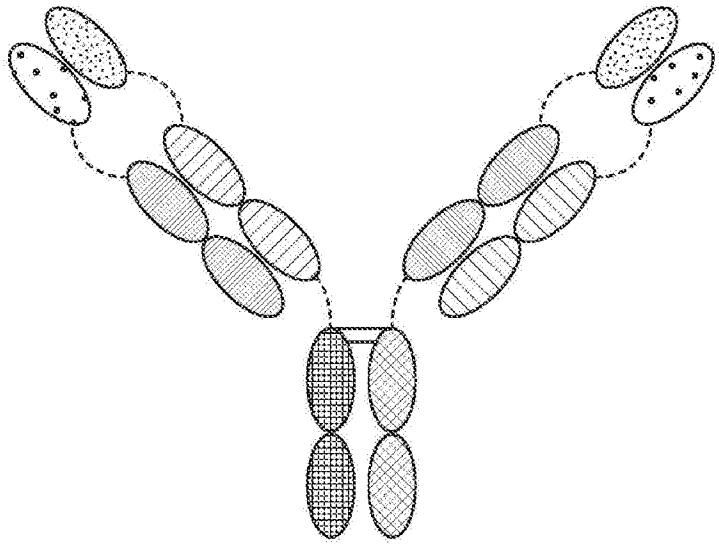


FIG. 23

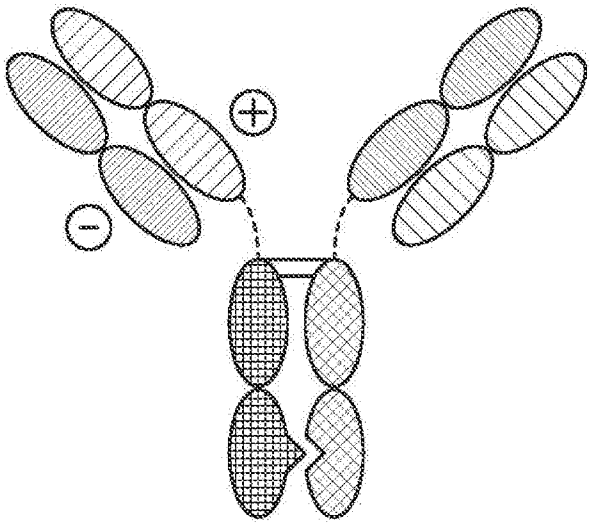


FIG. 24

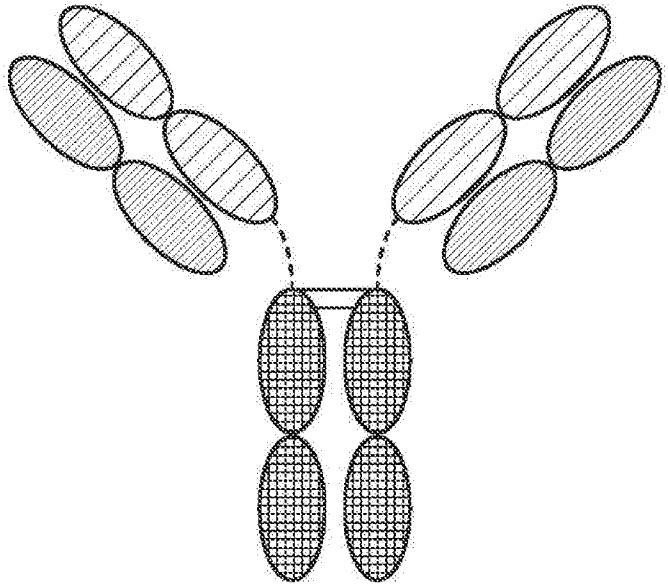


FIG. 25

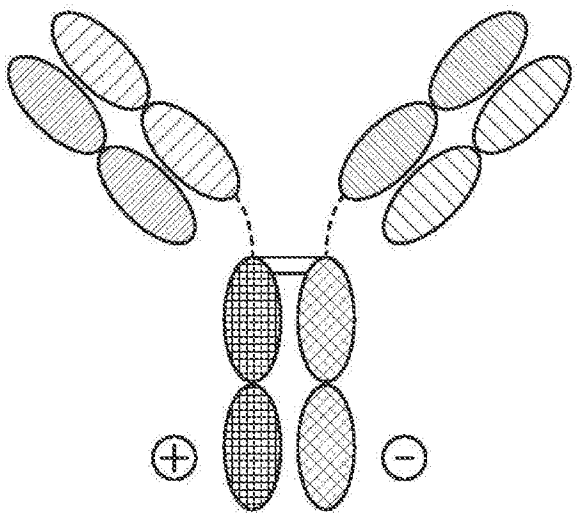


FIG. 26

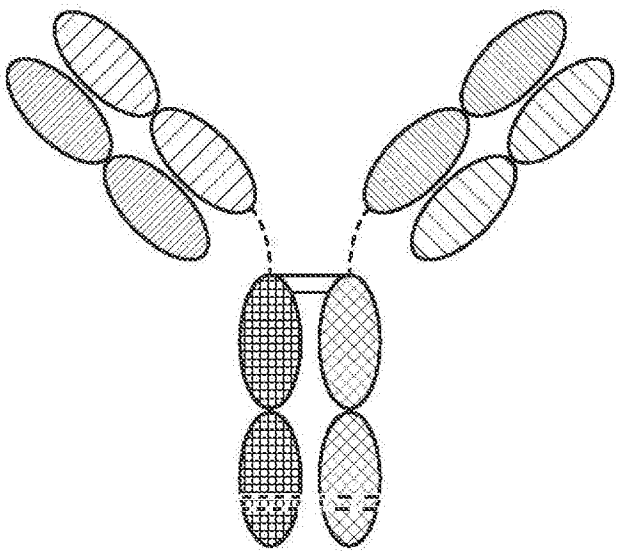


FIG. 27

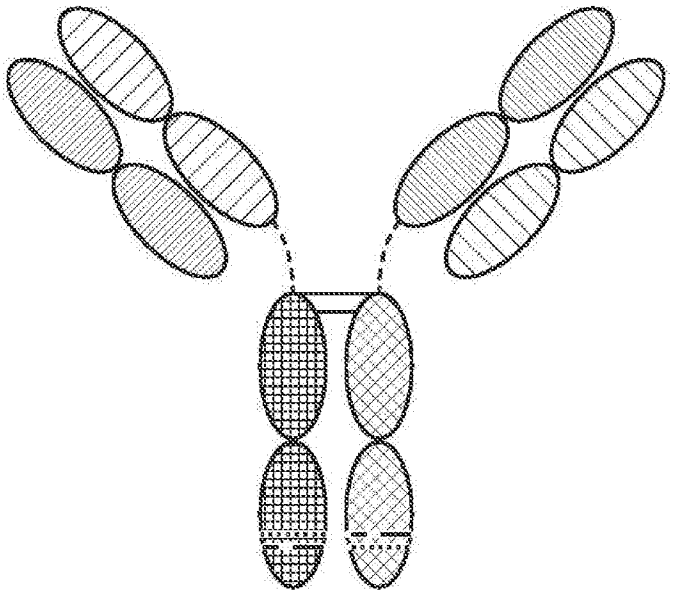


