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None

Description**Field of the Invention**

[0001] The present invention provides a combination epigenetic factors and bispecific compounds targeting CD33 and CD3 in the treatment of myeloid leukemia, wherein the epigenetic factor is hydroxyurea. Accordingly, the invention provides a pharmaceutical composition comprising a CD33 targeting compound and one epigenetic factor and an epigenetic factor for use in the amelioration, and/or treatment of a myeloid leukemia, wherein the epigenetic factor increases the responsiveness of a patient to a CD33 targeting compound. Moreover, the invention provides the use of an epigenetic factor for increasing the responsiveness of a myeloid leukemia patient to a treatment with a CD33 targeting compound, a method for the treatment of a myeloid leukemia, the method comprising the administration of one epigenetic factor and a CD33 targeting compound to a patient in the need thereof and a kit comprising a pharmaceutical composition of the invention or an epigenetic factor of the invention and a bispecific CD33 targeting compound.

Background of the invention

[0002] Despite some gradual improvements over the last decades with the use of intensive therapies - including multiagent conventional chemotherapy and allogeneic stem cell transplantation (SCT) - the survival of patients with acute myeloid leukemia (AML) remains poor, and patient are at high risk of experiencing treatment-related morbidity and mortality. For example, although SCT has proven to provide a potent anti-leukemic effect that can lead to elimination of chemoresistant leukemic cells, a large number of patients will develop significant graft versus host (GvH) disease that will eventually be fatal in many. For many patients, in particular those who are not suitable for such intensive therapeutic strategies, novel therapeutic options including immunotherapeutic approaches are urgently sought after. A promising immunotherapeutic strategy devoid of GvH reactions is to recruit in-vivo the patient's own T-cells and retarget them directly at leukemic cells.

[0003] This approach became feasible by a novel class of bispecific single-chain antibodies, which direct cytotoxic T-lymphocytes at predefined surface antigens on tumor cells (Baeuerle et al. Curr Opin Mol Ther. 2009;11:22-30). Clinical proof of concept was provided by blinatumomab, a bispecific antibody directed at both the CD19 B-cell surface antigen and the CD3 ϵ component of the T-cell receptor complex. Its therapeutic efficacy was shown for patients with B-cell lymphomas and B precursor acute lymphoblastic leukemia (ALL).

[0004] Acute myeloid leukemia (AML) has served as paradigm for the therapeutic use of monoclonal antibodies because of well-defined cell surface antigens and easy tumor accessibility. The most investigated target so far is CD33, a sialic-acid-dependent cytoadhesion molecule known as a myeloid differentiation antigen found on AML blasts in most patients and, perhaps, leukemic stem cells in some. AIGNER M ET AL (LEUKEMIA APR 2013, vol. 27, no. 5, pages 1107-1115) disclose the bispecific antibody AMG330 for the treatment of AML. SIMONA LAPUSAN ET AL (INVESTIGATIONAL NEW DRUGS; THE JOURNAL OF NEW ANTICANCER AGENTS, KLUWER ACADEMIC PUBLISHERS, BO, vol. 30, no. 3, 26 April 2011, pages 1121-1131), US 2011/038856 A1, NANO SUCHA ET AL (LEUKEMIA & LYMPHOMA NOV 2008, vol. 49, no. 11, November 2008, pages 2141-2147), and BROSS P F ET AL (CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH JUN 2001, vol. 7, no. 6, pages 1490-1496) refer to various anti-CD33 antibodies which are disclosed in combination with various agents including hydroxyurea for use in the treatment of AML. While the intact humanized CD33 antibody lintuzumab induced complete remission in individual patients in a single-agent phase I and II trial, no survival benefit was found in a phase III trial when it was combined with a triple chemotherapy regimen.

Summary of the invention

[0005] The present invention provides a pharmaceutical composition comprising a CD33 targeting compound and an epigenetic factor, wherein

- (a) the CD33 targeting compound is a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and
- (b) the epigenetic factor is hydroxyurea.

[0006] In one embodiment the pharmaceutical composition as disclosed herein is characterized in a way that the at least one epigenetic factor is selected from the group comprising:

- (a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abex-

inostat, LAQ824, and valproic acid;

(b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (-)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and

(c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

[0007] The invention also provides a pharmaceutical composition, wherein

(a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;

(b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or

(c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

[0008] The invention further provides a pharmaceutical composition, wherein a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound.

[0009] Moreover, the invention further provides a pharmaceutical composition, wherein the administration of the epigenetic factor is continued during the administration of the CD33 targeting compound.

[0010] In one embodiment the pharmaceutical composition of the invention is characterized in a way that the bispecific construct is a bispecific antibody construct.

[0011] In preferred embodiment of the pharmaceutical composition of the invention the bispecific antibody construct is a bispecific single chain antibody construct.

[0012] It is also preferred for the pharmaceutical composition of the invention that the bispecific antibody construct binds to human and cynomolgous CD3 and human and cynomolgous CD33.

[0013] In one embodiment of the pharmaceutical composition of invention the bispecific antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and 132 and a VH chain having an amino acid sequence as depicted in SEQ ID NO: 1, 19, 37, 55, 73, 91, 109 and 127; and

- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 154, 157, 160, 163, 166, 169 and 172 and a VH chain having an amino acid sequence as depicted in SEQ ID NO: 155, 158, 161, 164, 167, 170 and 173.

[0014] In preferred embodiment of the pharmaceutical composition the bispecific antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.

[0015] The pharmaceutical composition of the invention is envisaged for use in the treatment of CD33 expressing myeloid leukemia. Preferably, the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.

[0016] In an alternative embodiment the invention provides an epigenetic factor for use in the amelioration and/or treatment of a myeloid leukemia, wherein the epigenetic factor increases the responsiveness of a patient to a CD33 targeting compound, wherein

(a) the CD33 targeting compound is a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and

(b) the epigenetic factor is hydroxyurea.

[0017] As disclosed herein, the epigenetic factor is selected from the group comprising

(a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abexinostat, LAQ824, and valproic acid;

(b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (-)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and

(c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

[0018] Moreover, in one embodiment of the epigenetic factor of the invention

- (a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;
- (b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or
- (c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

[0019] It is preferred for the epigenetic factor of the invention that a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound.

[0020] Preferably, the administration of the epigenetic factor of the invention is continued during the administration of the CD33 targeting compound.

[0021] It is also preferred for the epigenetic factor of the invention that the bispecific construct is a bispecific antibody construct.

[0022] In one embodiment of the epigenetic factor of the invention the bispecific antibody construct is a bispecific single chain antibody construct.

[0023] It is preferred for the epigenetic factor of the invention that the bispecific antibody construct binds to human and cynomolgous CD3 and CD33.

[0024] Also preferred for the epigenetic factor of the invention is that the bispecific antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and 132 and a VH chain having an amino acid sequence as depicted in SEQ ID NO: 1, 19, 37, 55, 73, 91, 109 and 127; and
- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 154, 157, 160, 163, 166, 169 and 172 and a VH chain having an amino acid sequence as depicted in SEQ ID NO: 155, 158, 161, 164, 167, 170 and 173.

[0025] In one embodiment of the epigenetic factor of the invention the bispecific antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.

[0026] In one embodiment of the epigenetic factor of the invention the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.

[0027] The present disclosure provides a use of an epigenetic factor for increasing the responsiveness of a myeloid leukemia patient to a treatment with a CD33 targeting compound, wherein

- (a) the CD33 targeting compound is a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and
- (b) the at least one epigenetic factor is selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid).

[0028] As disclosed herein, the epigenetic factor is selected from the group comprising

- (a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abexinostat, LAQ824, and valproic acid;
- (b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (-)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and
- (c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

[0029] As disclosed herein,

- (a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;
- (b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or
- (c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

[0030] In a preferred use of the present disclosure, a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound. Moreover, as disclosed herein the administration of the epigenetic factor is continued during the administration of the CD33 targeting compound.

[0031] As disclosed herein, the bispecific construct is a bispecific antibody construct.

[0032] As disclosed herein, the bispecific antibody construct is a bispecific single chain antibody construct.

[0033] In one embodiment of the use of the invention the bispecific antibody construct binds to human and cynomolgous CD3 and CD33.

[0034] As disclosed herein, the bispecific antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and 132 and a VH chain having an amino acid sequence as depicted in SEQ ID NO: 1, 19, 37, 55, 73, 91, 109 and 127; and
- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 154, 157, 160, 163, 166, 169 and 172 and a VH chain having an amino acid sequence as depicted in SEQ ID NO: 155, 158, 161, 164, 167, 170 and 173.

[0035] As disclosed herein, the bispecific antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.

[0036] Furthermore, as disclosed herein the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.

[0037] A further alternative embodiment of the invention provides a kit comprising a pharmaceutical composition of the invention or an epigenetic factor of the invention and a bispecific CD33 targeting compound comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3, to be employed in the amelioration and/or treatment of a myeloid leukemia.

Brief description of the drawings

[0038]

Figure 1:

Effect of panobinostat pretreatment on CD33 expression and AMG 330-induced cytotoxicity. Parental OCI-AML3 and KG-1a cells were either left untreated or pretreated with panobinostat for 72 hours. Subsequently, CD33 expression was quantified, and cells treated with/without AMG 330 (0-250 pg/mL) and various effector:target (E:T) cell ratios using healthy donor T-cells. 48 hours later, cell counts were determined and cytotoxicity was assessed with DAPI staining to quantify drug-specific cytotoxicity. Results are shown as mean $\pm$ SEM from 3 independent experiments performed in duplicate wells using a single healthy donor as source for exogenous T-cells.

Figure 2:

Effect of azacitidine pretreatment on CD33 expression and AMG 330-induced cytotoxicity. Parental KG-1a cells were either left untreated or pretreated with azacitidine for 72 hours. Subsequently, CD33 expression was quantified, and cells treated with/without AMG 330 (0-250 pg/mL) and various effector:target (E:T) cell ratios using healthy donor T-cells. 48 hours later, cell counts were determined and cytotoxicity was assessed with DAPI staining to quantify drug-specific cytotoxicity. Results are shown as mean $\pm$ SEM from 3 independent experiments performed in duplicate wells using a single healthy donor as source for exogenous T-cells.

Figure 3:

Hydroxyurea-concentration dependant up-regulation of CD33 on A) HL-60 and B) PL21 AML cells.

Figure 4:

Hydroxyurea dependant up-regulation of CD33 on primary AML cells from patient 2.

Figure 5:

G-CSF dependant up-regulation of CD33 on KG1 α AML cells after 10 days of incubation.

Figure 6:

G-CSF dependant up-regulation of CD33 on primary AML cells from patient 1 after 10 days of incubation.

Detailed description of the invention

Definitions:

- 5 **[0039]** It must be noted that as used herein, the singular forms "a", "an", and "the", include plural references unless the context clearly indicates otherwise. Thus, for example, reference to "a reagent" includes one or more of such different reagents and reference to "the method" includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.
- 10 **[0040]** Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.
- [0041]** The term "and/or" wherever used herein includes the meaning of "and", "or" and "all or any other combination of the elements connected by said term".
- 15 **[0042]** The term "about" or "approximately" as used herein means within $\pm 20\%$, preferably within $\pm 15\%$, more preferably within $\pm 10\%$, and most preferably within $\pm 5\%$ of a given value or range.
- [0043]** Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step.
- 20 When used herein the term "comprising" can be substituted with the term "containing" or "including" or sometimes when used herein with the term "having".
- [0044]** When used herein "consisting of" excludes any element, step, or ingredient not specified in the claim element. When used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim.
- 25 **[0045]** In each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms.
- [0046]** The term "CD33 targeting compound" defines in the context of the present invention a binding molecule capable of specifically binding to the extracellular domain of the cell surface molecule CD33. As mentioned above CD33, a sialic-acid-dependent cytoadhesion molecule, is known as a myeloid differentiation antigen found on AML blasts in most patients. As apparent from the description of the embodiments of the invention, the CD33 targeting compound in the sense of the invention is a bispecific compound comprising at least a binding domain for the extracellular domain of the cell surface molecule CD33 and the extracellular domain of the molecule CD3 expressed on T cells. It is emphasized that the CD33 targeting compound comprises in the sense of the invention at least the binding domain for CD33 and CD3 and may also comprise one or more additional binding domains for other target structures, which result in a tri- or multispecific compound. In other words, the term "CD33 targeting compound" in the sense of the present disclosure indicates any molecule capable of (specifically) binding to, interacting with or recognizing the target molecule CD33 on the surface of a target cell and CD3 on the surface of a T cell. Such molecules or constructs may include proteinaceous parts and non-proteinaceous parts (e.g. chemical linkers or chemical cross-linking agents such as glutaraldehyde).
- 30 **[0047]** The term "binding molecule" in the sense of the present disclosure indicates any molecule capable of (specifically) binding to, interacting with or recognizing the target molecule.
- [0048]** A binding molecule, so to say, provides the scaffold for said one or more binding domains so that said binding domains can bind/interact with the surface molecule on a target cell and CD3 receptor complex on a T cell. For example, such a scaffold could be provided by protein A, in particular, the Z-domain thereof (affibodies), ImmE7 (immunity proteins), BPTI/APPI (Kunitz domains), Ras-binding protein AF-6 (PDZ-domains), charybdotoxin (Scorpion toxin), CTLA-4, Min-23 (knottins), lipocalins (anticalins), neokarzinostatin, a fibronectin domain, an ankyrin consensus repeat domain (Stumpp et al., Curr Opin Drug Discov Devel. 10(2), 153-159 (2007)) or thioredoxin (Skerra, Curr. Opin. Biotechnol. 18, 295-304 (2005); Hosse et al., Protein Sci. 15, 14-27 (2006); Nicaise et al., Protein Sci. 13, 1882-1891 (2004); Nygren and Uhlen, Curr. Opin. Struc. Biol. 7, 463-469 (1997)). A preferred binding molecule is an antibody, more preferably a bispecific antibody.
- 40 **[0049]** The term "single chain binding molecule" defines in connection with the present invention that the disclosed binding molecules in its simplest form are monomers. The molecules or constructs may include proteinaceous parts and non-proteinaceous parts (e.g. chemical linkers or chemical cross-linking agents such as glutaraldehyde). Thus, the single chain binding molecule may comprising accordance with the invention non-peptide linkers preferably to link at least two of the binding domains. Also in line with this invention are herein defined peptide linkers.
- 50 **[0050]** The definition of the term "antibody" includes embodiments such as monoclonal, chimeric, single chain, humanized and human antibodies, as well as antibody fragments, like, inter alia, Fab fragments. Antibody fragments or derivatives further comprise $F(ab)_2$, Fv, scFv fragments or single domain antibodies such as domain antibodies or nanobodies, single variable domain antibodies or immunoglobulin single variable domain comprising merely one variable

domain, which might be VHH, VH or VL, that specifically bind an antigen or epitope independently of other V regions or domains; see, for example, Harlow and Lane (1988) and (1999), loc. cit.; Kontermann and Dübel, Antibody Engineering, Springer, 2nd ed. 2010 and Little, Recombinant Antibodies for Immunotherapy, Cambridge University Press 2009. Such immunoglobulin single variable domain encompasses not only an isolated antibody single variable domain polypeptide, but also larger polypeptides that comprise one or more monomers of an antibody single variable domain polypeptide sequence.

[0051] Monovalent antibody fragments in line with the above definition describe an embodiment of a binding domain in connection with this invention. Such monovalent antibody fragments bind to a specific antigen and can be also designated "antigen-binding domain", "antigen-binding fragment" or "antibody binding region".

[0052] In line with this definition all above described embodiments of the term antibody can be subsumed under the term "antibody construct". Said term also includes diabodies or Dual-Affinity Re-Targeting (DART) antibodies. Further envisaged are (bispecific) single chain diabodies, tandem diabodies (Tandab's), "minibodies" exemplified by a structure which is as follows: (VH-VL-CH3)₂, (scFv-CH3)₂ or (scFv-CH3-scFv)₂, "Fc DART" antibodies and "IgG DART" antibodies, and multibodies such as triabodies. Immunoglobulin single variable domains encompass not only an isolated antibody single variable domain polypeptide, but also larger polypeptides that comprise one or more monomers of an antibody single variable domain polypeptide sequence.

[0053] Various procedures are known in the art and may be used for the production of such antibody constructs (antibodies and/or fragments). Thus, (antibody) derivatives can be produced by peptidomimetics. Further, techniques described for the production of single chain antibodies (see, inter alia, US Patent 4,946,778, Kontermann and Dübel (2010), loc. cit. and Little(2009), loc. cit.) can be adapted to produce single chain antibodies specific for elected polypeptide(s). Also, transgenic animals may be used to express humanized antibodies specific for polypeptides and fusion proteins of this invention. For the preparation of monoclonal antibodies, any technique, providing antibodies produced by continuous cell line cultures can be used. Examples for such techniques include the hybridoma technique (Kohler and Milstein Nature 256 (1975), 495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor, Immunology Today 4 (1983), 72) and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985), 77-96). Surface plasmon resonance as employed in the BIAcore system can be used to increase the efficiency of phage antibodies which bind to an epitope of a target polypeptide, such as CD3 epsilon (Schier, Human Antibodies Hybridomas 7 (1996), 97-105; Malmberg, J. Immunol. Methods 183 (1995), 7-13). It is also envisaged in the context of this invention that the term "antibody" comprises antibody constructs, which may be expressed in a host as described herein below, e.g. antibody constructs which may be transfected and/or transduced via, inter alia, viruses or plasmid vectors.

[0054] Furthermore, the term "antibody" as employed herein also relates to derivatives or variants of the antibodies described herein which display the same specificity as the described antibodies. Examples of "antibody variants" include humanized variants of non-human antibodies, "affinity matured" antibodies (see, e.g. Hawkins et al. J. Mol. Biol. 254, 889-896 (1992) and Lowman et al., Biochemistry 30, 10832- 10837 (1991)) and antibody mutants with altered effector function(s) (see, e.g., US Patent 5, 648, 260, Kontermann and Dübel (2010), loc. cit. and Little(2009), loc. cit.).

[0055] The terms "antigen-binding domain", "antigen-binding fragment" and "antibody binding region" when used herein refer to a part of an antibody molecule that comprises amino acids responsible for the specific binding between antibody and antigen. The part of the antigen that is specifically recognized and bound by the antibody is referred to as the "epitope" as described herein above. As mentioned above, an antigen-binding domain may typically comprise an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH); however, it does not have to comprise both. Fd fragments, for example, have two VH regions and often retain some antigen-binding function of the intact antigen-binding domain. Examples of antigen-binding fragments of an antibody include (1) a Fab fragment, a monovalent fragment having the VL, VH, CL and CH1 domains; (2) a F(ab')₂ fragment, a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; (3) a Fd fragment having the two VH and CH1 domains; (4) a Fv fragment having the VL and VH domains of a single arm of an antibody, (5) a dAb fragment (Ward et al., (1989) Nature 341 :544-546), which has a VH domain; (6) an isolated complementarity determining region (CDR), and (7) a single chain Fv (scFv). Although the two domains of the Fv fragment, VL and VH are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Huston et al. (1988) Proc. Natl. Acad. Sci USA 85:5879-5883). These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are evaluated for function in the same manner as are intact antibodies.