FIG. 28

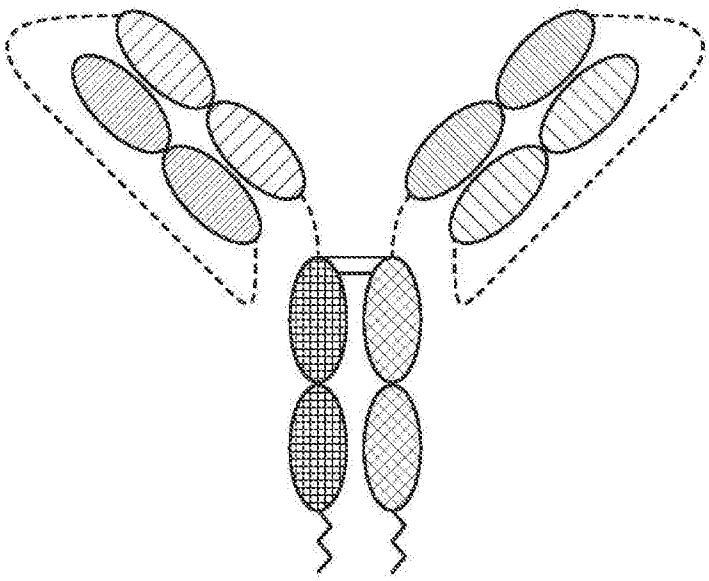


FIG. 29

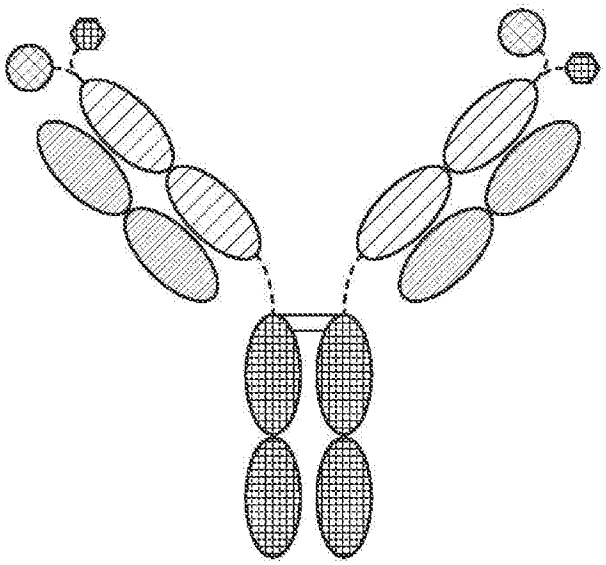


FIG. 30A

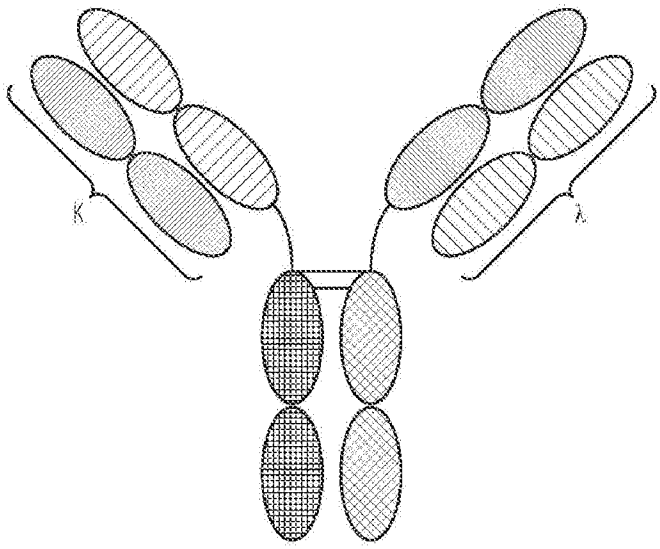


FIG. 30B

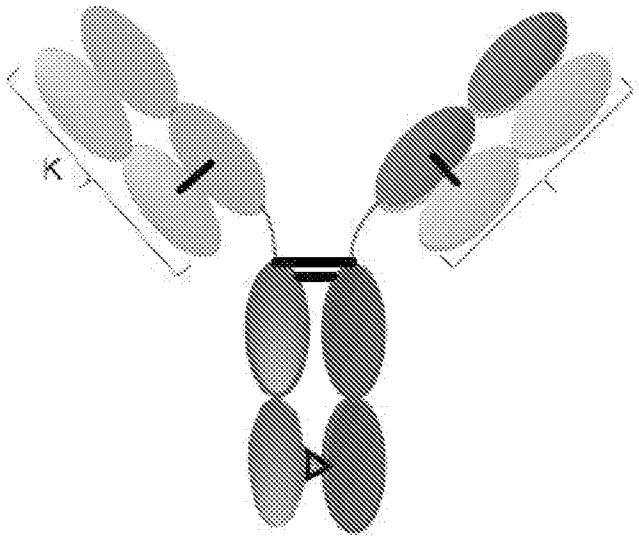


FIG. 31

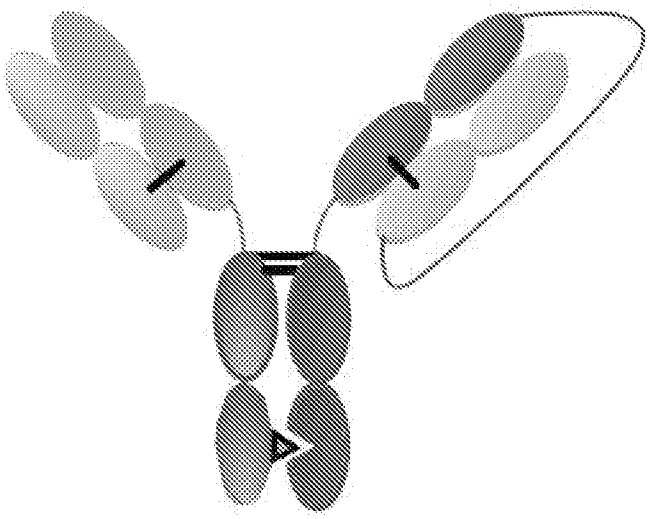


FIG. 32

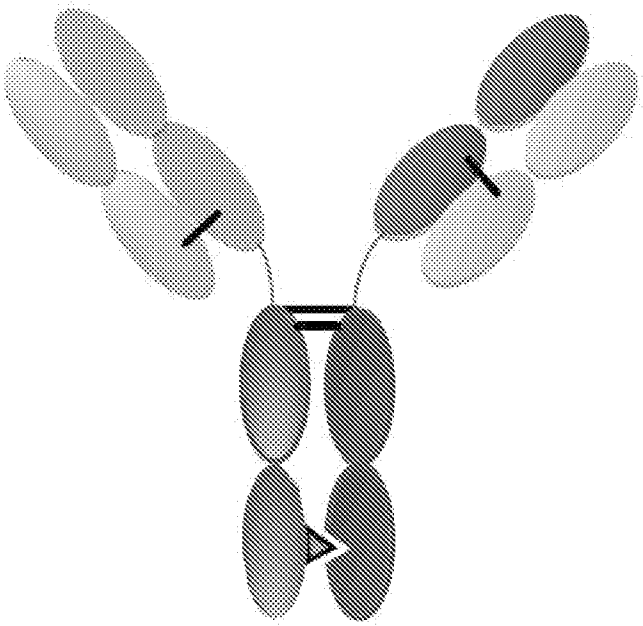


FIG. 33

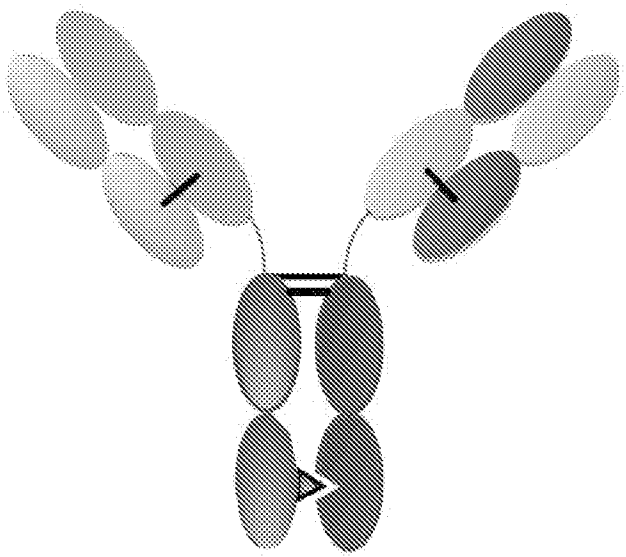


FIG. 34

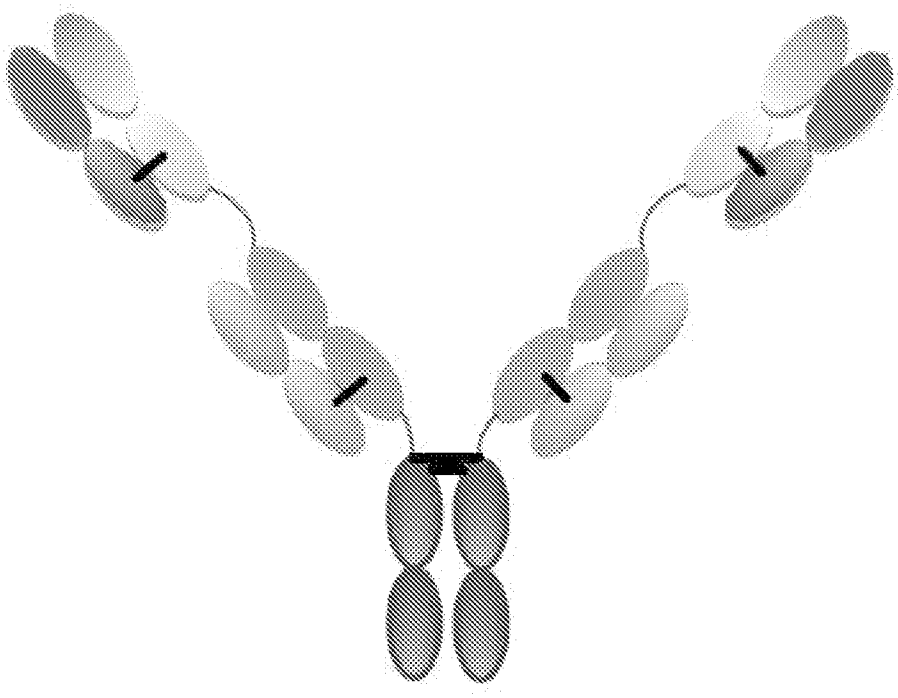


FIG. 35

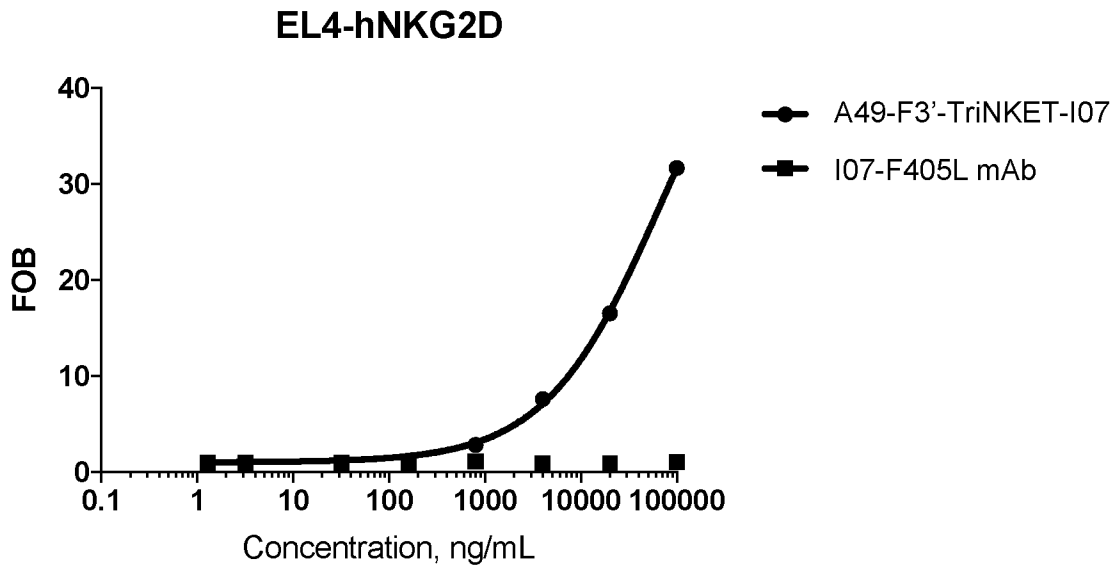

EL4-hNKG2D
FOB
40
30
20
10
0
0.1
1
10
100
1000
10000
100000
Concentration, ng/mL
A49-F3'-TriNKET-I07
I07-F405L mAb