[0056] In the event that a (synthetic) linker is used, this linker is preferably of a length and sequence sufficient to ensure that each of the first and second domains can, independently from one another, retain their differential binding specificities. Most preferably and as documented in the appended examples, the antibody construct of the invention is a "bispecific single chain antibody construct", more preferably a bispecific single chain Fv (scFv). Bispecific single chain molecules are known in the art and are described in WO 99/54440, Mack, J. Immunol. (1997), 158, 3965-3970, Mack, PNAS,

(1995), 92, 7021-7025, Kufer, *Cancer Immunol. Immunother.*, (1997), 45, 193-197, Loffler, *Blood*, (2000), 95, 6, 2098-2103, Brühl, *Immunol.*, (2001), 166, 2420-2426, Kipriyanov, *J. Mol. Biol.*, (1999), 293, 41-56. One example of a CD33 targeting compound in connection with the present invention, which is a bispecific single chain molecule is AMG330, which has also been used in the appended examples.

[0057] The said variable domains comprised in the herein described antibody constructs may be connected by additional linker sequences. The term "peptide linker" defines in accordance with the present invention an amino acid sequence by which the amino acid sequences of the first domain and the second domain of the antibody construct of the invention are linked with each other. An essential technical feature of such peptide linker is that said peptide linker does not comprise any polymerization activity. Preferred amino acid residues for a peptide linker include Gly, Ser and Thr are characterized by a length between 5 and 25 amino acid residues. Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233 or WO 88/09344. A preferred embodiment of a peptide linker is characterized by the amino acid sequence Gly-Gly-Gly-Gly-Ser, i.e. Gly₄Ser, or polymers thereof, i.e. (Gly₄Ser)_x, where x is an integer 1 or greater. The characteristics of said peptide linker, which comprise the absence of the promotion of secondary structures are known in the art and described e.g. in Dall'Acqua et al. (*Biochem.* (1998) 37, 9266-9273), Cheadle et al. (*Mol Immunol* (1992) 29, 21-30) and Raag and Whitlow (*FASEB* (1995) 9(1), 73-80). Peptide linkers which also do not promote any secondary structures are preferred. The linkage of said domains to each other can be provided by, e.g. genetic engineering, as described in the examples. Methods for preparing fused and operatively linked bispecific single chain constructs and expressing them in mammalian cells or bacteria are well-known in the art (e.g. WO 99/54440 or Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2001).

[0058] For peptide linkers, which connect the at least two binding domains in the antibody construct of the invention peptide linkers are preferred which comprise only a few number of amino acid residues, e.g. 12 amino acid residues or less. Thus, peptide linker of 12, 11, 10, 9, 8, 7, 6 or 5 amino acid residues are preferred. An envisaged peptide linker with less than 5 amino acids comprises 4, 3, 2 or one amino acid(s) wherein Gly-rich linkers are preferred. A particularly preferred "single" amino acid in context of said "peptide linker" is Gly. Accordingly, said peptide linker may consist of the single amino acid Gly.

[0059] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler et al., *Nature*, 256: 495 (1975), or may be made by recombinant DNA methods (see, e.g., U. S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., *Nature*, 352: 624-628 (1991) and Marks et al., *J. Mol. Biol.*, 222: 581-597 (1991), for example.

[0060] The term "human antibody" includes antibodies having variable and constant regions corresponding substantially to human germline immunoglobulin sequences known in the art, including, for example, those described by Kabat et al. (See Kabat et al. (1991) loc. cit.). The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs, and in particular, CDR3. The human antibody can have at least one, two, three, four, five, or more positions replaced with an amino acid residue that is not encoded by the human germline immunoglobulin sequence. It is emphasized that the definition of human antibodies as used herein also contemplates fully human antibodies, which include only non-artificially and/or genetically altered human sequences of antibodies as those can be derived by using technologies using systems such as the Xenomice.

[0061] Examples of "antibody variants" include humanized variants of non-human antibodies, "affinity matured" antibodies (see, e.g. Hawkins et al. *J. Mol. Biol.* 254, 889-896 (1992) and Lowman et al., *Biochemistry* 30, 10832- 10837 (1991)) and antibody mutants with altered effector function (s) (see, e.g., US Patent 5, 648, 260, Kontermann and Dübel (2010), loc. cit. and Little(2009), loc. cit.).

[0062] As used herein, "in vitro generated antibody" refers to an antibody where all or part of the variable region (e.g., at least one CDR) is generated in a non-immune cell selection (e.g., an in vitro phage display, protein chip or any other method in which candidate sequences can be tested for their ability to bind to an antigen). This term thus preferably excludes sequences generated by genomic rearrangement in an immune cell.

[0063] The pairing of a VH and VL together forms a single antigen-binding site. The CH domain most proximal to VH

is designated as CH1. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. The VH and VL domains consist of four regions of relatively conserved sequences called framework regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequences (complementarity determining regions, CDRs). The CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen. CDRs are referred to as CDR 1, CDR2, and CDR3. Accordingly, CDR constituents on the heavy chain are referred to as H1, H2, and H3, while CDR constituents on the light chain are referred to as L1, L2, and L3.

[0064] The term "variable" refers to the portions of the immunoglobulin domains that exhibit variability in their sequence and that are involved in determining the specificity and binding affinity of a particular antibody (i.e., the "variable domain(s)"). Variability is not evenly distributed throughout the variable domains of antibodies; it is concentrated in sub-domains of each of the heavy and light chain variable regions. These sub-domains are called "hypervariable" regions or "complementarity determining regions" (CDRs). The more conserved (i.e., non-hypervariable) portions of the variable domains are called the "framework" regions (FRM). The variable domains of naturally occurring heavy and light chains each comprise four FRM regions, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRM and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site (see Kabat *et al.*, loc. cit.). The constant domains are not directly involved in antigen binding, but exhibit various effector functions, such as, for example, antibody-dependent, cell-mediated cytotoxicity and complement activation.

[0065] The terms "CDR", and its plural "CDRs", refer to a complementarity determining region (CDR) of which three make up the binding character of a light chain variable region (CDRL1, CDRL2 and CDRL3) and three make up the binding character of a heavy chain variable region (CDRH1, CDRH2 and CDRH3). CDRs contribute to the functional activity of an antibody molecule and are separated by amino acid sequences that comprise scaffolding or framework regions. The exact definitional CDR boundaries and lengths are subject to different classification and numbering systems. CDRs may therefore be referred to by Kabat, Chothia, contact or any other boundary definitions, including the numbering system described herein. Despite differing boundaries, each of these systems has some degree of overlap in what constitutes the so called "hypervariable regions" within the variable sequences. CDR definitions according to these systems may therefore differ in length and boundary areas with respect to the adjacent framework region. See for example Kabat, Chothia, and/or MacCallum (Kabat *et al.*, loc. cit.; Chothia *et al.*, J. Mol. Biol. 1987, 196: 901; and MacCallum *et al.*, J. Mol. Biol. 1996, 262: 732). However, the numbering in accordance with the so-called Kabat system is preferred. The CDR3 of the light chain and, particularly, CDR3 of the heavy chain may constitute the most important determinants in antigen binding within the light and heavy chain variable regions. In some antibody constructs, the heavy chain CDR3 appears to constitute the major area of contact between the antigen and the antibody. In vitro selection schemes in which CDR3 alone is varied can be used to vary the binding properties of an antibody or determine which residues contribute to the binding of an antigen.

[0066] "Consisting essentially of" means that the amino acid sequence can vary by about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% relative to the recited SEQ ID NO: sequence and still retain biological activity, as described herein.

[0067] In some embodiments, the binding molecules described herein are isolated proteins or substantially pure proteins. An "isolated" protein is unaccompanied by at least some of the material with which it is normally associated in its natural state, for example constituting at least about 5%, or at least about 50% by weight of the total protein in a given sample. It is understood that the isolated protein may constitute from 5 to 99.9% by weight of the total protein content depending on the circumstances. For example, the protein may be made at a significantly higher concentration through the use of an inducible promoter or high expression promoter, such that the protein is made at increased concentration levels. The definition includes the production of an antigen binding protein in a wide variety of organisms and/or host cells that are known in the art.

[0068] For amino acid sequences, sequence identity and/or similarity is determined by using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith and Waterman, 1981, Adv. Appl. Math. 2:482, the sequence identity alignment algorithm of Needleman and Wunsch, 1970, J. Mol. Biol. 48:443, the search for similarity method of Pearson and Lipman, 1988, Proc. Nat. Acad. Sci. U.S.A. 85:2444, computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence program described by Devereux *et al.*, 1984, Nucl. Acid Res. 12:387-395, preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, Inc.

[0069] An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle,

1987, J. Mol. Evol. 35:351-360; the method is similar to that described by Higgins and Sharp, 1989, CABIOS 5:151-153. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

[0070] Another example of a useful algorithm is the BLAST algorithm, described in: Altschul et al., 1990, J. Mol. Biol. 215:403-410; Altschul et al., 1997, Nucleic Acids Res. 25:3389-3402; and Karin et al., 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873-5787. A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul et al., 1996, Methods in Enzymology 266:460-480. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

[0071] An additional useful algorithm is gapped BLAST as reported by Altschul et al., 1993, Nucl. Acids Res. 25:3389-3402. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions, charges gap lengths of k a cost of 10+k; Xu set to 16, and Xg set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to about 22 bits.

[0072] Generally, the amino acid homology, similarity, or identity between individual variant CDRs are at least 80% to the sequences depicted herein, and more typically with preferably increasing homologies or identities of at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and almost 100%. In a similar manner, "percent (%) nucleic acid sequence identity" with respect to the nucleic acid sequence of the binding proteins identified herein is defined as the percentage of nucleotide residues in a candidate sequence that are identical with the nucleotide residues in the coding sequence of the antigen binding protein. A specific method utilizes the BLASTN module of WU-BLAST-2 set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively.

[0073] Generally, the nucleic acid sequence homology, similarity, or identity between the nucleotide sequences encoding individual variant CDRs and the nucleotide sequences depicted herein are at least 80%, and more typically with preferably increasing homologies or identities of at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, and almost 100%.

[0074] Thus, a "variant CDR" is one with the specified homology, similarity, or identity to the parent CDR of the invention, and shares biological function, including, but not limited to, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the specificity and/or activity of the parent CDR.

[0075] While the site or region for introducing an amino acid sequence variation is predetermined, the mutation *per se* need not be predetermined. For example, in order to optimize the performance of a mutation at a given site, random mutagenesis may be conducted at the target codon or region and the expressed antigen binding protein CDR variants screened for the optimal combination of desired activity. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example, M13 primer mutagenesis and PCR mutagenesis. Screening of the mutants is done using assays of antigen binding protein activities, such as binding to an elected a cell surface molecule on a target cell.

[0076] The term "amino acid" or "amino acid residue" typically refers to an amino acid having its art recognized definition such as an amino acid selected from the group consisting of: alanine (Ala or A); arginine (Arg or R); asparagine (Asn or N); aspartic acid (Asp or D); cysteine (Cys or C); glutamine (Gln or Q); glutamic acid (Glu or E); glycine (Gly or G); histidine (His or H); isoleucine (He or I); leucine (Leu or L); lysine (Lys or K); methionine (Met or M); phenylalanine (Phe or F); pro line (Pro or P); serine (Ser or S); threonine (Thr or T); tryptophan (Trp or W); tyrosine (Tyr or Y); and valine (Val or V), although modified, synthetic, or rare amino acids may be used as desired. Generally, amino acids can be grouped as having a nonpolar side chain (e.g., Ala, Cys, He, Leu, Met, Phe, Pro, Val); a negatively charged side chain (e.g., Asp, Glu); a positively charged sidechain (e.g., Arg, His, Lys); or an uncharged polar side chain (e.g., Asn, Cys, Gln, Gly, His, Met, Phe, Ser, Thr, Trp, and Tyr). The term "hypervariable region" (also known as "complementarity determining regions" or CDRs) when used herein refers to the amino acid residues of an antibody which are (usually three or four short regions of extreme sequence variability) within the V-region domain of an immunoglobulin which form the antigen-binding site and are the main determinants of antigen specificity. There are at least two methods for identifying the CDR residues: (1) An approach based on cross-species sequence variability (i. e., Kabat *et al.*, loc. cit.); and (2) An approach based on crystallographic studies of antigen-antibody complexes (Chothia, C. et al., J. Mol. Biol. 196: 901-917 (1987)). However, to the extent that two residue identification techniques define regions of overlapping, but not identical regions, they can be combined to define a hybrid CDR. However, in general, the CDR residues are preferably identified in accordance with the so-called Kabat (numbering) system.

[0077] The term "framework region" refers to the art-recognized portions of an antibody variable region that exist between the more divergent (i.e., hypervariable) CDRs. Such framework regions are typically referred to as frameworks 1 through 4 (FR1, FR2, FR3, and FR4) and provide a scaffold for the presentation of the six CDRs (three from the heavy chain and three from the light chain) in three dimensional space, to form an antigen-binding surface. Typically, CDRs

form a loop structure that can be classified as a canonical structure. The term "canonical structure" refers to the main chain conformation that is adopted by the antigen binding (CDR) loops. From comparative structural studies, it has been found that five of the six antigen binding loops have only a limited repertoire of available conformations. Each canonical structure can be characterized by the torsion angles of the polypeptide backbone. Correspondent loops between antibodies may, therefore, have very similar three dimensional structures, despite high amino acid sequence variability in most parts of the loops (Chothia and Lesk, J. Mol. Biol., 1987, 196: 901; Chothia et al., Nature, 1989, 342: 877; Martin and Thornton, J. Mol. Biol, 1996, 263: 800). Furthermore, there is a relationship between the adopted loop structure and the amino acid sequences surrounding it. The conformation of a particular canonical class is determined by the length of the loop and the amino acid residues residing at key positions within the loop, as well as within the conserved framework (i.e., outside of the loop). Assignment to a particular canonical class can therefore be made based on the presence of these key amino acid residues. The term "canonical structure" may also include considerations as to the linear sequence of the antibody, for example, as catalogued by Kabat (Kabat *et al.*, loc. cit.). The Kabat numbering scheme (system) is a widely adopted standard for numbering the amino acid residues of an antibody variable domain in a consistent manner and is the preferred scheme applied in the present invention as also mentioned elsewhere herein. Additional structural considerations can also be used to determine the canonical structure of an antibody. For example, those differences not fully reflected by Kabat numbering can be described by the numbering system of Chothia et al and/or revealed by other techniques, for example, crystallography and two or three-dimensional computational modeling. Accordingly, a given antibody sequence may be placed into a canonical class which allows for, among other things, identifying appropriate chassis sequences (e.g., based on a desire to include a variety of canonical structures in a library). Kabat numbering of antibody amino acid sequences and structural considerations as described by Chothia *et al.*, loc. cit. and their implications for construing canonical aspects of antibody structure, are described in the literature.

[0078] CDR3 is typically the greatest source of molecular diversity within the antibody-binding site. H3, for example, can be as short as two amino acid residues or greater than 26 amino acids. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, eds. Harlow et al., 1988. One of skill in the art will recognize that each subunit structure, e.g., a CH, VH, CL, VL, CDR, FR structure, comprises active fragments, e.g., the portion of the VH, VL, or CDR subunit that binds to the antigen, i.e., the antigen-binding fragment, or, e.g., the portion of the CH subunit that binds to and/or activates, e.g., an Fc receptor and/or complement. The CDRs typically refer to the Kabat CDRs, as described in Sequences of Proteins of Immunological Interest, US Department of Health and Human Services (1991), eds. Kabat *et al.* Another standard for characterizing the antigen binding site is to refer to the hypervariable loops as described by Chothia. See, e.g., Chothia, et al. (1987; J. Mol. Biol. 227:799-817); and Tomlinson et al. (1995) EMBO J. 14: 4628-4638. Still another standard is the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, generally, e.g., Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). Embodiments described with respect to Kabat CDRs can alternatively be implemented using similar described relationships with respect to Chothia hypervariable loops or to the AbM-defined loops.

[0079] The sequence of antibody genes after assembly and somatic mutation is highly varied, and these varied genes are estimated to encode 10^{10} different antibody molecules (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, CA, 1995). Accordingly, the immune system provides a repertoire of immunoglobulins. The term "repertoire" refers to at least one nucleotide sequence derived wholly or partially from at least one sequence encoding at least one immunoglobulin. The sequence(s) may be generated by rearrangement in vivo of the V, D, and J segments of heavy chains, and the V and J segments of light chains. Alternatively, the sequence(s) can be generated from a cell in response to which rearrangement occurs, e.g., in vitro stimulation. Alternatively, part or all of the sequence(s) may be obtained by DNA splicing, nucleotide synthesis, mutagenesis, and other methods, see, e.g., U.S. Patent 5,565,332. A repertoire may include only one sequence or may include a plurality of sequences, including ones in a genetically diverse collection.

[0080] It is also envisaged that the CD33 targeting compound described herein has, apart from its function to bind to the cell surface molecule CD33 on a target cell and CD3 on the cell surface of a T cell, may have an additional function. In this format, the compound is a multifunctional compound by targeting cells through binding to CD33 on the cell surface of a target cell, mediating cytotoxic T cell activity through CD3 binding and providing a further function such as a fully functional Fc constant domain mediating antibody-dependent cellular cytotoxicity through recruitment of effector cells like NK cells, a half life extending domain such as an albumin binding domain or a modified Fc constant domain lacking antibody-dependent cellular cytotoxicity but extending the molecular weight of the compound, mediation of a label (fluorescent etc.), a therapeutic agent such as, e.g. a toxin or radionuclide, and/or means to enhance serum half-life, etc.

[0081] The term "epitope" refers to a site on an antigen to which a binding domain, such as an antibody or immunoglobulin or derivative or fragment of an antibody or of an immunoglobulin, specifically binds. An "epitope" is antigenic and thus the term epitope is sometimes also referred to herein as "antigenic structure" or "antigenic determinant". Thus, the binding domain is an "antigen-interaction-site". Said binding/interaction is also understood to define a "specific

recognition". In one example, said binding domain which (specifically) binds to / interacts with a given target epitope of CD33 on a cell surface molecule on a target cell or CD3 is an antibody or immunoglobulin, and said binding domain is a VH and/or VL region of an antibody or of an immunoglobulin.

[0082] "Epitopes" can be formed both by contiguous amino acids or non-contiguous amino acids juxtaposed by tertiary folding of a protein. A "linear epitope" is an epitope where an amino acid primary sequence comprises the recognized epitope. A linear epitope typically includes at least 3 or at least 4, and more usually, at least 5 or at least 6 or at least 7, for example, about 8 to about 10 amino acids in a unique sequence.

[0083] A "conformational epitope", in contrast to a linear epitope, is an epitope wherein the primary sequence of the amino acids comprising the epitope is not the sole defining component of the epitope recognized (e.g., an epitope wherein the primary sequence of amino acids is not necessarily recognized by the binding domain). Typically a conformational epitope comprises an increased number of amino acids relative to a linear epitope. With regard to recognition of conformational epitopes, the binding domain recognizes a three-dimensional structure of the antigen, preferably a peptide or protein or fragment thereof (in the context of the present invention, the antigen for one of the binding domains is comprised within a cell surface molecule on a target cell). For example, when a protein molecule folds to form a three-dimensional structure, certain amino acids and/or the polypeptide backbone forming the conformational epitope become juxtaposed enabling the antibody to recognize the epitope. Methods of determining the conformation of epitopes include, but are not limited to, x-ray crystallography, two-dimensional nuclear magnetic resonance (2D-NMR) spectroscopy and site-directed spin labelling and electron paramagnetic resonance (EPR) spectroscopy. Moreover, the provided examples describe a further method to characterize a given binding domain by way of binning, which includes a test whether the given binding domain binds to one or more epitope cluster(s) of a given protein, in particular a cell surface molecule on a target cell.

[0084] As used herein, the term "epitope cluster" denotes the entirety of epitopes lying in a defined contiguous stretch of an antigen. An epitope cluster can comprise one, two or more epitopes. The concept of epitope cluster is also used in the characterization of the features of the binding molecules of the invention.

[0085] The terms "(capable of) binding to", "specifically recognizing", "directed to" and "reacting with" mean in accordance with this invention that a binding domain is capable of specifically interacting with one or more, preferably at least two, more preferably at least three and most preferably at least four amino acids of an epitope.

[0086] As used herein, the terms "specifically interacting", "specifically binding" or "specifically bind(s)" mean that a binding domain exhibits appreciable affinity for a particular protein or antigen and, generally, does not exhibit significant reactivity with proteins or antigens other than CD33 or CD3. "Appreciable affinity" includes binding with an affinity of about 10^{-6} M (KD) or stronger. Preferably, binding is considered specific when binding affinity is about 10^{-12} to 10^{-8} M, 10^{-12} to 10^{-9} M, 10^{-12} to 10^{-10} M, 10^{-11} to 10^{-8} M, preferably of about 10^{-11} to 10^{-9} M. Whether a binding domain specifically reacts with or binds to a target can be tested readily by, *inter alia*, comparing the reaction of said binding domain with a target protein or antigen with the reaction of said binding domain with proteins or antigens other than CD33 or CD3. Preferably, a binding domain of the invention does not essentially bind or is not capable of binding to proteins or antigens other than CD33 or CD3 (i.e. the first binding domain is not capable of binding to proteins other than CD33 and the second binding domain is not capable of binding to proteins other than CD3).

[0087] The term "does not essentially bind", or "is not capable of binding" means that a binding domain of the present invention does not bind another protein or antigen other than CD33 or CD3, i.e., does not show reactivity of more than 30%, preferably not more than 20%, more preferably not more than 10%, particularly preferably not more than 9%, 8%, 7%, 6% or 5% with proteins or antigens other than CD33 or CD3, whereby binding to CD33 or CD3, respectively, is set to be 100%.

[0088] Specific binding is believed to be effected by specific motifs in the amino acid sequence of the binding domain and the antigen. Thus, binding is achieved as a result of their primary, secondary and/or tertiary structure as well as the result of secondary modifications of said structures. The specific interaction of the antigen-interaction-site with its specific antigen may result in a simple binding of said site to the antigen. Moreover, the specific interaction of the antigen-interaction-site with its specific antigen may alternatively or additionally result in the initiation of a signal, e.g. due to the induction of a change of the conformation of the antigen, an oligomerization of the antigen, etc.

[0089] Proteins (including fragments thereof, preferably biologically active fragments, and peptides, usually having less than 30 amino acids) comprise one or more amino acids coupled to each other via a covalent peptide bond (resulting in a chain of amino acids). The term "polypeptide" as used herein describes a group of molecules, which consist of more than 30 amino acids. Polypeptides may further form multimers such as dimers, trimers and higher oligomers, i.e. consisting of more than one polypeptide molecule. Polypeptide molecules forming such dimers, trimers etc. may be identical or non-identical. The corresponding higher order structures of such multimers are, consequently, termed homo- or heterodimers, homo- or heterotrimers etc. An example for a heteromultimer is an antibody molecule, which, in its naturally occurring form, consists of two identical light polypeptide chains and two identical heavy polypeptide chains. The terms "polypeptide" and "protein" also refer to naturally modified polypeptides/proteins wherein the modification is effected e.g. by post-translational modifications like glycosylation, acetylation, phosphorylation and the like. A "polypeptide" when

referred to herein may also be chemically modified such as pegylated. Such modifications are well known in the art.

[0090] "Isolated" when used to describe the CD33 targeting compound disclosed herein, means a compound that has been identified, separated and/or recovered from a component of its production environment. Preferably, the isolated compound is free of association with all other components from its production environment. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the compound will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Ordinarily, however, an isolated compound will be prepared by at least one purification step.

[0091] Amino acid sequence modifications of the CD33 targeting compound described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the compound. Amino acid sequence variants of the CD33 targeting compounds are prepared by introducing appropriate nucleotide changes into the compounds nucleic acid, or by peptide synthesis.

[0092] Such modifications include, for example, deletions from, and/or insertions into, and/or substitutions of, residues within the amino acid sequences of the compound. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the compound, such as changing the number or position of glycosylation sites. Preferably, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids may be substituted in a CDR, while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acids may be substituted in the framework regions (FRs). The substitutions are preferably conservative substitutions as described herein. Additionally or alternatively, 1, 2, 3, 4, 5, or 6 amino acids may be inserted or deleted in each of the CDRs (of course, dependent on their length), while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acids may be inserted or deleted in each of the FRs.

[0093] A useful method for identification of certain residues or regions of the CD33 targeting compounds that are preferred locations for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells in Science, 244: 1081-1085 (1989). Here, a residue or group of target residues within the compound is/are identified (e.g. charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with the epitope.

[0094] Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* needs not to be predetermined. For example, to analyze the performance of a mutation at a given site, ala scanning or random mutagenesis is conducted at a target codon or region and the expressed compound variants are screened for the desired activity.

[0095] Preferably, amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. An insertional variant of the CD33 targeting compound includes the fusion to the N-or C-terminus of the antibody to an enzyme or a fusion to a polypeptide which increases the serum half-life of the antibody.

[0096] Another type of variant is an amino acid substitution variant. These variants have preferably at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues in the compound replaced by a different residue. The sites of greatest interest for substitutional mutagenesis include the CDRs of the heavy and/or light chain, in particular the hypervariable regions, but FR alterations in the heavy and/or light chain are also contemplated.

[0097] For example, if a CDR sequence encompasses 6 amino acids, it is envisaged that one, two or three of these amino acids are substituted. Similarly, if a CDR sequence encompasses 15 amino acids it is envisaged that one, two, three, four, five or six of these amino acids are substituted.

[0098] Generally, if amino acids are substituted in one or more or all of the CDRs of the heavy and/or light chain, it is preferred that the then-obtained "substituted" sequence is at least 60%, more preferably 65%, even more preferably 70%, particularly preferably 75%, more particularly preferably 80% identical to the "original" CDR sequence. This means that it is dependent of the length of the CDR to which degree it is identical to the "substituted" sequence. For example, a CDR having 5 amino acids is preferably 80% identical to its substituted sequence in order to have at least one amino acid substituted. Accordingly, the CDRs of the CD33 targeting compound may have different degrees of identity to their substituted sequences, e.g., CDRL1 may have 80%, while CDRL3 may have 90%.

[0099] Preferred substitutions (or replacements) are conservative substitutions. However, any substitution (including non-conservative substitution or one or more from the "exemplary substitutions" listed in Table 1, below) is envisaged as long as the CD33 targeting compound retains its capability to bind to CD33 via the first binding domain and to CD3 epsilon via the second binding domain and/or its CDRs have an identity to the then substituted sequence (at least 60%, more preferably 65%, even more preferably 70%, particularly preferably 75%, more particularly preferably 80% identical

to the "original" CDR sequence).

[0100] Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 1, or as further described below in reference to amino acid classes, may be introduced and the products screened for a desired characteristic.

Table 1: Amino Acid Substitutions

Original	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val, leu, ile	val
Arg (R)	lys, gln, asn	lys
Asn (N)	gln, his, asp, lys, arg	gln
Asp (D)	glu, asn	glu
Cys (C)	ser, ala	ser
Gln (Q)	asn, glu	asn
Glu (E)	asp, gln	asp
Gly (G)	ala	ala
His (H)	asn, gln, lys, arg	arg
Ile (I)	leu, val, met, ala, phe	leu
Leu (L)	norleucine, ile, val, met, ala	ile
Lys (K)	arg, gln, asn	arg
Met (M)	leu, phe, ile	leu
Phe (F)	leu, val, ile, ala, tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr, phe	tyr
Tyr (Y)	trp, phe, thr, ser	phe
Val (V)	ile, leu, met, phe, ala	leu

[0101] Substantial modifications in the biological properties of the CD33 targeting compound described herein are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties: (1) hydrophobic: norleucine, met, ala, val, leu, ile; (2) neutral hydrophilic: cys, ser, thr; (3) acidic: asp, glu; (4) basic: asn, gln, his, lys, arg; (5) residues that influence chain orientation: gly, pro; and (6) aromatic: trp, tyr, phe.

[0102] Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Any cysteine residue not involved in maintaining the proper conformation of the CD33 targeting compound may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the compound in case the compound is an antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

[0103] A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e. g. a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e. g. 6-7 sites) are mutated to generate all possible amino acid substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened

for their biological activity (e. g. binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the binding domain and, e.g., human CD33 or CD3. Such contact residues and neighbouring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

[0104] Other modifications of the CD33 targeting compound are contemplated herein. For example, the CD33 targeting compound may be linked to one of a variety of non-proteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol. The CD33 targeting compound may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatine-microcapsules and poly (methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules), or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

[0105] The CD33 targeting compound disclosed herein may also be formulated as immuno-liposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the compound are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang et al., Proc. Natl Acad. Sci. USA, 77: 4030 (1980); US Pat. Nos. 4,485,045 and 4,544,545; and WO 97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in US Patent No. 5,013, 556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al. J. Biol. Chem. 257: 286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al. J. National Cancer Inst. 81 (19) 1484 (1989).

[0106] When using recombinant techniques, the CD33 targeting compound can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody construct is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., Bio/Technology 10: 163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*.

[0107] The CD33 targeting compounds prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique.

[0108] The CD33 targeting compounds described herein may be provided in form of a fusion protein comprising at least two binding domains, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233 or WO 88/09344.

[0109] Another method for preparing CD33 targeting compounds described herein in form of oligomeric antibody construct derivatives involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, Science 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, FEBS Letters 344:191. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, Semin. Immunol. 6:267-78. In one approach, recombinant fusion proteins comprising a CD33 and a CD3 antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric CD33 and CD3 antibody fragments or derivatives that form are recovered from the culture supernatant.

[0110] Covalent modifications of antigen binding proteins are included within the scope of this invention, and are generally, but not always, done post-translationally. For example, several types of covalent modifications of the antigen binding protein are introduced into the molecule by reacting specific amino acid residues of the antigen binding protein with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

[0111] Cysteiny residues most commonly are reacted with α -haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteiny residues also are derivatized by reaction with bromotrifluoroacetone, α -bromo- β -(5-imidozoyl)propionic acid, chloroacetyl phosphate,

N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

[0112] Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1M sodium cacodylate at pH 6.0.

[0113] Lysiny and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysiny residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimide; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

[0114] Arginy residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

[0115] The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using ¹²⁵I or ¹³¹I to prepare labeled proteins for use in radioimmunoassay, the chloramine T method described above being suitable.

[0116] Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R'-N=C=N-R'), where R and R' are optionally different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginy and glutaminy residues by reaction with ammonium ions.

[0117] Derivatization with bifunctional agents is useful for crosslinking antigen binding proteins to a water-insoluble support matrix or surface for use in a variety of methods. Commonly used crosslinking agents include, e.g., 1,1-bis(di-azoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimide yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

[0118] Glutaminy and asparaginy residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

[0119] Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threony residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, *Proteins: Structure and Molecular Properties*, W. H. Freeman & Co., San Francisco, 1983, pp. 79-86), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0120] Another type of covalent modification of the antigen binding protein included within the scope of this invention comprises altering the glycosylation pattern of the protein. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (e.g., the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

[0121] Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0122] Addition of glycosylation sites to the antigen binding protein is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antigen binding protein amino acid sequence is preferably altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[0123] Another means of increasing the number of carbohydrate moieties on the antigen binding protein is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require

production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330 published Sep. 11, 1987, and in Aplin and Wriston, 1981, CRC Crit. Rev. Biochem., pp. 259-306.

[0124] Removal of carbohydrate moieties present on the starting antigen binding protein may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin et al., 1987, Arch. Biochem. Biophys. 259:52 and by Edge et al., 1981, Anal. Biochem. 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo- glycosidases as described by Thotakura et al., 1987, Meth. Enzymol. 138:350. Glycosylation at potential glycosylation sites may be prevented by the use of the compound tunicamycin as described by Duskin et al., 1982, J. Biol. Chem. 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

[0125] Another type of covalent modification of the antigen binding protein comprises linking the antigen binding protein to various non-proteinaceous polymers, including, but not limited to, various polyols such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. In addition, as is known in the art, amino acid substitutions may be made in various positions within the antigen binding protein to facilitate the addition of polymers such as PEG.

[0126] In some embodiments, the covalent modification of the antigen binding proteins described herein comprises the addition of one or more labels.

[0127] The term "labelling group" means any detectable label. Examples of suitable labelling groups include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent groups (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic groups (e.g., horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotiny groups, or predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labelling group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and may be used in performing the present invention.

[0128] In general, labels fall into a variety of classes, depending on the assay in which they are to be detected: a) isotopic labels, which may be radioactive or heavy isotopes; b) magnetic labels (e.g., magnetic particles); c) redox active moieties; d) optical dyes; enzymatic groups (e.g. horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase); e) biotinylated groups; and f) predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.). In some embodiments, the labelling group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and may be used in performing the present invention.

[0129] Specific labels include optical dyes, including, but not limited to, chromophores, phosphors and fluorophores, with the latter being specific in many instances. Fluorophores can be either "small molecule" fluo- or proteinaceous fluo-.

[0130] By "fluorescent label" is meant any molecule that may be detected *via* its inherent fluorescent properties. Suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade BlueJ, Texas Red, IAEDANS, EDANS, BODIPY FL, LC Red 640, Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes, Eugene, OR), FITC, Rhodamine, and Texas Red (Pierce, Rockford, IL), Cy5, Cy5.5, Cy7 (Amersham Life Science, Pittsburgh, PA). Suitable optical dyes, including fluorophores, are described in Molecular Probes Handbook by Richard P. Haugland.

[0131] Suitable proteinaceous fluorescent labels also include, but are not limited to, green fluorescent protein, including a Renilla, Ptilosarcus, or Aequorea species of GFP (Chalfie et al., 1994, Science 263:802-805), EGFP (Clontech Laboratories, Inc., Genbank Accession Number U55762), blue fluorescent protein (BFP, Quantum Biotechnologies, Inc. 1801 de Maisonneuve Blvd. West, 8th Floor, Montreal, Quebec, Canada H3H 1J9; Stauber, 1998, Biotechniques 24:462-471; Heim et al., 1996, Curr. Biol. 6:178-182), enhanced yellow fluorescent protein (EYFP, Clontech Laboratories, Inc.), luciferase (Ichiki et al., 1993, J. Immunol. 150:5408-5417), β galactosidase (Nolan et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:2603-2607) and Renilla (WO92/15673, WO95/07463, WO98/14605, WO98/26277, WO99/49019, U.S. Patent Nos. 5292658, 5418155, 5683888, 5741668, 5777079, 5804387, 5874304, 5876995, 5925558).

[0132] A CD33 targeting compound described herein may also comprise additional domains, which e.g. are helpful

in the isolation of the molecule or relate to an adapted pharmacokinetic profile of the molecule.

[0133] Domains helpful for the isolation of an antibody construct may be elected from peptide motives or secondarily introduced moieties, which can be captured in an isolation method, e.g. an isolation column. A non-limiting embodiment of such additional domains comprise peptide motives known as Myc-tag, HAT-tag, HA-tag, TAP-tag, GST-tag, chitin binding domain (CBD-tag), maltose binding protein (MBP-tag), Flag-tag, Strep-tag and variants thereof (e.g. StrepII-tag) and His-tag. All herein disclosed antibody constructs characterized by the identified CDRs are preferred to comprise a His-tag domain, which is generally known as a repeat of consecutive His residues in the amino acid sequence of a molecule, preferably of six His residues.

[0134] The term "epigenetic factor" in connection with the present invention defines a compound which is capable of changing the gene expression or cellular phenotype of a cell population upon administration. It is understood that such change refers to one or more functional relevant modifications to the genome without involving a change in the nucleic acid sequence. Examples of such modifications are DNA methylation and histone modification, which are both important for the regulation of gene expression without altering the underlying DNA sequence. Particular examples for epigenetic factors suitable in the combination therapy approach according to the invention are selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid).

[0135] Histone deacetylases (HDACs) are a class of enzymes, that remove acetyl groups from ϵ -N-acetyl lysine amino acid on a histone. The deacetylated histone is suitable to wrap the DNA more tightly which negatively effects the expression genes in the region of the wrapped DNA. Accordingly, HDAC inhibitors inhibit the enzymatic deacetylation of histone and allow for the expression or enhancement of expression of those genes located in the region of the acetylated histone. Non-limiting examples for HDAC inhibitors in connection with this invention comprise panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisino-stat, abexinostat, LAQ824, and valproic acid.

[0136] DNA methyltransferase (DNMT) I is an enzyme, which catalyze the transfer of a methyl group to DNA. The degree of DNA methylation is also decisive for the expression of genes. Non-limiting examples for DNMT I inhibitors in connection with this invention comprise 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (-)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110.

[0137] Histone methyltransferases (HMT) are histone-modifying enzymes that catalyze the transfer of one, two, or three methyl groups to lysine and arginine residues of histone proteins. Methylation of histones is important biologically because it is the principal epigenetic modification of chromatin that determines gene expression, genomic stability, stem cell maturation, cell lineage development, genetic imprinting, DNA methylation, and cell mitosis. Non-limiting examples for HMT inhibitors in connection with this invention comprise LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

[0138] ATRA (All Trans-retinoic acid) is the carboxylic acid form of vitamin A and is also known as Tretinoin.

[0139] Hydroxyurea is also known as Hydroxycarbamide and is used as an antineoplastic drug. The compound is described to decrease the production of deoxyribonucleotides via inhibition of the enzyme ribonucleotide reductase.