FIG. 36A

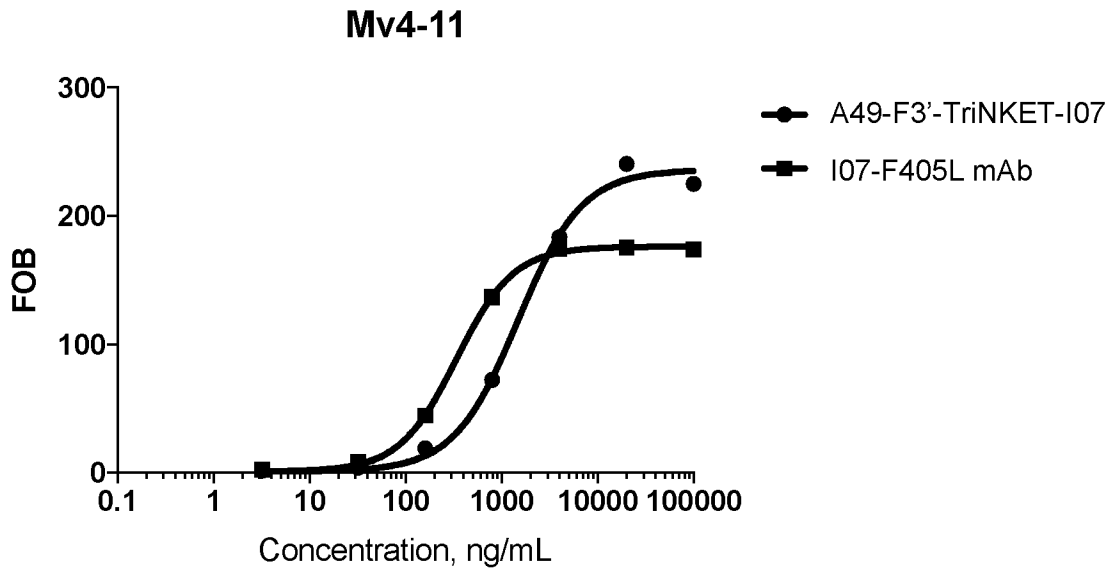


FIG. 36B

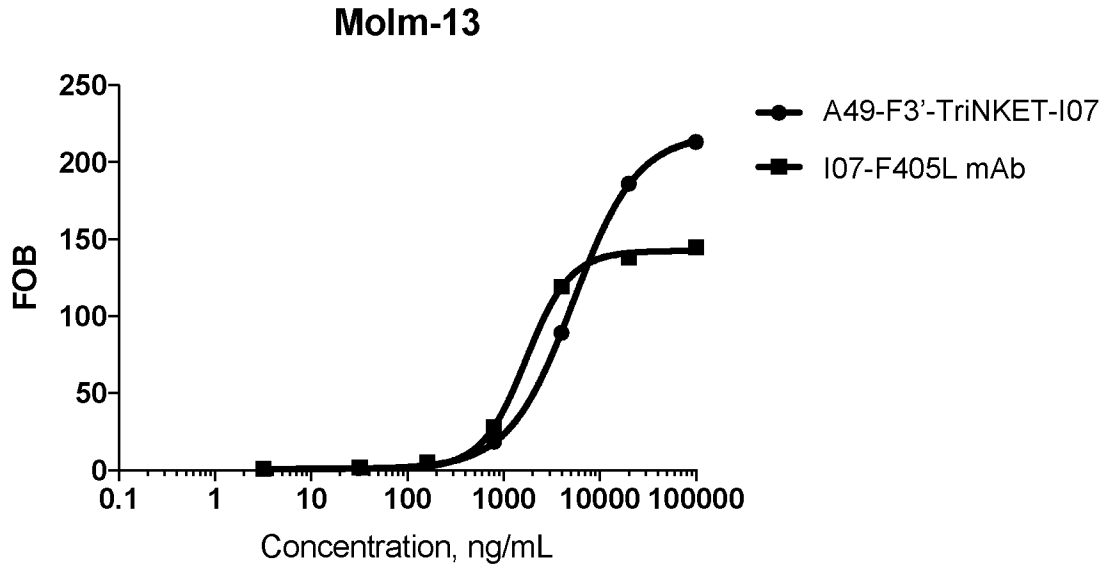


FIG. 37A

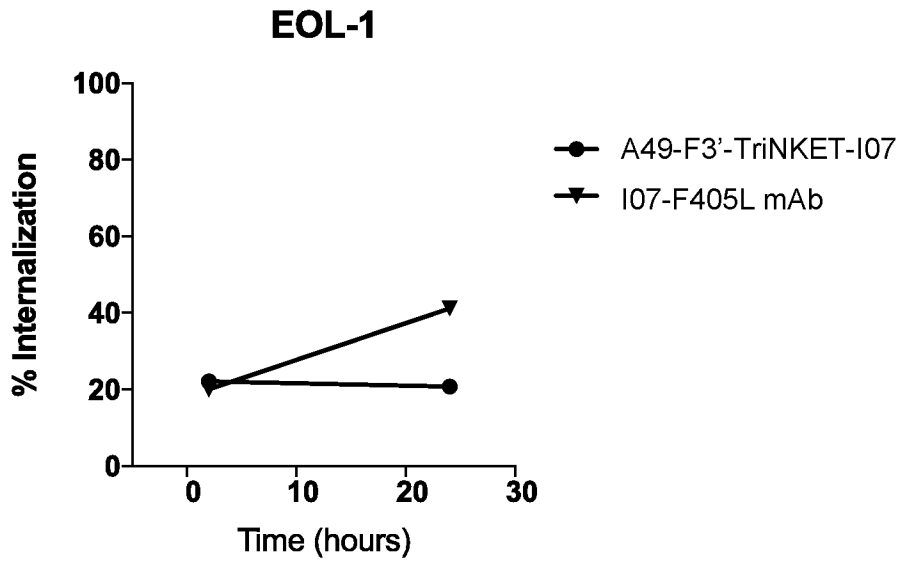


FIG. 37B

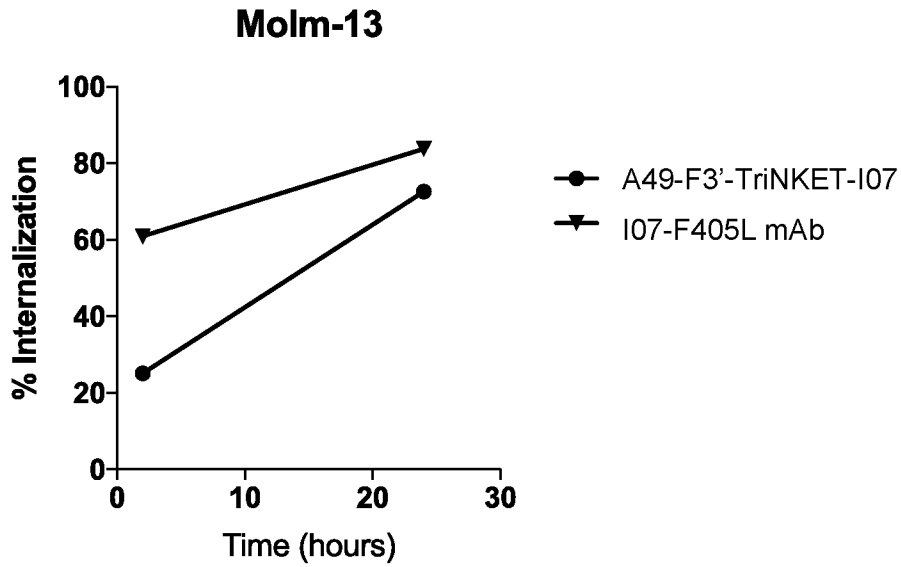


FIG. 38A

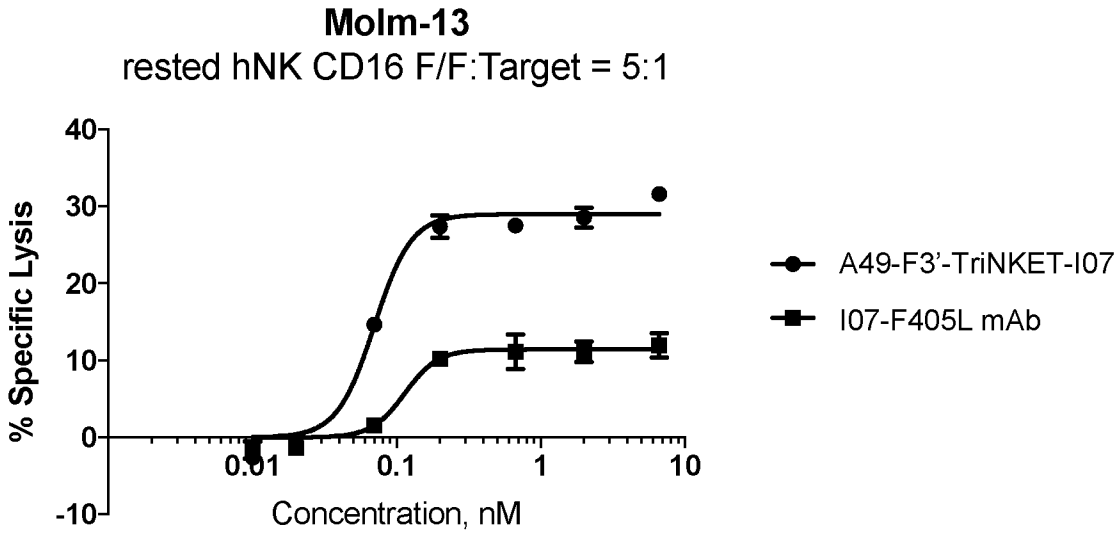


FIG. 38B

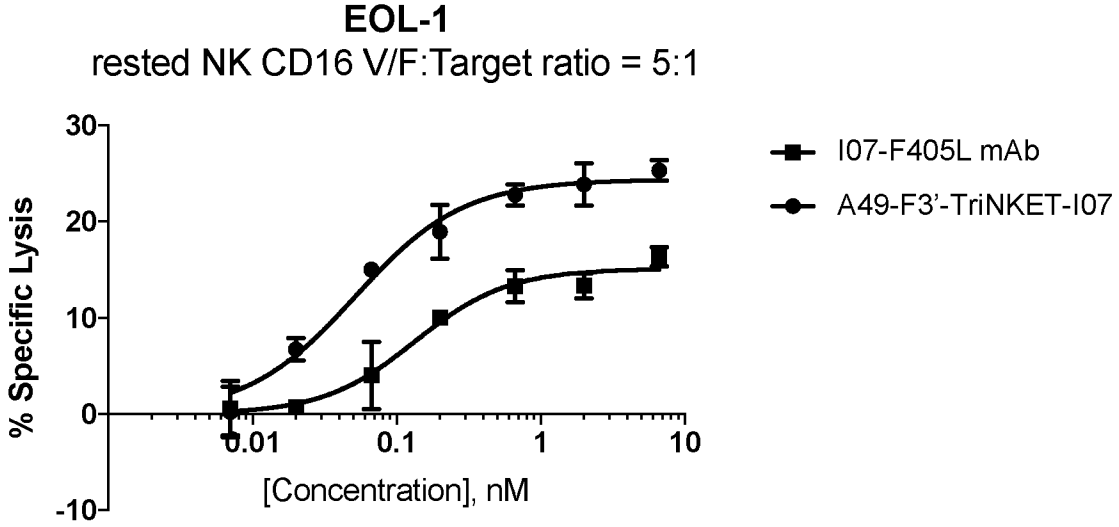


FIG. 38C

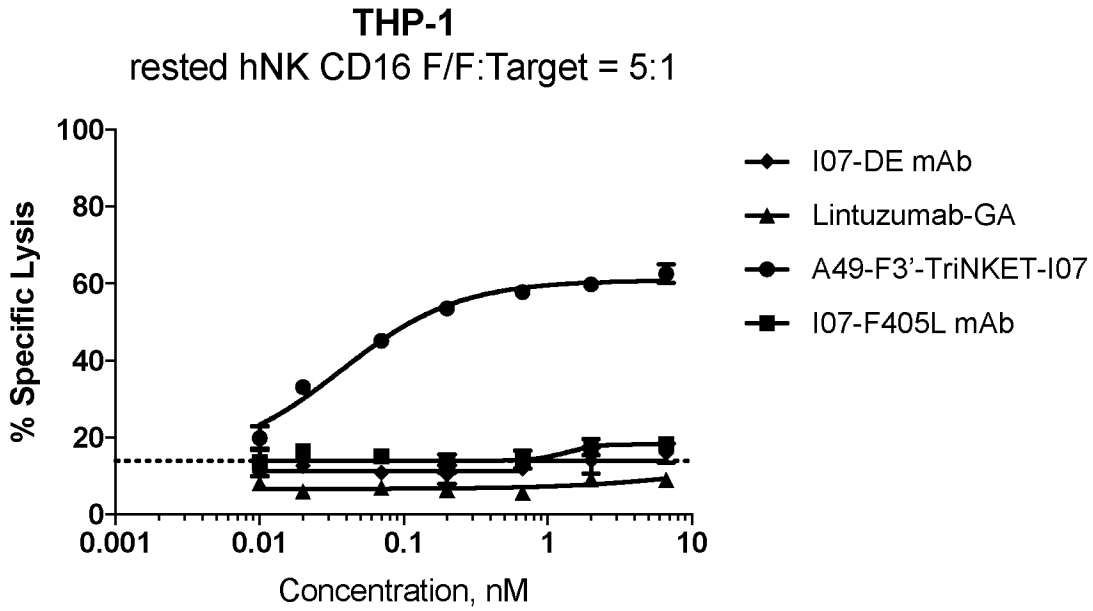


FIG. 38D

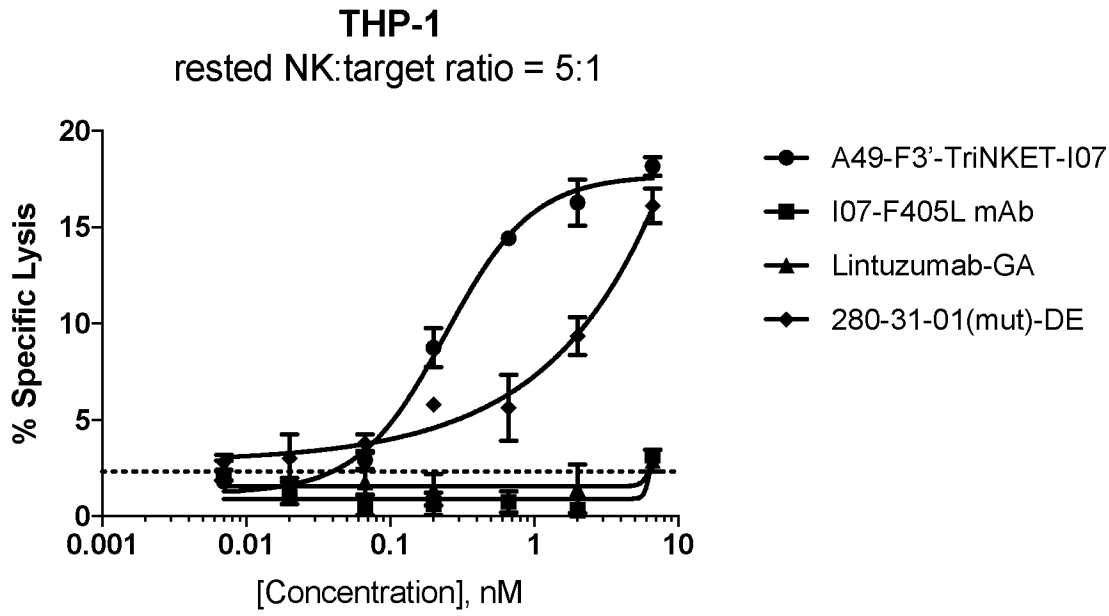


FIG. 39