[0140] Granulocyte-colony stimulating factor (G-CSF or GCSF), also known as colony-stimulating factor 3 (CSF 3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. Functionally, it is a cytokine and hormone, a type of colony-stimulating factor, and is produced by a number of different tissues. The pharmaceutical analogs of naturally occurring G-CSF are called filgrastim and lenograstim.

[0141] The term "nucleic acid" is well known to the skilled person and encompasses DNA (such as cDNA) and RNA (such as mRNA). The nucleic acid can be double stranded and single stranded, linear and circular. Said nucleic acid molecule is preferably comprised in a vector which is preferably comprised in a host cell. Said host cell is, e.g. after transformation or transfection with the nucleic acid sequence described herein, capable of expressing the CD33 targeting compound. For that purpose the nucleic acid molecule is operatively linked with control sequences.

[0142] A vector is a nucleic acid molecule used as a vehicle to transfer (foreign) genetic material into a cell. The term "vector" encompasses - but is not restricted to - plasmids, viruses, cosmids and artificial chromosomes. In general, engineered vectors comprise an origin of replication, a multicloning site and a selectable marker. The vector itself is generally a nucleotide sequence, commonly a DNA sequence that comprises an insert (transgene) and a larger sequence that serves as the "backbone" of the vector. Modern vectors may encompass additional features besides the transgene insert and a backbone: promoter, genetic marker, antibiotic resistance, reporter gene, targeting sequence, protein purification tag. Vectors called expression vectors (expression constructs) specifically are for the expression of the transgene in the target cell, and generally have control sequences such as a promoter sequence that drives expression of the transgene. Insertion of a vector into the target cell is usually called "transformation" for bacteria, "transfection" for eukaryotic cells, although insertion of a viral vector is also called "transduction".

[0143] As used herein, the term "host cell" is intended to refer to a cell into which a nucleic acid encoding the CD33 targeting compound described herein is introduced by way of transformation, transfection and the like. It should be understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influ-

ences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0144] As used herein, the term "expression" includes any step involved in the production of a CD33 targeting compound described herein including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion.

[0145] The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

[0146] A nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

[0147] The terms "host cell," "target cell" or "recipient cell" are intended to include any individual cell or cell culture that can be or has/have been recipients for vectors or the incorporation of exogenous nucleic acid molecules, polynucleotides and/or proteins. It also is intended to include progeny of a single cell, and the progeny may not necessarily be completely identical (in morphology or in genomic or total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. The cells may be prokaryotic or eukaryotic, and include but are not limited to bacteria, yeast cells, animal cells, and mammalian cells, e.g., murine, rat, macaque or human.

[0148] Suitable eukaryotic host cells include yeasts, fungi, insect cells and mammalian cells.

[0149] The CD33 targeting compound described herein can be produced in bacteria. After expression, the CD33 targeting compound, preferably the antibody construct is isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., affinity chromatography and/or size exclusion. Final purification can be carried out similar to the process for purifying antibody expressed e.g., in CHO cells.

[0150] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for the CD33 targeting compound described herein. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*, *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12424), *K. bulgaricus* (ATCC 16045), *K. wickerhamii* (ATCC 24178), *K. waltii* (ATCC 56500), *K. drosophilae* (ATCC 36906), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402 226); *Pichia pastoris* (EP 183 070); *Candida*; *Trichoderma reesia* (EP 244 234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

[0151] Suitable host cells for the expression of glycosylated CD33 targeting compounds described herein, preferably antibody derived antibody constructs are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruit fly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

[0152] Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, Arabidopsis and tobacco can also be utilized as hosts. Cloning and expression vectors useful in the production of proteins in plant cell culture are known to those of skill in the art. See e.g. Hiatt et al., *Nature* (1989) 342: 76-78, Owen et al. (1992) *Bio/Technology* 10: 790-794, Artsaenko et al. (1995) *The Plant J* 8: 745-750, and Fecker et al. (1996) *Plant Mol Biol* 32: 979-986. However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen Virol.* 36 : 59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77: 4216 (1980)); mouse sertoli cells (TM4, Mather, *Biol. Reprod.* 23: 243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL1587) ; human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, 1413 8065); mouse mammary tumor (MMT 060562, ATCC CCL5 1); TRI cells (Mather et al., *Annals N. Y Acad. Sci.* 383 :

44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

[0153] When using recombinant techniques, the CD33 targeting compound described herein can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody construct is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., *Bio/Technology* 10: 163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[0154] The CD33 targeting compound described herein prepared from the host cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique.

[0155] The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly (styrenedivinyl) benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the CD33 targeting compound described herein comprises a CH3 domain, the Bakerbond ABXMresin (J. T. Baker, Phillipsburg, NJ) is useful for purification. Other techniques for protein purification such as fractionation on an ionexchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE™ chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromato-focusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

[0156] The term "culturing" refers to the in vitro maintenance, differentiation, growth, proliferation and/or propagation of cells under suitable conditions in a medium.

[0157] As used herein, the term "pharmaceutical composition" relates to a composition for administration to a patient, preferably a human patient. The particular preferred pharmaceutical composition of this invention comprises a CD33 targeting compound and at least one epigenetic factor, either in one single formulation or in separate formulations. Preferably, the pharmaceutical composition comprises suitable formulations of carriers, stabilizers and/or excipients. In a preferred embodiment, the pharmaceutical composition comprises a composition for parenteral, transdermal, intraluminal, intraarterial, intrathecal and/or intranasal administration or by direct injection into tissue. It is in particular envisaged that said composition is administered to a patient via infusion or injection. Administration of the suitable compositions may be effected by different ways, e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration. In particular, the present invention provides for an uninterrupted administration of the suitable composition. As a non-limiting example, uninterrupted, i.e. continuous administration may be realized by a small pump system worn by the patient for metering the influx of therapeutic agent into the body of the patient. The pharmaceutical composition comprising the CD33 targeting compound or the CD33 targeting compound and at least one epigenetic factor can be administered by using said pump systems. Such pump systems are generally known in the art, and commonly rely on periodic exchange of cartridges containing the therapeutic agent to be infused. When exchanging the cartridge in such a pump system, a temporary interruption of the otherwise uninterrupted flow of therapeutic agent into the body of the patient may ensue. In such a case, the phase of administration prior to cartridge replacement and the phase of administration following cartridge replacement would still be considered within the meaning of the pharmaceutical means and methods of the invention together make up one "uninterrupted administration" of such therapeutic agent.

[0158] The continuous or uninterrupted administration of the CD33 targeting compound described herein or the CD33 targeting compound and at least one epigenetic factor described herein may be intravenous or subcutaneous by way of a fluid delivery device or small pump system including a fluid driving mechanism for driving fluid out of a reservoir and an actuating mechanism for actuating the driving mechanism. Pump systems for subcutaneous administration may include a needle or a cannula for penetrating the skin of a patient and delivering the suitable composition into the patient's body. Said pump systems may be directly fixed or attached to the skin of the patient independently of a vein, artery or blood vessel, thereby allowing a direct contact between the pump system and the skin of the patient. The pump system can be attached to the skin of the patient for 24 hours up to several days. The pump system may be of small size with a reservoir for small volumes. As a non-limiting example, the volume of the reservoir for the suitable pharmaceutical composition to be administered can be between 0.1 and 50 ml.

[0159] The continuous administration may be transdermal by way of a patch worn on the skin and replaced at intervals. One of skill in the art is aware of patch systems for drug delivery suitable for this purpose. It is of note that transdermal administration is especially amenable to uninterrupted administration, as exchange of a first exhausted patch can advantageously be accomplished simultaneously with the placement of a new, second patch, for example on the surface of the skin immediately adjacent to the first exhausted patch and immediately prior to removal of the first exhausted patch. Issues of flow interruption or power cell failure do not arise.

[0160] The inventive compositions may further comprise a pharmaceutically acceptable carrier. Examples of suitable pharmaceutical carriers are well known in the art and include solutions, e.g. phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions, liposomes, etc. Compositions comprising such carriers can be formulated by well known conventional methods. Formulations can comprise carbohydrates, buffer solutions, amino acids and/or surfactants. Carbohydrates may be non-reducing sugars, preferably trehalose, sucrose, octasulfate, sorbitol or xylitol. In general, as used herein, "pharmaceutically acceptable carrier" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed and include: additional buffering agents; preservatives; co-solvents; antioxidants, including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g., Zn-protein complexes); biodegradable polymers, such as polyesters; salt-forming counter-ions, such as sodium, polyhydric sugar alcohols; amino acids, such as alanine, glycine, asparagine, 2-phenylalanine, and threonine; sugars or sugar alcohols, such as trehalose, sucrose, octasulfate, sorbitol or xylitol, stachyose, mannose, sorbose, xylose, ribose, myoinositol, galactose, lactitol, ribitol, myoinositol, galactitol, glycerol, cyclitols (e.g., inositol), polyethylene glycol; sulfur containing reducing agents, such as glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, [alpha]-monothioglycerol, and sodium thio sulfate; low molecular weight proteins, such as human serum albumin, bovine serum albumin, gelatin, or other immunoglobulins; and hydrophilic polymers, such as polyvinylpyrrolidone. Such formulations may be used for continuous administrations which may be intravenous or subcutaneous with and/or without pump systems. Amino acids may be charged amino acids, preferably lysine, lysine acetate, arginine, glutamate and/or histidine. Surfactants may be detergents, preferably with a molecular weight of >1.2 KD and/or a polyether, preferably with a molecular weight of >3 KD. Non-limiting examples for preferred detergents are Tween 20, Tween 40, Tween 60, Tween 80 or Tween 85. Non-limiting examples for preferred polyethers are PEG 3000, PEG 3350, PEG 4000 or PEG 5000. Buffer systems used in the present invention can have a preferred pH of 5-9 and may comprise citrate, succinate, phosphate, histidine and acetate.

[0161] The compositions of the present invention comprising the CD33 targeting compound and at least one epigenetic factor in a single or separate formulations can be administered to the subject at a suitable dose which can be determined e.g. by dose escalating studies by administration of increasing doses of the polypeptide described herein exhibiting cross-species specificity described herein to non-chimpanzee primates, for instance macaques. As set forth above, the CD33 targeting composition described herein exhibiting cross-species specificity described herein can be advantageously used in identical form in preclinical testing in non-chimpanzee primates and as drug in humans. The composition or these compositions can also be administered in combination with additional other proteinaceous and non-proteinaceous drugs. These drugs may be administered simultaneously with the composition comprising the polypeptide described herein as defined herein or separately before or after administration of said polypeptide in timely defined intervals and doses. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depend upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently.

[0162] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, inert gases and the like. In addition, the composition of the present invention might comprise proteinaceous carriers, like, e.g., serum albumin or immunoglobulin, preferably of human origin. It is envisaged that the composition of the invention might comprise, in addition to the polypeptide described herein defined herein, further biologically active agents, depending on the intended use of the composition. Such agents might be drugs acting on the gastrointestinal system, drugs acting as cytostatics, drugs preventing hyperuricemia, drugs inhibiting immunoreactions (e.g. corticosteroids), drugs modulating the inflammatory response, drugs acting on the circulatory system and/or agents such as cytokines known in the art. It is also envisaged that the composition of the present invention comprising the CD33 targeting compound and at least one epigenetic factor in a single or separate formulations is applied in an additional co-therapy, i.e., in combination with another anti-cancer medicament.

[0163] The biological activity of the pharmaceutical composition defined herein can be determined for instance by cytotoxicity assays, as described in the following examples, in WO 99/54440 or by Schlereth et al. (Cancer Immunol. Immunother. 20 (2005), 1-12). "Efficacy" or "*in vivo* efficacy" as used herein refers to the response to therapy by the pharmaceutical composition of the invention, using e.g. standardized NCI response criteria. The success or *in vivo* efficacy of the therapy using a pharmaceutical composition of the invention refers to the effectiveness of the composition

for its intended purpose, i.e. the ability of the composition to cause its desired effect, i.e. depletion of pathologic cells, e.g. tumor cells. The *in vivo* efficacy may be monitored by established standard methods for the respective disease entities including, but not limited to white blood cell counts, differentials, Fluorescence Activated Cell Sorting, bone marrow aspiration. In addition, various disease specific clinical chemistry parameters and other established standard methods may be used. Furthermore, computer-aided tomography, X-ray, nuclear magnetic resonance tomography (e.g. for National Cancer Institute-criteria based response assessment [Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999 Apr;17(4):1244]), positron-emission tomography scanning, white blood cell counts, differentials, Fluorescence Activated Cell Sorting, bone marrow aspiration, lymph node biopsies/histologies, and various lymphoma specific clinical chemistry parameters (e.g. lactate dehydrogenase) and other established standard methods may be used.

[0164] Another major challenge in the development of drugs such as the pharmaceutical composition of the invention is the predictable modulation of pharmacokinetic properties. To this end, a pharmacokinetic profile of the drug candidate, i.e. a profile of the pharmacokinetic parameters that affect the ability of a particular drug to treat a given condition, can be established. Pharmacokinetic parameters of the drug influencing the ability of a drug for treating a certain disease entity include, but are not limited to: half-life, volume of distribution, hepatic first-pass metabolism and the degree of blood serum binding. The efficacy of a given drug agent can be influenced by each of the parameters mentioned above.

[0165] "Half-life" means the time where 50% of an administered drug are eliminated through biological processes, e.g. metabolism, excretion, etc.

[0166] By "hepatic first-pass metabolism" is meant the propensity of a drug to be metabolized upon first contact with the liver, i.e. during its first pass through the liver.

[0167] "Volume of distribution" means the degree of retention of a drug throughout the various compartments of the body, like e.g. intracellular and extracellular spaces, tissues and organs, etc. and the distribution of the drug within these compartments.

[0168] "Degree of blood serum binding" means the propensity of a drug to interact with and bind to blood serum proteins, such as albumin, leading to a reduction or loss of biological activity of the drug.

[0169] Pharmacokinetic parameters also include bioavailability, lag time (Tlag), Tmax, absorption rates, more onset and/or Cmax for a given amount of drug administered. "Bioavailability" means the amount of a drug in the blood compartment. "Lag time" means the time delay between the administration of the drug and its detection and measurability in blood or plasma.

[0170] "Tmax" is the time after which maximal blood concentration of the drug is reached, and "Cmax" is the blood concentration maximally obtained with a given drug. The time to reach a blood or tissue concentration of the drug which is required for its biological effect is influenced by all parameters. Pharmacokinetic parameters of comprising a CD33 targeting compound such as a bispecific single chain antibody exhibiting cross-species specificity, which may be determined in preclinical animal testing in non-chimpanzee primates as outlined above, are also set forth e.g. in the publication by Schlereth et al. (Cancer Immunol. Immunother. 20 (2005), 1-12).

[0171] The term "toxicity" as used herein refers to the toxic effects of a drug manifested in adverse events or severe adverse events. These side events might refer to a lack of tolerability of the drug in general and/or a lack of local tolerance after administration. Toxicity could also include teratogenic or carcinogenic effects caused by the drug.

[0172] The term "safety", "*in vivo* safety" or "tolerability" as used herein defines the administration of a drug without inducing severe adverse events directly after administration (local tolerance) and during a longer period of application of the drug. "Safety", "*in vivo* safety" or "tolerability" can be evaluated e.g. at regular intervals during the treatment and follow-up period. Measurements include clinical evaluation, e.g. organ manifestations, and screening of laboratory abnormalities. Clinical evaluation may be carried out and deviations to normal findings recorded/coded according to NCI-CTC and/or MedDRA standards. Organ manifestations may include criteria such as allergy/immunology, blood/bone marrow, cardiac arrhythmia, coagulation and the like, as set forth e.g. in the Common Terminology Criteria for adverse events v3.0 (CTCAE). Laboratory parameters which may be tested include for instance hematology, clinical chemistry, coagulation profile and urine analysis and examination of other body fluids such as serum, plasma, lymphoid or spinal fluid, liquor and the like. Safety can thus be assessed e.g. by physical examination, imaging techniques (i.e. ultrasound, x-ray, CT scans, Magnetic Resonance Imaging (MRI), other measures with technical devices (i.e. electrocardiogram), vital signs, by measuring laboratory parameters and recording adverse events. For example, adverse events in non-chimpanzee primates in the uses and methods according to the invention may be examined by histopathological and/or histochemical methods.

[0173] The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term "therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the infection and the general state of the subject's own immune system. The

term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

[0174] The term "effective and non-toxic dose" as used herein refers to a tolerable dose of a pharmaceutical composition (i.e. a pharmaceutical composition comprising the CD33 targeting compound and an epigenetic factor in a single or separate formulations) which is high enough to cause depletion of pathologic cells, tumor elimination, tumor shrinkage or stabilization of disease without or essentially without major toxic effects. Such effective and non-toxic doses may be determined e.g. by dose escalation studies described in the art and should be below the dose inducing severe adverse side events (dose limiting toxicity, DLT). The above terms are also referred to e.g. in the Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6; ICH Harmonised Tripartite Guideline; ICH Steering Committee meeting on July 16, 1997.

[0175] The appropriate dosage, or therapeutically effective amount, of a pharmaceutical composition comprising the CD33 targeting compound and at an epigenetic factor in a single or separate formulations will depend on the condition to be treated, the severity of the condition, prior therapy, and the patient's clinical history and response to the therapeutic agent. The proper dose can be adjusted according to the judgment of the attending physician such that it can be administered to the patient one time or over a series of administrations. The pharmaceutical composition can be administered as a sole therapeutic or in combination with additional therapies such as anti-cancer therapies as needed.

[0176] The pharmaceutical compositions of this invention are particularly useful for parenteral administration, i.e., subcutaneously, intramuscularly, intravenously, intra-articular and/or intra-synovial. Parenteral administration can be by bolus injection or continuous infusion.

[0177] If the pharmaceutical composition has been lyophilized, the lyophilized material is first reconstituted in an appropriate liquid prior to administration. The lyophilized material may be reconstituted in, e.g., bacteriostatic water for injection (BWI), physiological saline, phosphate buffered saline (PBS), or the same formulation the protein had been in prior to lyophilization.

[0178] As disclosed herein, specific groups of epigenetic factors relate to an increase of the potency of a therapy approach making use of the engagement of T cells to CD33 positive target cells. 5-azacytidine (Vidaza™) and 5-aza-2'deoxyctidine (decitabine, Dacogen™) are nucleoside analogs that belong to a class of epigenetic therapeutics and are known to be capable of inducing tumor cell killing through the disruption of protein synthesis and inhibition of DNA methylation. Co-therapy approaches using the CD33 specific antibody lintuzumab and 5-azacytidine lead to an improved lintuzumab-mediated ADCC against AML target cells. However, in such study the incubation of AML cells or macrophages did not affect the CD33 expression on those cells (Sutherland et al. MAb. 2010 Jul-Aug; 2(4): 440-448). Accordingly it has been concluded that since for the mode-of-action of lintuzumab requires a functional interaction between the F_C domain of lintuzumab and the $F_{C\gamma}$ receptor of immune effector cells is required the pretreatment with epigenetic compounds increases the specific phagocytosis of target cells by the effector cells.

[0179] Thus the present finding are especially in the light of those known effect surprisingly, since the mode-of-action underlying the target cells lysis by T cells when engaged by the CD33 targeting compounds described herein is completely independent of any F_C - $F_{C\gamma}$ receptor interaction. In contrast to the previous studies, an increase of CD33 surface expression by treatment of target cells with epigenetic factors described herein was observed. Also, as apparent from the mode-of-action underlying the target cells lysis by T cells the observed synergistic effect is independent of any signal-transduction-effect which might be triggered by antibody binding to the CD33 surface molecule (e.g. a signaling pathway involving SHP-1, Syk, or both).

[0180] Moreover, as the speed and extent of myeloid leukemia cell blast lysis at a given time point was proportional to CD33 expression, this finding supports that the combination of an epigenetic therapy and a CD33 directed T cell engager would be synergistically more effective than either therapy administered separately. Accordingly, the described administration of one or more CD33 targeting compound in combination with epigenetic factors described herein may allow for lower doses of a bispecific T cell engager to be effective at a given time point.

[0181] As described above, examples for epigenetic factors suitable in the combination therapy approach as described herein are selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone demethylase inhibitors and ATRA (All Trans-retinoic acid). The redirected lysis of target cells via the recruitment of T cells by a multispecific, at least bispecific, construct involves cytolytic synapse formation and delivery of perforin and granzymes. The engaged T cells are capable of serial target cell lysis, and are not affected by immune escape mechanisms interfering with peptide antigen processing and presentation, or clonal T cell differentiation; see, for example, WO 2007/042261.

[0182] The cytotoxic activity mediated by CD33/CD3 bispecific compounds described herein such as bispecific antibody constructs is preferably measured in a cell-based cytotoxicity assay. It is represented by the EC_{50} value, which corresponds to the half maximal effective concentration (concentration of the compound which induces a cytotoxic response halfway between the baseline and maximum). Preferably, the EC_{50} value of the CD33/CD3 bispecific antibody constructs is ≤ 20.000 pg/ml, more preferably ≤ 5000 pg/ml, even more preferably ≤ 1000 pg/ml, even more preferably ≤ 500 pg/ml, even more preferably ≤ 350 pg/ml, even more preferably ≤ 320 pg/ml, even more preferably ≤ 250 pg/ml, even more preferably ≤ 100 pg/ml, even more preferably ≤ 50 pg/ml, even more preferably ≤ 10 pg/ml, and most preferably ≤ 5 pg/ml.

[0183] Any of the above given EC_{50} values can be combined with any one of the indicated scenarios of a cell-based cytotoxicity assay. For example, when (human) CD8 positive T cells or a macaque T cell line are used as effector cells, the EC_{50} value of the CD33/CD3 bispecific antibody construct is preferably ≤ 1000 pg/ml, more preferably ≤ 500 pg/ml, even more preferably ≤ 250 pg/ml, even more preferably ≤ 100 pg/ml, even more preferably ≤ 50 pg/ml, even more preferably ≤ 10 pg/ml, and most preferably ≤ 5 pg/ml. If in this assay the target cells are (human or macaque) CD33 transfected cells such as CHO cells, the EC_{50} value of the CD33/CD3 bispecific antibody construct is preferably ≤ 150 pg/ml, more preferably ≤ 100 pg/ml, even more preferably ≤ 50 pg/ml, even more preferably ≤ 30 pg/ml, even more preferably ≤ 10 pg/ml, and most preferably ≤ 5 pg/ml.

[0184] If the target cells are a CD33 positive natural expresser cell line, then the EC_{50} value is preferably ≤ 350 pg/ml, more preferably ≤ 320 pg/ml, even more preferably ≤ 250 pg/ml, even more preferably ≤ 200 pg/ml, even more preferably ≤ 100 pg/ml, even more preferably ≤ 150 pg/ml, even more preferably ≤ 100 pg/ml, and most preferably ≤ 50 pg/ml, or lower.

[0185] When (human) PBMCs are used as effector cells, the EC_{50} value of the CD33/CD3 bispecific antibody construct is preferably ≤ 1000 pg/ml, more preferably ≤ 750 pg/ml, more preferably ≤ 500 pg/ml, even more preferably ≤ 350 pg/ml, even more preferably ≤ 320 pg/ml, even more preferably ≤ 250 pg/ml, even more preferably ≤ 100 pg/ml, and most preferably ≤ 50 pg/ml, or lower.

[0186] The difference in cytotoxic activity between the monomeric and the dimeric isoform of individual CD33/CD3 bispecific antibody constructs is referred to as "potency gap". This potency gap can e.g. be calculated as ratio between EC_{50} values of the molecule's monomeric and dimeric form. Potency gaps of the CD33/CD3 bispecific antibody constructs described herein are preferably ≤ 5 , more preferably ≤ 4 , even more preferably ≤ 3 , even more preferably ≤ 2 and most preferably ≤ 1 .

[0187] It is particularly preferred for the CD33 targeting compound described herein that the second binding domain capable of binding to the T cell CD3 receptor complex comprises a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from:

(a) CDR-L1 as depicted in SEQ ID NO: 27 of WO 2008/119567, CDR-L2 as depicted in SEQ ID NO: 28 of WO 2008/119567 and CDR-L3 as depicted in SEQ ID NO: 29 of WO 2008/119567;

(b) CDR-L1 as depicted in SEQ ID NO: 117 of WO 2008/119567, CDR-L2 as depicted in SEQ ID NO: 118 of WO 2008/119567 and CDR-L3 as depicted in SEQ ID NO: 119 of WO 2008/119567; and

(c) CDR-L1 as depicted in SEQ ID NO: 153 of WO 2008/119567, CDR-L2 as depicted in SEQ ID NO: 154 of WO 2008/119567 and CDR-L3 as depicted in SEQ ID NO: 155 of WO 2008/119567.

[0188] In an alternatively preferred embodiment of the CD33 targeting compound described herein, the second binding domain capable of binding to the T cell CD3 receptor complex comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 selected from:

(a) CDR-H1 as depicted in SEQ ID NO: 12 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 13 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 14 of WO 2008/119567;

(b) CDR-H1 as depicted in SEQ ID NO: 30 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 31 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 32 of WO 2008/119567;

(c) CDR-H1 as depicted in SEQ ID NO: 48 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 49 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 50 of WO 2008/119567;

(d) CDR-H1 as depicted in SEQ ID NO: 66 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 67 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 68 of WO 2008/119567;

(e) CDR-H1 as depicted in SEQ ID NO: 84 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 85 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 86 of WO 2008/119567;

(f) CDR-H1 as depicted in SEQ ID NO: 102 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 103 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 104 of WO 2008/119567;

(g) CDR-H1 as depicted in SEQ ID NO: 120 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 121 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 122 of WO 2008/119567;

(h) CDR-H1 as depicted in SEQ ID NO: 138 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 139 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 140 of WO 2008/119567;

(i) CDR-H1 as depicted in SEQ ID NO: 156 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 157 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 158 of WO 2008/119567; and

(j) CDR-H1 as depicted in SEQ ID NO: 174 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 175 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 176 of WO 2008/119567.

[0189] It is further preferred for the CD33 targeting compound described herein that the second binding domain capable of binding to the T cell CD3 receptor complex comprises a VL region selected from the group consisting of a VL region

as depicted in SEQ ID NO: 35, 39, 125, 129, 161 or 165 of WO 2008/119567.

[0190] It is alternatively preferred that the second binding domain capable of binding to the T cell CD3 receptor complex comprises a VH region selected from the group consisting of a VH region as depicted in SEQ ID NO: 15, 19, 33, 37, 51, 55, 69, 73, 87, 91, 105, 109, 123, 127, 141, 145, 159, 163, 177 or 181 of WO 2008/119567.

[0191] More preferably, the CD33 targeting compound described herein is characterized by the second binding domain capable of binding to the T cell CD3 receptor complex comprising a VL region and a VH region selected from the group consisting of:

(a) a VL region as depicted in SEQ ID NO: 17 or 21 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 15 or 19 of WO 2008/119567;

(b) a VL region as depicted in SEQ ID NO: 35 or 39 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 33 or 37 of WO 2008/119567;

(c) a VL region as depicted in SEQ ID NO: 53 or 57 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 51 or 55 of WO 2008/119567;

(d) a VL region as depicted in SEQ ID NO: 71 or 75 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 69 or 73 of WO 2008/119567;

(e) a VL region as depicted in SEQ ID NO: 89 or 93 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 87 or 91 of WO 2008/119567;

(f) a VL region as depicted in SEQ ID NO: 107 or 111 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 105 or 109 of WO 2008/119567;

(g) a VL region as depicted in SEQ ID NO: 125 or 129 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 123 or 127 of WO 2008/119567;

(h) a VL region as depicted in SEQ ID NO: 143 or 147 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 141 or 145 of WO 2008/119567;

(i) a VL region as depicted in SEQ ID NO: 161 or 165 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 159 or 163 of WO 2008/119567; and

(j) a VL region as depicted in SEQ ID NO: 179 or 183 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 177 or 181 of WO 2008/119567.

[0192] According to a preferred embodiment of the CD33 targeting compound described herein, in particular the second binding domain capable of binding to the T cell CD3 receptor complex, the pairs of VH-regions and VL-regions are in the format of a single chain antibody (scFv). The VH and VL regions are arranged in the order VH-VL or VL-VH. It is preferred that the VH-region is positioned N-terminally to a linker sequence. The VL-region is positioned C-terminally of the linker sequence.

[0193] A preferred embodiment of the CD33 targeting compound described herein is characterized by the second binding domain capable of binding to the T cell CD3 receptor complex comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 25, 41, 43, 59, 61, 77, 79, 95, 97, 113, 115, 131, 133, 149, 151, 167, 169, 185 or 187 of WO 2008/119567.

[0194] The formulations described herein are useful as pharmaceutical compositions in the treatment, amelioration and/or prevention of the pathological medical condition as described herein in a patient in need thereof. The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Treatment includes the application or administration of the formulation to the body, an isolated tissue, or cell from a patient who has a disease/disorder, a symptom of a disease/disorder, or a predisposition toward a disease/disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptom of the disease, or the predisposition toward the disease.

[0195] Those "in need of treatment" include those already with the disorder, as well as those in which the disorder is to be prevented. The term "disease" is any condition that would benefit from treatment with the protein formulation described herein. This includes chronic and acute disorders or diseases including those pathological conditions that predispose the mammal to the disease in question. Non-limiting examples of diseases/disorders to be treated herein include the herein described myeloid leukemia.

[0196] In some embodiments, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or a plurality of the antibody construct described herein together with a pharmaceutically effective diluents, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. Pharmaceutical compositions described herein include, but are not limited to, liquid, frozen, and lyophilized compositions.

[0197] Preferably, formulation materials are nontoxic to recipients at the dosages and concentrations employed.

[0198] In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation

materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, proline, or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See, REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, (A. R. Genrmo, ed.), 1990, Mack Publishing Company.

[0199] In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antigen binding proteins described herein. In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefore. In certain embodiments of the invention, human antibody or antigen binding fragment thereof described herein or the antibody construct described herein compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, the human antibody or antigen binding fragment thereof described herein or the antibody construct described herein may be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0200] The pharmaceutical compositions described herein can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art. The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0201] When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired human antibody or antigen binding fragment thereof described herein or the antibody construct described herein in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antibody construct described herein is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that may provide controlled or sustained release of the product which can be delivered via depot injection. In certain embodiments, hyaluronic acid may also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the desired antigen binding protein.

[0202] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving the antibody construct described herein in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3,773,919 and European Patent Application Publication No. EP 058481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 2:547-556), poly (2-hydroxyethyl-methacrylate) (Langer et al., 1981, J. Biomed. Mater. Res. 15:167-277 and Langer, 1982, Chem. Tech. 12:98-105), ethylene vinyl acetate (Langer et al., 1981, *supra*) or poly-D(-)-3-hydroxybutyric acid (European Patent Application

Publication No. EP 133,988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. See, e.g., Eppstein et al., 1985, Proc. Natl. Acad. Sci. U.S.A. 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949.

[0203] Pharmaceutical compositions used for in vivo administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0204] Aspects of the invention includes self-buffering antibody construct formulations, which can be used as pharmaceutical compositions, as described in international patent application WO 2006/138181A2 (PCT/US2006/022599).

[0205] As discussed above, certain embodiments involve antibody construct protein compositions, particularly pharmaceutical compositions of the invention, that comprise, in addition to the antibody construct described herein, one or more excipients such as those illustratively described in this section and elsewhere herein. Excipients can be used in the invention in this regard for a wide variety of purposes, such as adjusting physical, chemical, or biological properties of formulations, such as adjustment of viscosity, and or processes to improve effectiveness and or to stabilize such formulations and processes against degradation and spoilage due to, for instance, stresses that occur during manufacturing, shipping, storage, pre-use preparation, administration, and thereafter.

[0206] A variety of expositions are available on protein stabilization and formulation materials and methods useful in this regard, such as Arakawa et al., "Solvent interactions in pharmaceutical formulations," Pharm Res. 8(3): 285-91 (1991); Kendrick et al., "Physical stabilization of proteins in aqueous solution," in: RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE, Carpenter and Manning, eds. Pharmaceutical Biotechnology. 13: 61-84 (2002), and Randolph et al., "Surfactant-protein interactions," Pharm Biotechnol. 13: 159-75 (2002).

[0207] Salts may be used in accordance with certain embodiments of the invention to, for example, adjust the ionic strength and/or the isotonicity of a formulation and/or to improve the solubility and/or physical stability of a protein or other ingredient of a composition in accordance with the invention.

[0208] As is well known, ions can stabilize the native state of proteins by binding to charged residues on the protein's surface and by shielding charged and polar groups in the protein and reducing the strength of their electrostatic interactions, attractive, and repulsive interactions. Ions also can stabilize the denatured state of a protein by binding to, in particular, the denatured peptide linkages (--CONH) of the protein. Furthermore, ionic interaction with charged and polar groups in a protein also can reduce intermolecular electrostatic interactions and, thereby, prevent or reduce protein aggregation and insolubility.

[0209] Ionic species differ significantly in their effects on proteins. A number of categorical rankings of ions and their effects on proteins have been developed that can be used in formulating pharmaceutical compositions in accordance with the invention. One example is the Hofmeister series, which ranks ionic and polar non-ionic solutes by their effect on the conformational stability of proteins in solution. Stabilizing solutes are referred to as "kosmotropic." Destabilizing solutes are referred to as "chaotropic." Kosmotropes commonly are used at high concentrations (e.g., >1 molar ammonium sulfate) to precipitate proteins from solution ("salting-out"). Chaotropes commonly are used to denature and/or to solubilize proteins ("salting-in"). The relative effectiveness of ions to "salt-in" and "salt-out" defines their position in the Hofmeister series.

[0210] Free amino acids can be used in the antibody construct formulations in accordance with various embodiments of the invention as bulking agents, stabilizers, and antioxidants, as well as other standard uses. Lysine, proline, serine, and alanine can be used for stabilizing proteins in a formulation. Glycine is useful in lyophilization to ensure correct cake structure and properties. Arginine may be useful to inhibit protein aggregation, in both liquid and lyophilized formulations. Methionine is useful as an antioxidant.

[0211] Polyols include sugars, e.g., mannitol, sucrose, and sorbitol and polyhydric alcohols such as, for instance, glycerol and propylene glycol, and, for purposes of discussion herein, polyethylene glycol (PEG) and related substances. Polyols are kosmotropic. They are useful stabilizing agents in both liquid and lyophilized formulations to protect proteins from physical and chemical degradation processes. Polyols also are useful for adjusting the tonicity of formulations.

[0212] Among polyols useful in select embodiments of the invention is mannitol, commonly used to ensure structural stability of the cake in lyophilized formulations. It ensures structural stability to the cake. It is generally used with a lyoprotectant, e.g., sucrose. Sorbitol and sucrose are among preferred agents for adjusting tonicity and as stabilizers to protect against freeze-thaw stresses during transport or the preparation of bulks during the manufacturing process. Reducing sugars (which contain free aldehyde or ketone groups), such as glucose and lactose, can glycate surface lysine and arginine residues. Therefore, they generally are not among preferred polyols for use in accordance with the invention. In addition, sugars that form such reactive species, such as sucrose, which is hydrolyzed to fructose and glucose under acidic conditions, and consequently engenders glycation, also is not among preferred polyols of the invention in this regard. PEG is useful to stabilize proteins and as a cryoprotectant and can be used in the invention in

this regard.

[0213] Embodiments of the antibody construct formulations further comprise surfactants. Protein molecules may be susceptible to adsorption on surfaces and to denaturation and consequent aggregation at air-liquid, solid-liquid, and liquid-liquid interfaces. These effects generally scale inversely with protein concentration. These deleterious interactions generally scale inversely with protein concentration and typically are exacerbated by physical agitation, such as that generated during the shipping and handling of a product.

[0214] Surfactants routinely are used to prevent, minimize, or reduce surface adsorption. Useful surfactants in the invention in this regard include polysorbate 20, polysorbate 80, other fatty acid esters of sorbitan polyethoxylates, and poloxamer 188.

[0215] Surfactants also are commonly used to control protein conformational stability. The use of surfactants in this regard is protein-specific since, any given surfactant typically will stabilize some proteins and destabilize others.

[0216] Polysorbates are susceptible to oxidative degradation and often, as supplied, contain sufficient quantities of peroxides to cause oxidation of protein residue side-chains, especially methionine. Consequently, polysorbates should be used carefully, and when used, should be employed at their lowest effective concentration. In this regard, polysorbates exemplify the general rule that excipients should be used in their lowest effective concentrations.

[0217] Embodiments of the antibody construct formulations further comprise one or more antioxidants. To some extent deleterious oxidation of proteins can be prevented in pharmaceutical formulations by maintaining proper levels of ambient oxygen and temperature and by avoiding exposure to light. Antioxidant excipients can be used as well to prevent oxidative degradation of proteins. Among useful antioxidants in this regard are reducing agents, oxygen/free-radical scavengers, and chelating agents. Antioxidants for use in therapeutic protein formulations in accordance with the invention preferably are watersoluble and maintain their activity throughout the shelf life of a product. EDTA is a preferred antioxidant in accordance with the invention in this regard.

[0218] Antioxidants can damage proteins. For instance, reducing agents, such as glutathione in particular, can disrupt intramolecular disulfide linkages. Thus, antioxidants for use in the invention are selected to, among other things, eliminate or sufficiently reduce the possibility of themselves damaging proteins in the formulation.

[0219] Formulations in accordance with the invention may include metal ions that are protein cofactors and that are necessary to form protein coordination complexes, such as zinc necessary to form certain insulin suspensions. Metal ions also can inhibit some processes that degrade proteins. However, metal ions also catalyze physical and chemical processes that degrade proteins.