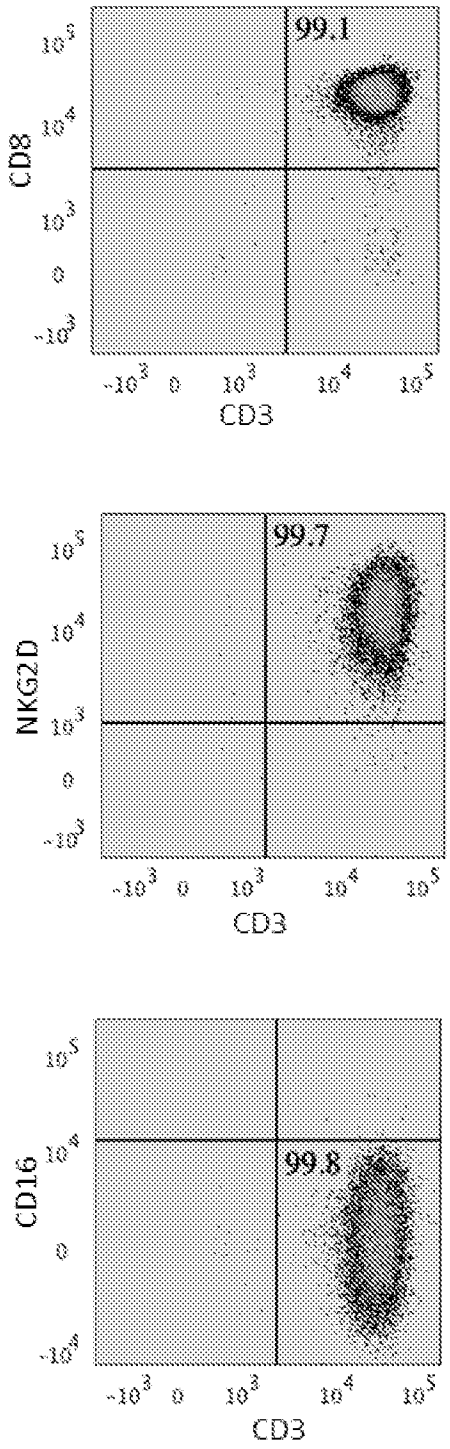


FIG. 40A

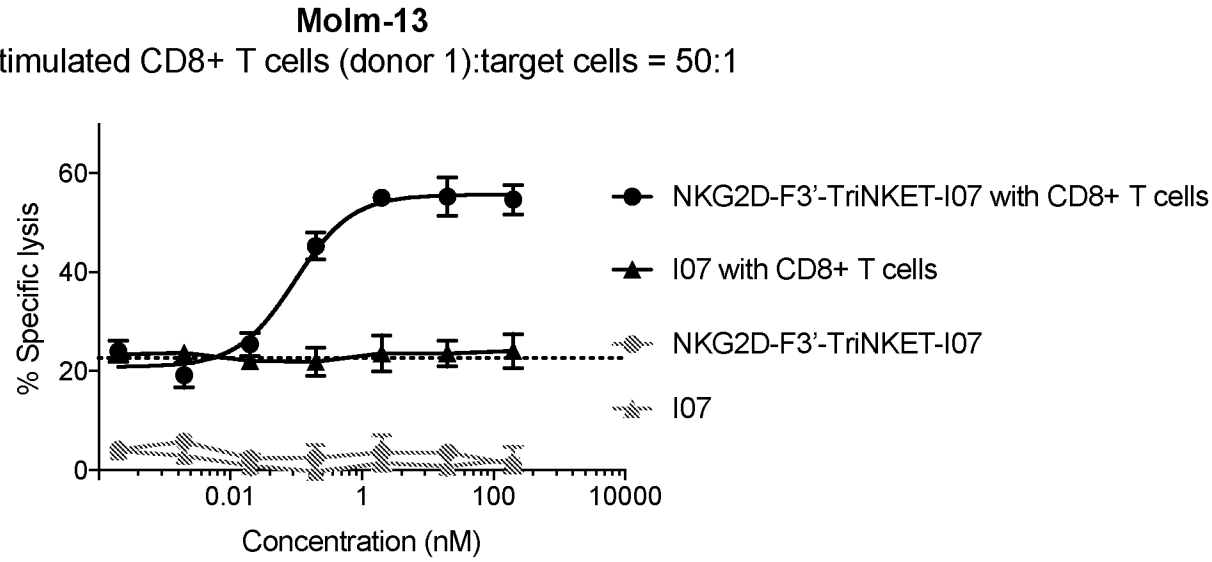


FIG. 40B

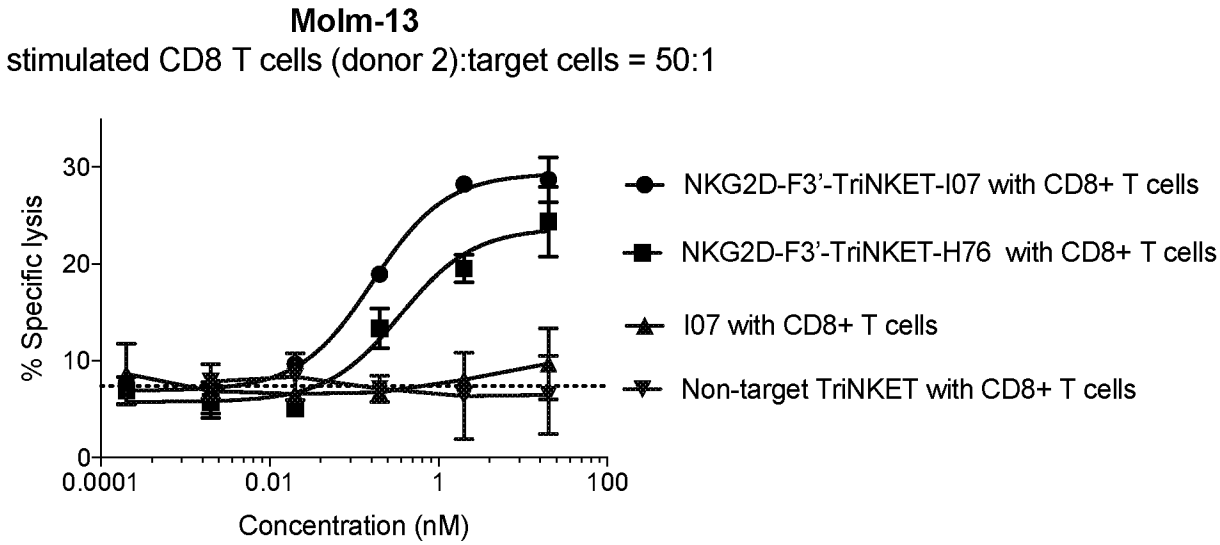
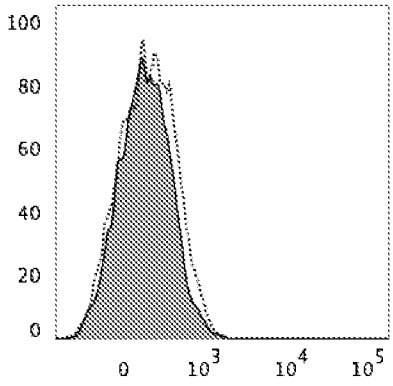
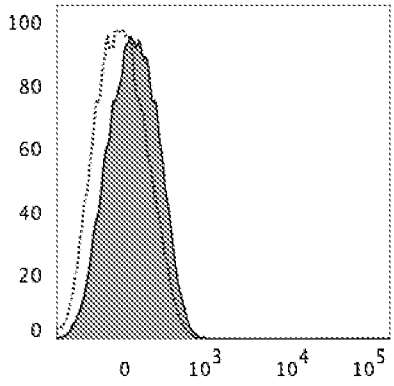