[0220] Magnesium ions (10-120 mM) can be used to inhibit isomerization of aspartic acid to isoaspartic acid. Ca^{+2} ions (up to 100 mM) can increase the stability of human deoxyribonuclease. Mg^{+2} , Mn^{+2} , and Zn^{+2} , however, can destabilize rhDNase. Similarly, Ca^{+2} and Sr^{+2} can stabilize Factor VIII, it can be destabilized by Mg^{+2} , Mn^{+2} and Zn^{+2} , Cu^{+2} and Fe^{+2} , and its aggregation can be increased by Al^{+3} ions.

[0221] Embodiments of the antibody construct formulations further comprise one or more preservatives. Preservatives are necessary when developing multi-dose parenteral formulations that involve more than one extraction from the same container. Their primary function is to inhibit microbial growth and ensure product sterility throughout the shelf-life or term of use of the drug product. Commonly used preservatives include benzyl alcohol, phenol and m-cresol. Although preservatives have a long history of use with small-molecule parenterals, the development of protein formulations that includes preservatives can be challenging. Preservatives almost always have a destabilizing effect (aggregation) on proteins, and this has become a major factor in limiting their use in multi-dose protein formulations. To date, most protein drugs have been formulated for single-use only. However, when multi-dose formulations are possible, they have the added advantage of enabling patient convenience, and increased marketability. A good example is that of human growth hormone (hGH) where the development of preserved formulations has led to commercialization of more convenient, multi-use injection pen presentations. At least four such pen devices containing preserved formulations of hGH are currently available on the market. Norditropin (liquid, Novo Nordisk), Nutropin AQ (liquid, Genentech) & Genotropin (lyophilized--dual chamber cartridge, Pharmacia & Upjohn) contain phenol while Somatropo (Eli Lilly) is formulated with m-cresol. Several aspects need to be considered during the formulation and development of preserved dosage forms. The effective preservative concentration in the drug product must be optimized. This requires testing a given preservative in the dosage form with concentration ranges that confer anti-microbial effectiveness without compromising protein stability.

[0222] As might be expected, development of liquid formulations containing preservatives are more challenging than lyophilized formulations. Freeze-dried products can be lyophilized without the preservative and reconstituted with a preservative containing diluent at the time of use. This shortens the time for which a preservative is in contact with the protein, significantly minimizing the associated stability risks. With liquid formulations, preservative effectiveness and stability should be maintained over the entire product shelf-life (about 18 to 24 months). An important point to note is that preservative effectiveness should be demonstrated in the final formulation containing the active drug and all excipient components.

[0223] The antibody construct described herein generally will be designed for specific routes and methods of admin-

istration, for specific administration dosages and frequencies of administration, for specific treatments of specific diseases, with ranges of bio-availability and persistence, among other things. Formulations thus may be designed in accordance with the invention for delivery by any suitable route, including but not limited to orally, aurally, ophthalmically, rectally, and vaginally, and by parenteral routes, including intravenous and intraarterial injection, intramuscular injection, and subcutaneous injection.

[0224] Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration. The invention also provides kits for producing a single-dose administration unit. The kits of the invention may each contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments of this invention, kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are provided. The therapeutically effective amount of an antibody construct protein-containing pharmaceutical composition to be employed will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will vary depending, in part, upon the molecule delivered, the indication for which the antibody construct described herein is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician may titrate the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 $\mu\text{g/kg}$ to up to about 30 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage may range from 1.0 $\mu\text{g/kg}$ up to about 20 mg/kg , optionally from 10 $\mu\text{g/kg}$ up to about 10 mg/kg or from 100 $\mu\text{g/kg}$ up to about 5 mg/kg .

[0225] A therapeutic effective amount of pharmaceutical composition of the invention comprising the CD33 targeting compound and an epigenetic factor in a single or separate formulations preferably results in a decrease in severity of disease symptoms, in increase in frequency or duration of disease symptom-free periods or a prevention of impairment or disability due to the disease affliction. For treating CD33-expressing tumors, a therapeutically effective amount of the CD33 targeting compound and an epigenetic factor in a single or separate formulations, e.g. an anti-CD33/CD3 antibody construct and the epigenetic factor, preferably inhibits cell growth or tumor growth by at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% relative to untreated patients. The ability of a compounds to inhibit tumor growth may be evaluated in an animal model predictive of efficacy in human tumors.

[0226] Pharmaceutical compositions may be administered using a medical device. Examples of medical devices for administering pharmaceutical compositions are described in U.S. Patent Nos. 4,475,196; 4,439,196; 4,447,224; 4,447,233; 4,486,194; 4,487,603; 4,596,556; 4,790,824; 4,941,880; 5,064,413; 5,312,335; 5,312,335; 5,383,851; and 5,399,163.

[0227] It should be understood that the inventions herein are not limited to particular methodology, protocols, or reagents, as such can vary. The discussion and examples provided herein are presented for the purpose of describing particular embodiments only and are not intended to limit the scope of the present invention, which is defined solely by the claims.

Examples:

[0228] The following examples are provided for the purpose of illustrating specific embodiments or features of the present invention. These examples should not be construed as to limit the scope of this invention. The examples are included for purposes of illustration, and the present invention is limited only by the claims.

Example 1 - Epigenetic modifying drugs as sensitizing agents for CD33 targeting compound-induced cytotoxicity

[0229] The level of CD33 expression was identified as a critical variable for the extent of activity of a CD33 targeting compound described herein such as AMG330 against human AML cells. Accordingly, it was surprising to observe the potential of epigenetic modifying drugs such as histone deacetylase (HDAC) inhibitors or DNA methyltransferase (DNMT) I inhibitors as sensitizing agents for AMG 330-induced cytotoxicity.

[0230] For the experimental settings mononuclear cells were collected from healthy adult volunteers via leukapheresis, and T cells enriched through magnetic cell sorting (Pan T Cell Isolation Kit II; Miltenyi Biotec, Auburn, CA). Thawed cell aliquots were labeled with 3 μM CellVue Burgundy (eBioscience, San Diego, CA) according to the manufacturer's instructions.

[0231] Human myeloid OCI-AML3, KG-1a, ML-1, NB4, TF-1, and HL-60 cells were maintained as previously described (Walter et al. Blood. 2003;102(4):1466-1473; Walter et al. Blood. 2004;103(11):4276-4284, Walter et al. Blood. 2005;105(3):1295-1302).

[0232] CD33 expression on parental AML cells and cell lines was quantified by flow cytometry using a phycoerythrin

(PE)-conjugated anti-CD33 antibody (clone P67.6; BD Biosciences, San Jose, CA, USA) (see Walter et al. Blood. 2005;105(3):1295-1302).

[0233] For the quantification of compound induces cytotoxicity AML cells were taken during exponential growth and incubated at 37°C (in 5% CO₂ and air) in 96-well round bottom plates (BD Falcon™) at 5-10 x 10³ cells/well in 225 µL culture medium containing various concentrations of AMG 330 as well as T-cells at different effector:target (E:T) cell ratios. After 48 hours, cell numbers and drug-induced cytotoxicity, using 4',6-diamidino-2-phenylindole (DAPI) to detect non-viable cells, were determined using a LSRII flow cytometer (BD Biosciences, San Jose, CA) and analyzed with FlowJo (Tree Star, Ashland, OR). AML cells were identified by forward/side scatter properties and negativity for CellVue Burgundy dye.

[0234] To determine CD33 modulation, aliquots of AML cells were left untreated or incubated with either AMG 330 (250 pg/mL) or an unconjugated, unlabeled anti-CD33 antibody (clone P67.6; BD Biosciences, San Jose, CA, USA; 2.5 µg/mL). After 48 hours, cells were washed in ice-cold Phosphate Buffered Saline (PBS, GIBCO Invitrogen) to remove unbound antibody and resuspended in PBS containing 2% fetal bovine serum. As AMG 330 does not compete for binding to CD33 with P67.6, aliquots of untreated and AMG 330-treated cells were incubated with P67.6 or no primary antibody followed by biotin-conjugated rat anti-mouse IgG₁ (used at 2.5 µg/mL in PBS/2% FBS) and streptavidin-phycoerythrin (PE) (used at 2.5 µg/mL in PBS/2% FBS; both from BD Biosciences). Likewise, aliquots of untreated and P67.6-treated cells were incubated with unconjugated P67.6 or without primary antibody; cells were then washed and incubated with biotin-conjugated rat anti-mouse IgG₁ monoclonal antibody followed by incubation with streptavidin-PE conjugate. To identify nonviable cells, all samples were stained with DAPI. At least 10,000 events were acquired, and DAPI⁺ cells were analyzed on a Canto flow cytometer (BD Biosciences) using FlowJo Software. Linear median fluorescence intensity (MFI) values were used to calculate the percentage of drug-bound CD33 internalization.

[0235] As shown in Figure 1, 3-day pretreatment with the HDAC inhibitor, panobinostat, resulted in significant increase in CD33 expression in OCI-AML3 and, markedly, KG-1a cells. More importantly, relative to untreated cells, cells pretreated with panobinostat for 3 days were modestly more sensitive to AMG 330-induced cytotoxicity (KG-1a > OCI-AML3). Pretreatment with the DNMT I inhibitor, azacitidine, for 3 days resulted in significant increase in CD33 expression on KG-1a. Consistently, after pretreatment with azacitidine, KG-1a cells became significantly more sensitive to AMG 330-induced cytotoxicity relative to untreated cells (Figure 2).

Example 2 - CD33 up-regulation on AML cells to increase AMG 330 mediated lysis efficacy

Hydroxyurea

Up-regulation of CD33 on AML cell lines:

[0236] AML cell lines HL-60, PL21, OCI-AML3, KG1a and MV4-11 were seeded in 24-well plates at 1x10⁶ cells/ml on day 0. Cells were either left untreated (UT) or treated with 10µM (H1) or 100µM (H2) hydroxyurea (Sigma) for three consecutive days (day 0, day 1 and day 2). On day 3, cells were harvested, counted and analyzed for changes in CD33 surface expression level by flow cytometry.

[0237] Figure 3 and Table 2 show an upregulation of CD33 on HL-60 and PL21 AML cells in a concentration dependant manner.

Table 2: CD33 MFI Ratios of HL-60 and PL21 AML cells after incubation with/without hydroxyurea determined by flow cytometry.

CD33 MFI Ratio	UT	H1	H2
HL-60	134.9	171.3	210.0
PL21	166.9	177.9	191.8

Up-regulation of CD33 on primary AML cells:

[0238] Three primary AML samples were seeded in a 12-well plates at 1x10⁶ cells/ml, as previously described (Krupka, Subklewe et.al, Blood 2014). Cells were either left untreated (UT) or treated with 10µM (H1) or 100µM (H2) hydroxyurea (Sigma) for three consecutive days (day 0, day 1 and day 2). On day 1 - day 3, cells were harvested, counted and analyzed for changes in CD33 surface expression by flow cytometry.

[0239] Figure 4 and Table 3 show an up-regulation of CD33 in 1 of 3 patient samples on day 1 and day 2 of incubation with hydroxyurea.

Table 3: CD33 MFI Ratios of primary AML cells from patient 2 after 1 and 2 days of incubation with hydroxyurea determined by flow cytometry.

CD33 MFI Ratio	UT	H1	H2
day 1 Patient 2	3.7	4.2	4.5
day 2 Patient 2	4.8	4.2	5.1

Granulocyte-Colony Stimulating Factor (G-CSF)

Up-regulation of CD33 on AML cell lines:

[0240] AML cell lines OCI-AML3 and KG1 α were seeded in 24-well plates at 5×10^5 cells/ml on day 0. Cells were either left untreated (UT) or treated with 200 ng/ml (C1) or 2000 ng/ml (C2) G-CSF (Peprotech) for 10 days. G-CSF was freshly added to the cultures biweekly. On day 10, cells were harvested and analyzed for changes in CD33 surface expression by flow cytometry.

[0241] Figure 5 and Table 4 show a low upregulation of CD33 on KG1 α AML cells in a concentration dependant manner.

Table 4: CD33 MFI Ratios of KG1 α AML cells after 10 days of incubation with/without G-CSF determined by flow cytometry.

CD33 MFI Ratio	UT	C1	C2
KG1 α	16.5	17.9	19.2

SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
1	CD33 VH of AH3	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWRQAPGQGLEWMGWINTYTGEPTYADDFKG RVTMSSDTSSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWQGTTVTVSS
2	CD33 HCDR1 of AH3	artificial	aa	NYGMN
3	CD33 HCDR2 of AH3	artificial	aa	WINTYGEPTYADDFKG
4	CD33 HCDR3 of AH3	artificial	aa	WSWSDGYVYFDY
5	CD33 VH of AH3	artificial	nt	CAGGTGCAGCTGGTGCGAGCTGGAGCTGAGGTGAAAAAGCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGCTAGCGGGTATACCTTCACAAACTATGGAATGAACCTGGTGAGGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACCTGGAGAGCCACATATGCTGATGACTTCAAGGGA CGGTTACCATGTCTTCGGATACCTCTACCAAGCATGCCTATTTGGAAATCAACAGCCTCAGAAGT GATGACACGGCTATATATTACTGTGCGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTTGAC TACTGGGGCCCAAGGCACTACGGTCACCGTCTCCTCA
6	CD33 VL of AH3	artificial	aa	DIVMTQSPDLSLTIVSLGERTTINCKSSQSVLDSKKNKNSLAWYQQKPGQPPLKLLLSWASTRESGIPD RFGSGSGTDFLTITDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK
7	CD33 LCDR1 of AH3	artificial	aa	KSSQSVLDSKKNKNSLA
8	CD33 LCDR2 of AH3	artificial	aa	WASTRES
9	CD33 LCDR3 of AH3	artificial	aa	QQSAHFPIIT
10	CD33 VL of AH3	artificial	nt	GACATCGTGATGACACAGTCCTCAGACTCCCTGACTGTGTCTCTGGGCGAGAGGACCAACCATCAAC TGCAAGTCCAGCCAGAGTGTTTTTAGACAGCTCCAAGAATAAGAACTCTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAATTACTCCTTTCTGGGCATCTACGGGGGAATCCGGGATCCCTGAC CGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGCCAAGGGACACGACTG GAGATTAAA
11	CD33 CD33 HL of AH3	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWRQAPGQGLEWMGWINTYTGEPTYADDFKG RVTMSSDTSSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWQGTTVTVSSGGGSGGGGS GGGSDIVMTQSPDLSLTIVSLGERTTINCKSSQSVLDSKKNKNSLAWYQQKPGQPPLKLLLSWASTRE SGIPDRFSGSGGTDFLTITDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK
12	CD33 HL of AH3	artificial	nt	CAGGTGCAGCTGGTGCGAGCTGGAGCTGAGGTGAAAAAGCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGCTAGCGGGTATACCTTCACAAACTATGGAATGAACCTGGTGAGGCAGGCTCCAGGACAGGGT

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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13	CD33 AH3 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYFTFTNYGMNWRQAPGQGLEWMGWINTYTGEPTYADDFKG RVTMSSDTSTSTAYLEINSLRSDDTAIYYCARWSWDGYVYFDYWGQGT'TVTVSSGGGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKKNKNSLAWYQQKPGQPPLKLLSWASTRE SGIPDRFSGSGSTDFTLTIDSLQPEDSATYYCQQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLIKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSSGGGGSGGGSGGGGS QTVVTTQEPSTLVSPGGTVTLTTCGSSTGAVTSGYYPNWRVQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGGKAALTLSGVQPEDEAEIYCALWYSNRWVFGGTKLTVL

(continued)

SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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				TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTCCGTGGAGGAACCAAACTGACTGTCTTA
15	CD33 AH3 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWRQAPGQGLEWMGWINTYTGEPTYADDFKG RVTMSDTSSTAYLEINSLRSDDTAIYYCARWSWSDGYVYFDYWQGTTVTVSSGGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGTDFTLTIDSLQPEDSATYYCQSAHFPITTFQGTRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNSYAMNWRQAPGKLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWQGTLVTVSSGGGSGGGGSGGGGS QTVVTVQEPSTLVSPGGTVTLTLCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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17	CD33 AH3 HL x I2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWRQAPGQGLEWMGWINTYTGEPTYADDFKG RVTMSDSTSTAYLEINSLRDDTAIYYCARWSWSDGYVYFDYWGGTTVTVSSGGSGSGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTIDSLQPEDSATYQCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQQGTLVTVSSGGSGSGGSGGGS
				QTAVTQEPSLTVSPGGTVTLTCCGSSTGAVTSGNYPNWVQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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19	CD33 VH of AF5	artificial	aa	QVQLVQSGAEVKKPGASVKVSKASGYTFITNYGMNWVKQAPGQGLKWMGWINTYTGPTYADDFKG RVTMTSDTSTSTAYLELHNLRSDDTAVYICARWSWSGYYVYFDYWGGTITVTVSS
20	CD33 HCDR1 of AF5	artificial	aa	NYGMN
21	CD33 HCDR2 of AF5	artificial	aa	WINTYGEPTYADDFKG
22	CD33 HCDR3 of AF5	artificial	aa	WSWSDGYVYFDY
23	CD33 VH of AF5	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGAGCGTCAGTCAAGGTCCTCTGC AAGCTAGCGGGTATACCTTCAAAAATGAACTGGTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATTTGAACTCCACAACTCAGAAAT

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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24	CD33 VL of AF5	artificial	aa	DIVMTQSPDLSLTIVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPGQPFPKLLLSWASTRESGIPD RFGSGSGTDFTLTIDSLQPEDSATYYCQSAHFPIITFGQGRLEIK
25	CD33 LCDR1 of AF5	artificial	aa	KSSQSVLDSSKNKNSLA
26	CD33 LCDR2 of AF5	artificial	aa	WASTRES
27	CD33 LCDR3 of AF5	artificial	aa	QQSAHFPIIT
28	CD33VL of AF5	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAGAGACCACCATCAAC TGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACACGAGACAGCTCTCTAAATTACTCTCTTCTCTGGGCATCTACGCGGAAATCCGGGATCCCTGAC CGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCAGTACCTTTGGCCAAAGGACACGACTG GAGATTAAA
29	CD33HL of AF5	artificial	aa	QVQLVQSGAEVKKPGASVKVCKASGYTFITNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTSDTSTSTAYLELHNLRSDDTAVYICARWSWSDGYVYFDYWGGTTVTVSSGGGGGGGS GGGSDIVMTQSPDLSLTIVSLGERTTINCKSSQSVLDSSKNKNSLAWYQQKPGQPFPKLLLSWASTRE SGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQSAHFPIITFGQGRLEIK
30	CD33 HL of AF5	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCTGGAGCGTCAGTCAAGGTCTCCTGC AAGGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATTTGAACTCCACAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCGTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCCAAGCACTACGGTCACCGTCTCCTCAGGTGGTGGTCTGGCGGCGGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAATTACTCTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCAGTACACCTTTGGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCAGTACACCTTTGGC CAAGGGACACGACTGGAGATTAAA

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
31	CD33 AF5 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGASVKVSCKASGYFTNFGMNWVKQAPGQGLKWMGWIINTYTGEPTYADDFKG RVMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWQGTTTVTVSSGGGGGGGGG GGGSDIVMTQSPDLSLTSLGERTTINCKSSQSVLDSKNKNSLAWYQQKPGQPPLKLLSWASTRE SGIPDRFSGSGSTDFLTIDSLQPEDSATYCCQSAHFPIITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSAASGFTFNKYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLIKTEDTAVYYCVRHGNFGNSYISYWAYWQGTLTVTVSSGGGGGGGGGGGGG QTAVTQEPSLTVSPGGTVTLTLCGSSTGAVTSGYYPNWVQKPGQAPRGLIGGTFKFLAPGTPARFSG
				SLLGKKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
32	CD33 AF5 HL x H2C HL	artificial	nt	CAGGTGCAGTGGTGCAGTCTGGAGCTGAGGTGAAGAGCCTGGAGCGTCAGTCAAGGTCTCCTGC AAGGCTAGCGGGTATACCTTCAAAAACATATGGAATGAATGGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATTGGAACCTCCACAACCTCAGAAGT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGGCGGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCAACATCAACTGAAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAGAGAAACAGGACAGCCTCCTAAATTACTCCTTTCTGGGCATCTACGCGGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGGTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGGACAGACTGGAGATTAAATCCGAGGTGGTGGTCCGAGGTGCAGTGGTCGAGTCTGGA GGAGGATTGGTGAGCCTGGAGGTCAATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AAGTACGCCATGAACCTGGGTCCGCCAGGCTCCAGGAAAGGGTTTGGAAATGGGTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTCACTGAAAGACAGGTTTCAACATCTCCAGA GATGATTCAAAAAACACTGCCCTATCTACAAATGAACAACTTGAAAACTGAGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTTCGGTAATAGCTACATATCTACTGGGCTTACTGGGGCCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGTCTCTGACTGGGGCTGTTACATCTGGTACTACCCAAACTGGTCCAACAAAAACAGGTGAG GCACCCCGTGGTCTAATAGGTGGACTAAGTTCCTCGCCCCGGTACTCTCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGGATGAGGCAGAAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTTCGGTGGAGAACCAAACTGACTGTCTCTA

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
33	CD33 AF5 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWDGYVFDYWGQGT'TVTVSSGGGGGGGGG GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKKNLSLAWYQQKPGQPPLKLLSWASTRE SGIPDRFSGSGGTDFLTIDSLQPEDSATYCYQQSAHFPIITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGSLKLSCAASGFTFNSYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQGLTVTVSSGGGGGGGGGGG QTAVTQEPSLTVSPGGTVTLTCSGSTGAVTSGNYPNWVQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLITVL
34	CD33 AF5 HL x F12Q HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAACCTGGAGCGTCAGTCAAGGTCTCCTGC AAGGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCAACATATGCTGATGACTTCAAGGGA CGGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATTTGGAACCTCCACAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCCTCAGTGGTGGTGGTCTGGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAATTACTCTTTCTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCTGCAACTTACTATTGTCAACAGTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGGACACGACTGGAGATTAAATCCGGAGGTGGTGGCTCCGAGGTGCAGCTGGTTCGAGTCTGGA GGAGGATTGGTGCAGCCTGGAGGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AGCTACGCCATGAACTGGGTCCGCCAGGCTCCAGGAAAGGGTTTGAATGGGTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTGAGTGAAGGCAGGTTCAACATCTCCAGA GATGATTCAAAAAACACTGCCTATCTACAAATGAACAACTTGAACACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGTACGTTTCTGGTGGCTTACTGGGGCCCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACTCACTTGT GGCTCCTCGACTGGGCTGTTACATCTGGCAACTACCCAACTGGGTCCAAACAAACCCAGGTGAG GCACCCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTTCGGTGGAGGAACCAAACTGACTGTCTCTA

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
35	CD33 AF5 HL x 12C HL	artificial	aa	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVMTSDTSTSTAYLELHNLRSDDTAVYYCARWSWDGYVYFDYWGGTTVTVSSGGGGGGGGG GGGSDIVMTQSPDLSLTSLGERTTINCKSSQSLDSSKNKNSLAWYQQKPGQPPLKLLSWASTRE SGIPDRFSGSGGTDFLTIDSLQPEDSATYCYQQSAHFPIITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNGFSYISYWAYWGQGLTVTVSSGGGGGGGGGGGGG QTAVTQEPSLTVSPGGTVTLTCSGSTGAVTSGNYPNWVQKPGQAPRGLIGGTFKLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
36	CD33 AF5 HL x 12C HL	artificial	nt	CAGGTGCAGCTGGTGCACTGTGGAGCTGAGGTGAAGAACCTGGAGCGTCAGTCAAGGTCTCTCTGC AAGGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCAACATATGCTGATGACTTCAAGGGA CGGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCATTTTGGAACTCCACAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCCTCAGTGGTGGTGGTCTGGCGGGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAGCAGAAACCAGGACAGCTCTAAATTAATCTCTTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTGAGTGGCAGCGGTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGGACACGACTGGAGATTAAATCCGGAGGTGGTGGCTCCGAGGTGCAGCTGGTCGAGTCTGGA GGAGGATTGGTGCAGCCTGGAGGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AAGTACGCCATGAACTGGGTCCGCCAGGCTCCAGGAAAGGGTTTGGAAATGGGTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTGAGTGAAGACAGGTTCAACCATCTCCAGA GATGATTCAAAAAACACTGCCTATCTACAAATGAACAACTTGAAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCCAAGGG ACTCTGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGGCGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACTCACTTGT GGCTCCTCGACTGGGCTGTTACATCTGGCAACTACCCAACTGGGTCCAAACAAAAACAGGTGAG GCACCCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCCGGTACTCTCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTTCGGTGGAGGAACCAAACTGACTGTCCCTA
37	CD33 VH of AC8	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVMTMTDTSTSTAYMEIRNLRNDDTAVYYCARWSWDGYVYFDYWGGTTVTVSS

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
38	CD33 HCDR1 of AC8	artificial	aa	NYGMN
39	CD33 HCDR2 of AC8	artificial	aa	WINTYTGPTYADDFKG
40	CD33 HCDR3 of AC8	artificial	aa	WSWSDGYVYVFDY
41	CD33 VH of AC8	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACATATGCTGATGACTTCAAGGGA CGGGTTACCATGACTACGGATACCTCTACACAGCACTGCCATATATGAAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTTGAC TACTGGGGCCAAGCACTACGGTCACCGTCTCCTCA
42	CD33 VL of AC8	artificial	aa	DIVMTQSPDSLTVSLGERTTINCKSSQSVDSSKNKNSLAWYQQKPGQPPKLLLSWASTRESGIPD RFGSGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK
43	CD33 LCDR1 of AC8	artificial	aa	KSSQSVDSSKNKNSLA
44	CD33 LCDR2 of AC8	artificial	aa	WASTRES
45	CD33 LCDR3 of AC8	artificial	aa	QQSAHFPIIT
46	CD33 VL of AC8	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGAGAGGACCAACATCAAC TGCAAGTCCAGCCAGAGTGTTTTAGACAGCTCCAAGAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAATTACTCCTTCTGGGCATCTACGCGGGAATCCGGGATCCCTGAC CGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACCTCTCACTATTGACAGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCCGATCACCTTTGGCCAAAGGACACGACTG
				GAGATTAAA
47	CD33 HL of AC8	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYFTFTNYGMNWVKQAPGQGLKWMGWINTYTGPTYADDFKG RVTMTTDTSTSTAYMEIRNLRNDDTAVYYCARWSWSGDGYVYFDYWGQGTFTTVSSGGGGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVDSSKNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
48	CD33 HL of AC8	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCACAAACTATGGAATGAACCTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTACGGATACCTCTACCAAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTGAC TACTGGGGCCAAGGCACTACGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAAGAAACCAAGCAGCAGCTCCTAAATTACTCTTCTCTGGGCATCTACGCGGAA TCCGGATCCCTGACCGATTCACTGGCAGCGGGTCTGGACAGATTTCACTCTCACTATTGACAGC CTGACGCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCAGTACACCTTTGGC CAAGGCACAGCTGGAGATTAA
49	CD33 AC8 HL x H2C HL	artificial	aa	QVQLVQSGAEVKPGESVKVSCKASGYTFITNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTDTSTSTAYMEIRNLNRDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKKNKNSLAWYQQKPGQPPLKLLLSWASTRE SGIPDRFSGSGSDTFTLTIDSLQPEDSATYYCQQSAHPITFGQTRLEIKSGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLTEDTAVYYCVRHGNFGNSYISYWAYWGQTLVTVSSGGSGGGSGGGGS QTVVTQEPISLTVSPGGTFTLTCSGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGTKLTIVL
50	CD33 AC8 HL x H2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCACAAACTATGGAATGAACCTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTACGGATACTCTACCAAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTGAC TACTGGGGCCAAGGCACTACGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAAGAAACCAAGCAGCAGCTCCTAAATTACTCTTCTCTGGGCATCTACGCGGAA TCCGGATCCCTGACCGATTCACTGGCAGCGGGTCTGGACAGATTTCACTCTCACTATTGACAGC CTGACGCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCAGTACCTTTGGC CAAGGCACAGCTGGAGATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGGATTGGTGCAGCCTGGAGGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTACCTTCAAT AAGTACGCCATGAACCTGGTCCGCCAGGCTCCAGGAAAGGGTTTGAATGGTTGCTCGCATAAGA

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
				AGTAAATATAATAATTATGCAACATATTATGCCGATTTCAGTGAAGACAGGTTCCACCATCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGCGCGCGGCTCCGGTGGTGGTGTCT CAGACTGTTGTGACTCAGGAACCTTCACCTACCGTATCACCTGGTGGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGCTGTTACATCTGGCTACTACCCAACTGGGTCCAACAAAAACCAGGTCAG GCACCCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCCCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTTCGGTGGAGGAACCAAACTGACTGTCTCTA
51	CD33 AC8 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYFTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTTDTSTSTAYMEIRNLRNDDTAVYCARWSWSDGYIYFDYWQGTTTVTVSSGGGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFTLTIDSLQPEDSATYQCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNNLKTEDTAVYCVRHGNFGNSYVSWWAYWGQGLTVTVSSGGGGSGGGSGGGGS QTAVTQEPSTLVSPGGTVTLTLCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEIYCIVLWYSNRWVFGGGTKLITVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
52	CD33 AC8 HL x F12Q HL	artificial	nt	CAGGTGCAGTGGTGCAGTCTGGAGCTGAGGTGAAGAACCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAAGTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAAATATGCTGATGACTTCAAGGGA CGGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTAAGTGTGGCGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTCTGGCGCGGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAG AGGACCAACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGTCCAAGAATAAGAACTCCTTA GCTTGGTACAGAGAAAACAGGACAGCTCTCTAAATTAATCTCTTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTAGTGGCAGCGGTCTGGACAGATTCTACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTCTCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGAGCTGGAGGTCAATGAAACTCTCATGTGCAGCTCTGGATTCACTTCAAT AGCTACGCCATGAAGTGGTCCGCCAGGTCCAGGAAAGGTTTGAATGGTTGCTCGCATAAGA AGTAAATATAATAATATGCAACATATATGCCGATTGATGAAAGGAGGTTCAACATCTCCAGA GATGATTCAAAAAACACTGCCATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACGTTTCTGGTGGGCTTACTGGGGCCAAAGG ACTTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGCGCGGCTCCGGTGGTGGTGGTCTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGTCTCTCGACTGGGGCTGTACATCTGGCAACTACCAAACTGGGTCCAACAAAAACAGGTGAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCCTCGCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGGATGAGGCAGAAATAT
53	CD33 AC8 HL x 12C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFNNGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTTDTSTSTAYMEIRNLNRDDTAVYYCARWSWSDGYVYFDYWGQTTVTVSSGGSGSGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKNKNSLAWYQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTIDSLQPEDSATYCCQSAHFPITFGQGTREIKSGGGSEVQLVESG GGLVQPGSLKLSCAASGFTFNKYAMNWRQAPGKLEWVARI RSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISYAWYWGQTLVTVSSGGSGSGGSGGGS QTVVTQEPSTLVSPGGTTLTCCGSTGAVTSGNYPNWVQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGTGKLTIVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
54	CD33 AC8 HL x 12C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATGAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACACAGAGAAACAGGACAGCCTCTAAATTAATCTCTTCTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTAGTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTCGAGTCTGGA GGAGATTGGTGACAGCTGGAGGTCAATGAACTCTCATGTGAGCCTCTGGATTCACCTTCAAT AAGTACGCCATGAAGTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTAGTGAAGACAGGTTCAACATCTCCAGA GATGATTCAAAAACACTGCCATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGGCGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTACATCTGGCAACTACCCAAACTGGGTCCAACAAAAACAGGTGAG GCACCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCGGTACTCTGCGCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGTGTTCGGTGGAGGAACCAAACTGACTGTCTCTA
55	CD33 VH of AH11	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFITNYGMNWVKQAPGQGLKWMGWINTYTGPTYADDFKG RVTMTSDTSTSTAYMEISSLRSDDTAVYICARWSWSGDIYVFDYWGQTTVTVSS
56	CD33 HCDR1 of AH11	artificial	aa	NYGMN
57	CD33 HCDR2 of AH11	artificial	aa	WINTYTGPTYADDFKG
58	HCDR3	artificial	aa	WSWSDGYVYFDY

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
59	CD33 VH of AH11	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATATGAAATCAGCAGCCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCCTCA
60	CD33 VL of AH11	artificial	aa	DIVMTQSPDSLTVSLGERTTINCKSSQSVDSSKNKNSLAWYQQKPGQPPKLLLSWASTRESGIPD RFGSGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK
61	CD33 LCDR1 of AH11	artificial	aa	KSSQSVLDSSKNKNSLA
62	CD33 LCDR2 of AH11	artificial	aa	WASTRES
63	CD33LCDR3 of AH11	artificial	aa	QQSAHFPIIT
64	CD33 VL of AH11	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGGCGAGAGACCACCATCAAC TGCAAGTCCAGCCAGAGTGTTTAGACAGCTCCAAGAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAATTACTCCTTTCTCTGGCATCTACGCGGGAATCCGGGATCCCTGAC CGATTGAGTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCGATCACCTTTGGCCCAAGGACACGACTG GAGATTAAA
65	CD33 HL of AH11	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTSDTSTSTAYMEISSLRSDDTAVYYCARWSWSDGYVYFDYWGGQTTVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVDSSKNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
66	CD33 HL of AH11	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATATGGAATCAGCAGCCTCAGAAAT GATGACACGGCTGTATATTAAGTGTGCGGCTGAGTGGAGTGGTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGGCGGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACAGCAGAAACAGGACAGCTCCTAAATTAATCTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTGAGTGGCAGCGGCTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCACCTTCCCAGATCACCTTTGGC CAAGGGACACGACTGGAGATTAAA
67	CD33 AH11 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFITNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKG RVTMTSDTSTSTAYMEISSLRDDTAIVYCARWSWSDGYVYFDYWQGTITVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKKNKSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTITISLQPEDSATYQCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYVCVRHGNFGNSYISYWAYWGQGLTVTVSSGGSGGGSGGGGS QTVVTQEPSTLVSPGGTVTLTCGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
68	CD33 AH11 HL x H2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATATGAAATCAGCAGCCTCAGAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGCGCGCGGCTCC GGTGGTGGTGGTCTTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACAGAGAAACAGGACAGCCTCCTAAATTACTCCTTTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTAGTGGCAGCGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTCCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTCCAGTCTGGA GGAGATTGGTGACAGCTGGAGGTCAATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AAGTACGCCATGAACTGGTCCGCCAGGTCCAGGAAAGGTTTGAATGGTTGCTCGCATAAAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTAGTGAAGACAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGTCTTGCGCGCGGCTCCGGTGGTGGTGTCT CAGACTGTTGTGACTCAGGAACCTTCACCTACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTACATCTGGCTACTACCCAAACTGGGTCCAACAAAAACAGGTGAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTCCGTGGAGGAACCAAACTGACTGTCTCTA
69	CD33 AH11 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFITNYGMNWVKQAPGQGLKWMGWINTYTGPTYADDFKG RVMTSDTSTSTAYMEISSLRDDTAVYYCARWSWSDGYVYFDYWQGTTTVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSKNKNSLAWYQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPKGLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYVSWWAYWQGQTLTVSSGGSGGGSGGGGS QTVVTQEP SLTVSPGGT VTLT CGS STGA VTSGNYPNWVQKPGQAPRGLIGGTKFLAPGTPARFSG
				SLLGKKAALTL SGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
70	CD33 AH11 HL x F12Q HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAAACATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATATGGAATCAGCAGCCTCAGAAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTGTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCCTCTTAAATTACTCCTTTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTCTAGTGGCAGCGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCAGTACACTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGACAGCTGGAGGTCAATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AGTACGCCATGAAGTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTCTAGTGAAGGAGGTTTCCATCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGTACGTTTCTGGTGGGCTTACTGGGGCCAAAGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGCGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTACATCTGGCAACTACCCAACTGGGTCCAACAAAAACAGGTCTAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTCGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCCGGTGGAGGAACCAACTGACTGTCTCTA
71	CD33 AH11 HL x I2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGPTYADDFKG RVTMTSDTSTSTAYMEISSLRDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGSGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSKKNLSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGSLKLSCAASGFTFNKYAMNWVRQAPKGLEWVARI RSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISYWAYWQGQTLTVSSGGSGSGGSGGGS QTVVTPQEPSTVSPGGTITLTCSGSTGAVTSGNYFNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGTTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
72	CD33 AH11 HL x I2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCCTCCTGC AAGGTAGCGGGTATACCTTCAAAAATGAACTGGTGAAGCAGGCTCCAGGACAGGTT TTAAAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAAATATGCTGATGACTTCAAGGGA CGGTTACCATGACTTCGGATACCTCTACCAGCACTGCCTATATGAAATCAGCAGCCTCAGAAAT GATGACACGGCTGTATATTAAGTGGCGCTGGAGTTGGAGTATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCCTCAGGTGGTGGTCTTCTGGCGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG
73	CD33 VH of B3	artificial	aa	AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAAGAATAAGAACTCCTTA GCTTGGTACCAGAGAAAACAGGACAGCTCTAAATTAATCTCTTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTAATTTGTCAACAGTCTGCCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGTTAAATCCGGAGTGGTGGTCCGAGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGCAGCTGGAGGTCATTGAACTCTCATGTGCAGCTCTGGATTCACTTCAAT AAGTACGCCATGAAGTGGTCCGCCAGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAAGA AGTAAATATAATAATATGCAACATATATGCCGATTCACTGAAAGACAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCCATCTACAAATGAACAATGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGGCGCGCGGCTCCGGTGGTGGTGGTCTT CAGACTGTTGTGACTCAGGAACTTCACTCACCGTATCACCTGGTGGAAACAGTCACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCAACTACCAAACTGGGTCCAACAAAAACAGGTCAAG GCACCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCGGTACTCTTCCAGAGTTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGTGGTGTTCGGTGGAGGAACCAAACTGACTGTCTCTA
74	CD33 HCDR1 of B3	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFITNYGMNWVKQAPGQGLEWMGWINTYTGETNYADKFFQG RVFTFTSDTSTSTAYMELRNLRNLKSDDTAVYYCARWSWSWDGYVYFDYWGQGTITVTVSS
75	CD33 HCDR2 of B3	artificial	aa	NYGMN
76	CD33 HCDR3 of B3	artificial	aa	WINTYGETNYADKFFQG
		artificial	aa	WSWSDGYVYVFDY