FIG. 41A



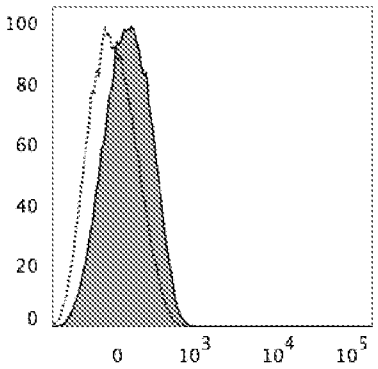
NK cells

FIG. 41B



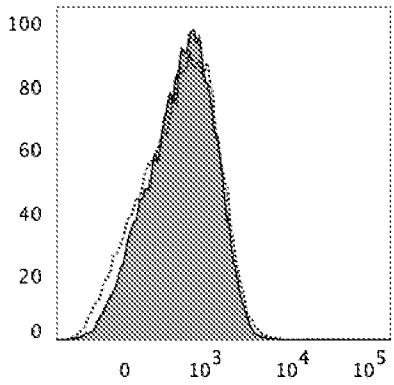
$CD8^+$ T cells

FIG. 41C



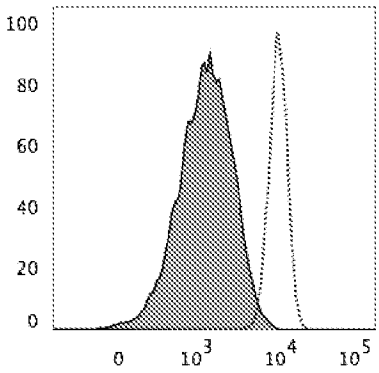
$CD4^+$ T cells

FIG. 41D



B cells

FIG. 41E



Monocytes

FIG. 42A

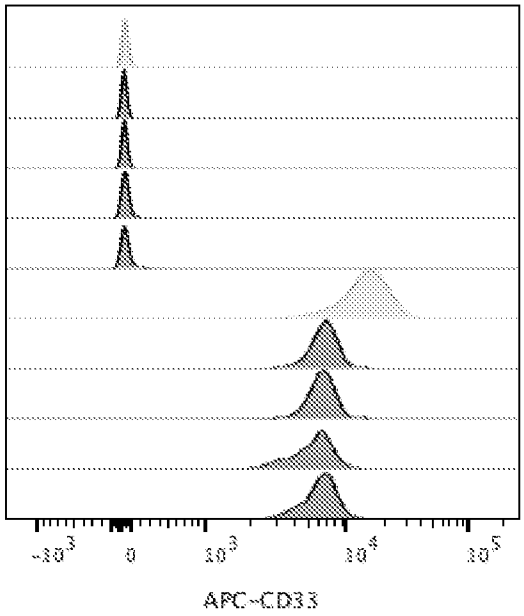


FIG. 42B

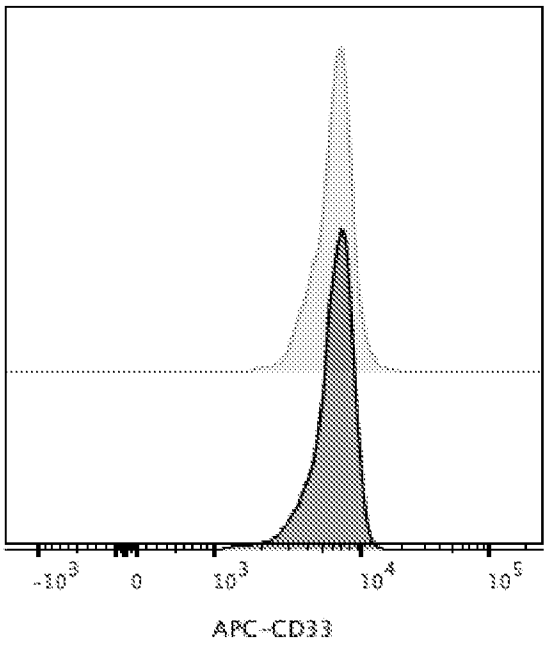


FIG. 43A

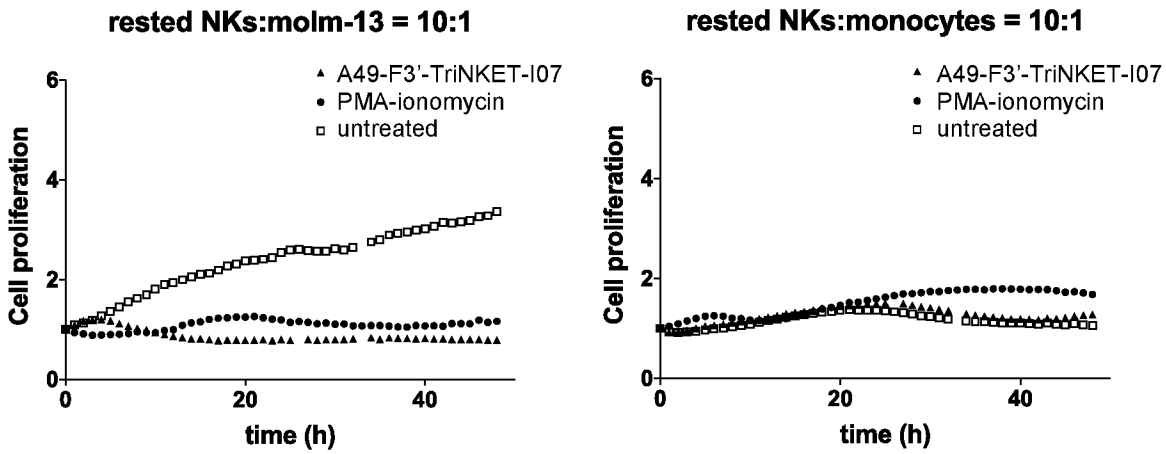


FIG. 43B

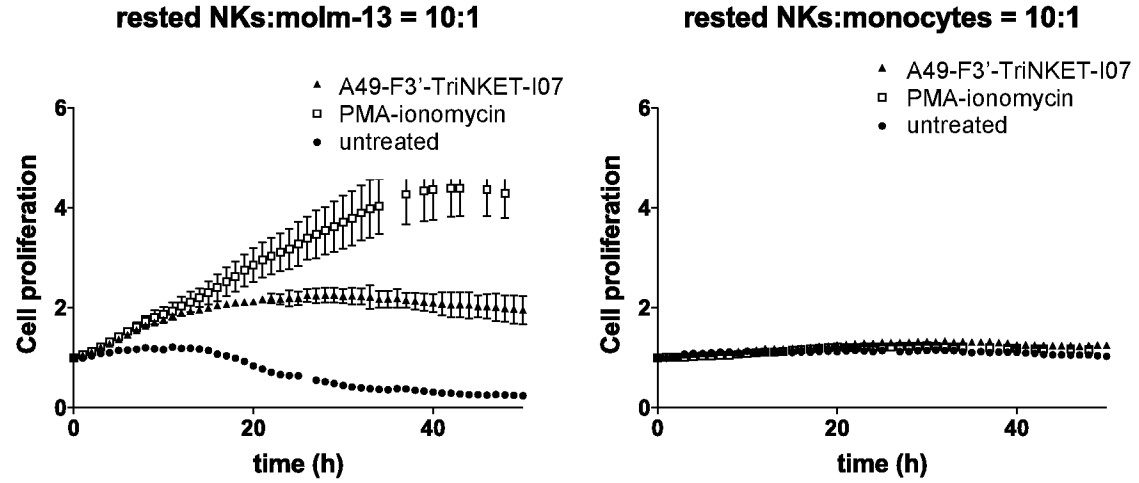
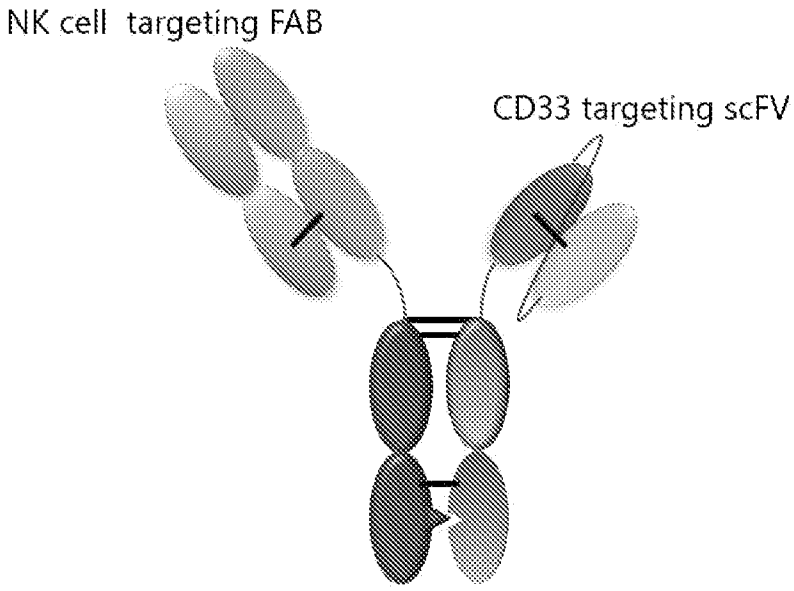


FIG. 44



F3' format

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/18751

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28, C07K 16/32 (2019.01)
CPC - C07K 16/2851, C07K 16/2803, C07K 16/283

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	US 2017/0368169 A1 (ELSTAR THERAPEUTICS, INC.) 28 December 2017 (28.12.2017) claim 1; para [0099]-[0104]; [0273]; [0281]-[0284]; [0472]; [0478].	1, 2 --- 3, 4 --- 26-28
Y	WO 2016/109774 A1 (DYAX CORP) 07 July 2016 (07.07.2016) p. 1, ln 19-25; p. 2, ln 6-12.	3, 4
A	US 2012/0058906 A1 (SMIDER et al.) 08 March 2012 (08.03.2012) para [0553]; SEQ ID NO: 1712.	26-28
A	US 2017/0114141 A1 (HOFFMANN-LA ROCHE INC.) 27 April 2017 (27.04.2017) abstract; Table 4; SEQ ID NO: 134.	26-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2019	01 JUL 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/18751

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-25, 29-46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--continued on first extra sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4 and 26-28 limited to SEQ ID NOs: 1, 2, 87, 88 (SEQ ID Nos: 192, 112, 193, 114, 115, 116)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

--continued from Box III: Observations where unity of invention is lacking--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+, claims 1-4 and 26-28, directed to a protein comprising a first antigen-binding site that binds NKG2D and a second antigen-binding site that binds CD33. The protein will be searched to the extent that the CD33 antigen binding site heavy and light chain variable domain (VH and VL) sequences encompass SEQ ID Nos: 1 and 2, respectively [note, these are the first VH and VL sequences listed in Table 1], the NKG2D antigen binding site VH sequence encompasses SEQ ID Nos: 87 (comprising VH CDR1-3 sequences SEQ ID Nos: 192, 112, 193, respectively), and the NKG2D antigen binding site VL sequence encompasses SEQ ID NO: 88 (comprising VL CDR1-3 sequences SEQ ID Nos: 114, 115, 116, respectively). It is believed that claims 1-4 and 26-28 encompass this first named invention, and thus these claims will be searched without fee to the extent that the CD33 site VH and VL sequences encompass SEQ ID Nos: 1 and 2, and the NKG2D site VH and VL sequences encompass SEQ ID Nos: 87 and 88 (including CDR SEQ ID Nos: 192, 112, 193, 114, 115, 116). Additional CD33 site sequence(s) and NKG2D site sequence(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected CD33 site sequence(s) and NKG2D site sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a protein comprising CD33 site VH and VL sequences SEQ ID NO: 3 and 4 [note, these are the second VH and VL sequences listed in Table 1], and NKG2D site VH and VL sequences comprising SEQ ID Nos: 87 and 88 (including CDR SEQ ID Nos: 192, 112, 193, 114, 115, 116), (claims 1-4 and 26-28).

The inventions listed as Group I+ do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

The inventions of Group I+ each include the special technical feature of a unique amino acid sequence. Each amino acid sequence encodes a unique peptide, and is considered a distinct technical feature.

Common technical features

No technical features are shared between the protein CD33 and NKG2D antigen binding site amino acid sequences of Group I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Group I+ were considered to share the technical features of including: a protein comprising:
(a) a first antigen-binding site comprising an Fab fragment that binds NKG2D;
(b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds CD33 comprising a heavy chain variable domain and a light chain variable domain; and
(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16, wherein the scFv is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser or Gly-Ala-Ser, these shared technical features are previously made obvious by US 2017/0368169 A1 to Elstar Therapeutics, Inc., (hereinafter Elstar).

Elstar teaches a protein comprising:
(a) a first antigen-binding site comprising a Fab fragment that binds NKG2D (claim 1 "multispecific or multifunctional molecule polypeptide, comprising: (i) a first tumor-targeting moiety that binds to a cancer antigen; and two or all of: (ii) an immune cell engager chosen from an NK cell engager"; [0102] "Exemplary NK cell engagers can be chosen from an antibody molecule, e.g., an antigen binding domain, or ligand that binds to (e.g., activates...NKG2D"; para [0284] "Partner A, partner B, partner C and partner D can each be, independently, an antibody molecule (e.g., a single chain antibody molecule (e.g., a scFv) or a Fab), a receptor molecule, a ligand molecule (e.g., a receptor ligand, or a cytokine molecule), e.g., as described herein...In embodiments, partner A is a tumor targeting moiety and partner B, partners C and D are each independently chosen from...an NK cell engager");
(b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds CD33 comprising a heavy chain variable domain and a light chain variable domain (claim 1 "multispecific or multifunctional molecule polypeptide, comprising: (i) a first tumor-targeting moiety that binds to a cancer antigen"; para [0099] "the cancer antigen can be chosen from CD19, CD33"; [0281] "Partner A and partner B can be, independently, an antibody molecule (e.g., a single chain antibody molecule (e.g., a scFv) or a Fab)"); and
(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 (claim 1 "multispecific or multifunctional molecule polypeptide, comprising: (i) a first tumor-targeting moiety that binds to a cancer antigen; and two or all of: (ii) an immune cell engager chosen from an NK cell engager"; [0102] "Exemplary NK cell engagers can be chosen from an antibody molecule, e.g., an antigen binding domain, or ligand that binds to (e.g., activates...CD16"; [0104] "In other embodiments of the multispecific or multifunctional molecule the NK cell engager is a ligand, optionally, the ligand further comprises an immunoglobulin constant region, e.g., an Fc region...the ligand of CD16 is a CD16a/b ligand, e.g., a CD16a/b ligand further comprising an antibody Fc region"), wherein the scFv is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16 (para [0273] " In embodiments of a trispecific format, partners A and B are connected, e.g., via a linker, to the scFv as binding moieties 2 and 3, respectively (FIG. 1C)"; [0284] "Partner A, partner B, partner C and partner D can each be, independently, an antibody molecule (e.g., a single chain antibody molecule (e.g., a scFv) or a Fab), a receptor molecule, a ligand molecule (e.g., a receptor ligand, or a cytokine molecule), e.g., as described herein...In embodiments, partner A is a tumor targeting moiety and partner B, partners C and D are each independently chosen from...an NK cell engager"), via a hinge (para [0478] "Fc-containing entities, also known as mini-antibodies, can be generated by fusing scFv to the C-termini of constant heavy region domain 3 (CH3-scFv) and/or to the hinge region (scFv-hinge-Fc) of an antibody with a different specificity"). Elstar does not specifically teach said hinge region comprises Ala-Ser or Gly-Ala-Ser. However, it was well known in the art of molecular biology to determine the optimal sequence for a short hinge region during the ordinary course of experimentation, in order to optimize molecule activity. Therefore, it would have been obvious to one of ordinary skill in the art to have determined the hinge region to be Ala-Ser in the Elstar peptides during the ordinary course of experimentation, in order to optimize molecule activity.

--continued on next sheet--

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As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I+ inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

NOTE, claims 5-25, 29-46 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).