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
77	CD33 VH of B3	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAACCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCCTCA
78	CD33 VL of B3	artificial	aa	DIVMTQSPDSMTVSLGERTTINCKSSQSVDLSSTNKNSLAWYQQKPGQPPKLLLSWASTRESGIPD RFGSGSGTDFLTITIDSLQPEDSATYYCQQSAHFPIITFGQGRLLDIK
79	CD33 LCDR1 of B3	artificial	aa	KSSQSVDLSSTNKNSLA
80	CD33 LCDR2 of B3	artificial	aa	WASTRE
81	CD33LCDR3 of B3	artificial	aa	QQSAHFPIIT
82	CD33 VL of B3	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCATGACTGTGTCTCTGGGCGAGAGGACCACCATCAAC TGCAAGTCCAGCCAGAGTGTTTAGACAGCTCCACGAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACAGGACAGCCTCCTAAATTACTCCTTTCTCTGGGCATCTACGCGGGAATCCGGGATCCCTGAC CGATTGAGTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCGATCACCTTTGGCCCAAGGGACACGACTG GACATTAAA
83	CD33 HL of B3	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYFTFTNYGMNWKQAPGQGLEWMGWINTYTGENTYADKFKQG RVTFTSDTSTSTAYMELRNLIKSDDTAVYYCARWSWSDGYVYFDYWGQGTFTTVTVSSGGGGSGGGGS GGGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVDLSSTNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSGTDFTLTITIDSLQPEDSATYYCQQSAHFPIITFGQGRLLDIK

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
84	CD33 HL of B3	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTTCCAGGGA CGGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTATGTTACTACGTTTACTTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCATGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCTCTCTAAATTACTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCTAGTGGCAGCGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCTTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCCACTTCCCAGTCAACCTTTGGC CAAGGACACGACTGGACATTTAA
85	CD33 B3 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFITNYGMNWVKQAPGQGLEWMGWINTYTGENTYADKFKQ RVFTSDTSTSTAYMELRNLIKSDDTAVYYCARWSWSDGYVYFDYWQGTITVTVSSGGSGSGGGS GGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNLSAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLDIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQGTLLTVSSGGSGSGGSGSGGGS QTVVTQEPSTLTVSPGGTITLTGSGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
86	CD33 B3 HL x H2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTTCCAGGGA CGGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTATGTTACTACGTTTACTTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCATGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCTCTCTAAATTACTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCTAGTGGCAGCGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCTTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCCACTTCCCAGTCAACCTTTGGC

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
				CAAGGGACACGACTGGACATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTCTGGA GGAGATTGGTGCAGCCTGGAGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTCACCTTCAAT AAGTACGCCATGAACTGGTCCGCCAGGTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTAGTGAAGACAGGTTACCATCTCCAGA GATGATTCAAAAACACTGCCATCTACAAATGAACAACCTTGAACACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTTACTGGCTTACTGGGGCCAAAGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGGCGCGCGGCTCCGGTGGTGGTGGTTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCTACTACCAAACTGGGTCCAACAAAAACAGGTCA GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGTGAGGCAGAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTCCGGTGGAGGAACCAAACTGACTGTCTTA
87	CD33 B3 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGETNYADKFQ RVTFSTDTSTSTAYMELRNLSKDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGGGGS GGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLDSSTNKNLSAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTITISLQPEDSATYQCQSAHFPITTFGQGTSLDIKSGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAWYQGTSLTVSSGGSGGGSGGGGS QTVVTQEPSTLVSPGGTVTLTCSGSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
88	CD33 B3 HL x F12Q HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGCTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTGTCTGGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCATGACTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTTTATAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACCAGCAGAAAACAGGACAGCCTCCTAAATTACTCTCTTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTCACTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCTGAAGATTCTGAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGACATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGCAGCTGGAGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AGTACGCCATGAACTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATCCGATTCACTGAAAGCAGGTTCACTCTCCAGA GATGATTCAAAAAACACTGCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACGTTTCTGGTGGCTTACTGGGGCCAAAGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT
89	CD33 B3 HL x I2C HL	artificial	aa	QVLVQSGAEVKKPGESVKVSCKASGYFTNYGMNWVKQAPGQGLEWMGWINTYTGETNYADKFQ RVFTSDTSTSTAYMELRNLSKDDTAVYCARWSWDGYVYFDYWGQTTVTVSSGGSGGGGS GGGSDIVMTQSPDSMTVSLGERTTINCKSSQSVLSDSTNKNLSAWYQKPGQPPKLLLSWASTRE SGIPDRFSGSGTDFTLTIDSLQPEDSATYCYQSAHFPITFGQGTRLDIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQGTLVTVSSGGSGGGSGGGGS QTVVTQEPSTLVSPGGTVTLTCSSTGAVTSGNYPNWVQKPGQAPRGLIGGTFKLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
90	CD33 B3 HL x I2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGCGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGCTGAGTGGAGTGGAGTATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCATGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCCTCTAAATTAATCTCTTCTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTAGTGGCAGCGGCTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCAGTCACTTTGGC CAAGGGACACGACTGGACATTAAATCCGGAGTGGTGGCTCCGAGGTGCAGTGGTCGAGTCTGGA GGAGGATTGGTGACGCTGGAGGTCATTGAACTCTCATGTGAGCCTCTGGATTCACTTCAAT AAGTACGCCATGAAGTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATCCGATTCACTGAAAGACAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGGCCAAAGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGGCGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCAACTACCCAAACTGGGTCCAAACAAACACAGGTGAG GCACCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCCGGTACTCTGCGCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCCGGTGGAGGAACCAAACTGACTGTCTCTA
91	CD33 VH of F2	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFITNYGMNWVKQAPGQGLEWMGWINTYTGENTYADKFFQ RVFTSDTSTSTAYMELRNLRNLKSDDTAVYICARWSWSGDIYVYFDYWGGTITVTVSS
92	CD33 HCDR1 of F2	artificial	aa	NYGMN
93	CD33 HCDR2 of F2	artificial	aa	WINTYGETNYADKFFQ
94	CD33 HCDR3 of F2	artificial	aa	WSWSDGYVYFDY

(continued)

SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
95	CD33 VH of F2	artificial	nt	CAGGTGCAGCTGGTGCACTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGGTTACCTTCACCTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTTAC TACTGGGGCCCAAGCACTACGGTCACCGTCTCCTCA
96	CD33 VL of F2	artificial	aa	DIVMTQSPDLSVSLGERTTINCKSSQSVDLSSTNKNLSAWYQQKPGQPPLKLLSWASTRESGIPD RFGSGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK
97	CD33 LCDR1 of F2	artificial	aa	KSSQSVDLSSTNKNLSLA
98	CD33 LCDR2 of F2	artificial	aa	WASTRES
99	CD33 LCDR3 of F2	artificial	aa	QQSAHFPIIT
100	CD33 VL of F2	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCCTGTCTGTGTCTCTGGCGAGAGGACCACCATCAAC TGCAAGTCCAGCCAGAGTGTTTACAGAGCTCCACGAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAATTACTCCTTTCTCTGGCATCTACGCGGGAATCCGGGATCCCTGAC CGATTGAGTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCCGATCACCTTTGGCCCAAGGACACGACTG GAGATTAAA
101	CD33 HL of F2	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGETNYADKFQG RVFTSDTSTSTAYMELRNLIKSDDTAVYYCARWSWSDGYVYFDYWGGTTVTVSSGGGGGGGGG GGGSDIVMTQSPDLSVSLGERTTINCKSSQSVDLSSTNKNLSAWYQQKPGQPPLKLLSWASTRE SGIPDRFSGSGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
102	CD33 HL of F2	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCCTCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGGAACCTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGGCTGAGTTGGAGTGGAGTACGTTACTGTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTTGACATCGTGATGACACAGTCTCCAGACTCCCTGTCTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTTTATAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAGAAACAGGACAGCTCTCTAAATTACTCTTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGCTCTGGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCCACTTCCCCGATCACCTTTGGC CAAGGGACAGACTGGAGATTAAA
103	CD33 F2 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGENTYADKFQG RVTFSTSTSTAYMELRNLIKSDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGGGGS GGGSDIVMTQSPDSLVSLEGGTINCKSSQSVLDSSTNKNLSAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFLTIDSLQPEDSATYQCQSAHFPITFGQGRLEIKSGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSSGGSGGGSGGGGS QTVVTQEPSTLVSPGGTVTLTCGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
104	CD33 F2 HL x H2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGCGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGTCTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCCTCTAAATTACTCCTTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTAGTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTCCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTCCAGTCTGGA GGAGATTGGTGACAGCTGGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTGTCTCGCATAGA AAGTACGCCATGAAGTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTGTCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTAGTGAAGACAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGTCTGGCGGCGGCTCCGGTGGTGGTGGTCTT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGTCTCTCGACTGGGGCTGTTACATCTGGCTACTACCCAACTGGGTCCAACAAAAACAGGTCAAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTCCGGTGGAGGAACCAAACTGACTGTCTCTA
105	CD33 F2 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGENTYADKFQG RVTFTSDTSTSTAYMELRNLIKSDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGGGGS GGGSDIVMTQSPDSLVS LGERTTINCKSSQSLDSSTNKNLSAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFLTIDSLQPEDSATYYCQQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSAASGFTFNSYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWQGTLVTVSSGGSGGGSGGGGS QTVVTPQEPSTLVSPGGTVTTLTCSGSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVOPEDAEAYCYVLWYSNRWVFGGTTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
106	CD33 F2 HL x F12Q HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATGAACTGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTTCAGGGA CGCGTTACCTTCACTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGGCGGCGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGTCTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACCAGCAGAAAACAGGACAGCCTCCTAAATTACTCTCTTCTGGGCATCTACGCGGGA TCCGGGATCCCTGACCGATTCACTGGCAGCGGTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTCGAGTCTGGA GGAGATTGGTGACGCTGGAGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AGTACGCCATGAACTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATCCGATTCACTGAAAGCAGGTTCACTATCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAACACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGGAACTTCGGTAATAGTACGTTTCTGTGGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCAACTACCCAAACTGGGTCCAACAAAAACAGGTCA GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCCGGTGGAGGAACCAAACTGACTGTCTCTA
107	CD33 F2 HL x I2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGENTYADKFQ RVFTSDTSTSTAYMELRNLIKSDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGGGGS GGGSDIVMTQSPDLSVSLGERTTINCKSSQSVLDSSTNKNLSAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFLTIDSLQPEDSATYYCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGSLKLSAASGFTFNKYAMNWRQAPKGLEWVARI RSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQGQTLTVSSGGSGGGSGGGGS QTVVTQEPSTLTVSPGGTVTLTCSGSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGTGKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
108	CD33 F2 HL x 12C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCCTCTGC AAGGTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGACAAACTATGCTGATAAGTCCAGGGA CGCGTTACCTTCACCTTCGGATACCTCTACCAGCACTGCCTATATGAACTCCGCAACCTCAAAAGT GATGACACGGCTGTATATTAAGTGTGCGGCTGAGTGGAGTGGAGTATGCTTACTAGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGGCGGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGTCTGTGTCTCTGGGCGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTTTAGACAGCTCCACGAATAAGAACTCCTTA
				GCTTGGTACCAGCAGAAAACAGGACAGCTCTCTAAATTAATCTCTTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGCTCCGAGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGCAGCTGGAGGTCATTGAAACTCTCATGTGCAGCTCTGGATTCACTTCAAT AAGTACGCCATGAACTGGTCCGCCAGCTCCAGGAAAGGTTTGAATGGTGTCTCGCATAGA AGTAAATATAATAATATGCAACATATATGCCGATTCACTGAAAGACAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCCATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGCGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACTTCACTCACCGTATCACCTGGTGAACAGTCACTCACTTGT GGTCCTCGACTGGGGCTGTTACATCTGGCAACTACCAAACTGGGTCCAAACAAACCAAGTCAAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCCTCGCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGTGGTGGTGGTGGAGGAACCAAACTGACTGTCTTA
109	CD33 VH of B10	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFITNYGMNWVKQAPGQGLEWMGWINTYTGEPTYADKFFQ RVTMTTDTSTSTAYMEIRNLRSDDTAVYYCARWSWSGGYVYFDYWGQGTITVTVSS -----
110	CD33 HCDR1 of B10	Artificial	aa	NYGMN
111	CD33HCDR2 of B10	artificial	aa	WINTYGEPTYADKFFQ
112	CD33 HCDR3 of B10	artificial	aa	WSWSGGYVYFDY

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
113	CD33 VH of B10	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGTGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCACAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACTATGCTGATAAGTCCAGGGA CGGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGGAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCCTCA
114	CD33 VL of B10	artificial	aa	DIVMTQSPDRLTVSLGERTTINCKSSQSVLDSSNNKNSLAWYQQKPGQPPKLLLSWASTRESGIPD RFSGSGSGTDFTLTIDGLQPEDSATYYCQQSAHFPIITFGQGRLEIK
115	CD33 LCDR1 of B10	artificial	aa	KSSQSVLDSSNNKNSLA
116	CD33 LCDR2 of B10	artificial	aa	WASTRES
117	CD33 LCDR3 of B10	artificial	aa	QQSAHFPIIT
118	CD33 VL of B10	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGGCGAGAGGACCACCATCAAC TGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAACAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAATTACTCTCTTCTGGGCATCTACGCGGGAATCCGGGATCCCTGAC CGATTGAGTGGCAGCGGTTCTGGGACAGATTTCACTCTCACTATTGACGGCCTGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCAGATCACCTTTGGCCCAAGGACACGACTG GAGATTAAA
119	CD33 HL of B10	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWKQAPGQGLEWMGWINTYTGEPTYADKFAQ RVTMTTDTSTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWGGQTTVTVSSGGGSGGGGS GGGSDIVMTQSPDRLTVSLGERTTINCKSSQSVLDSSNNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSGTDFTLTIDGLQPEDSATYYCQQSAHFPIITFGQGRLEIK

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
120	CD33 HL of B10	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGTGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAAATGAACTGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTTCCAGGGA CGCGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGCGCGCGGCTCC GGTGGTGGTGGTCTTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAACAATAAGAACTCCTTA GCTTGGTACCAAGAGAAACAGGACAGCTCTCTAAATTAATCTCTCTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTAGTGGCAGCGGTTCTGGGACAGATTTCACTCTCACTATTGACGGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCCACTTCCCCGATCACCTTTGGC CAAGGGACACGACTGGAGATTAAA
121	CD33 B10 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTYGEPTYADKFFQ RVTTMTDTSTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWQGTITVTVSSGGSGSGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSNNKNSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTIDGLQPEDSATYQCQSAHFPITFGQGRLEIKSGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQGTITVTVSSGGSGSGGSGGGS QTVVTQEPSTVSPGGTITLTCSGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCALWYSNRWVFGGTKLTVL
122	CD33 B10 HL x H2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGTGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAAATGAACTGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTTCCAGGGA CGCGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGCGCGCGGCTCC GGTGGTGGTGGTCTTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAACAATAAGAACTCCTTA GCTTGGTACCAGAGAAACAGGACAGCTCTCTAAATTAATCTCTCTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTAGTGGCAGCGGTTCTGGGACAGATTTCACTCTCACTATTGACGGC

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
				CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCACCTTCCCAGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTCGAGTCTGGA GGAGGATTGGTCAGCCTGGAGGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTACCTTCAAT AAGTACGCCATGAAC TGGTCCGCCAGGCTCCAGGAAAGGTTTGGAAATGGTTGCTCGCATAAGA AGTAAATATAATAATTATGCAACATATTATCCGATTGAGTGAAGACAGGTTACCATCTCCAGA GATGATTCAAAAAACACTGCCCTATCTACAAATGAACAACTTGAAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGGCTTACTGGGGCCCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGCGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCTACTACCAAACTGGGTCCAACAAAAACAGGT CAG GCACCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGTGGTGGAGGAACCAAACTGACTGTCTTA
123	CD33 B10 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGE SVKVSCKASGYTFITNYGMNWVKQAPGQGLEWMGWINTYTGEPTYADKFQG RVTMTTDTSTSTAYMEIRNLRSDDTAVYCARWSWSDGYVYFDYWQGTTVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSNNKNSLAWYQQKPGQPPKLLLSWASTRE SGI PDRFSGSGSGTDFTLTIDGLQPEDSATYQCQSAHFPITFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNNLKTEDTAVYCVRHGNFGNSYVSWWAWYWGQGTLVTVSSGGSGGGSGGGGS QTVVTQEPSTLVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
124	CD33 B10 HL x F12Q HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGTGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCACAAACTATGGAATGAACCTGGTGAGCAGGCTCCAGGACAGGTT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACTATGCTGATAAGTTCAGAGGA CGCGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGGAATCCGCAACCTCAGAAGT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAGGCACACGGTCACCGTCTCCTCAGGTGGTGGTTCTTGGCGCGCGGCTCC GGTGGTGGTGGTTCTTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGGGAG AGGACACCATCAACTGCAAGTCCAGCCAGAGTGTTTTAGACAGCTCCAACAATAAGAACTCCTTA GCTTGGTACCAGAGAAACAGGACAGCCTCTAAATTACTCTTTCTTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGTTCTGGGACAGATTTCACTCTCACTATTGACGGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGGACACGACTGGAGATTAATCCGAGGTGGTGGCTCCGAGGTGCAGTGGTCAGTCTGGA GGAGATTGGTGAGCCTGGAGGTCATTGAACTCTCATGTGCAGCCTCTGGATTCACTTCAAT AGCTACGCCATGAACCTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGGTGCTCGCATAAAG AGTAAATATAATAATTATGCAACATATTATGCCGATTCACTGAAAGGCAGGTTCACCATCTCCAGA GATGATTCAAAAACACTGCCCTATCTACAAATGAACAACTTGAAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGGAACCTTCGGTAATAGCTACGTTTCTGGTGGGCTTACTGGGGCCAAAGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTTCTGGCGCGCGGCTCCGGTGGTGGTGGTCTT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGGAAACAGTCACACTCACTTGT GGCTCCTCGACTGGGCTGTACATCTGGCAACTACCCAACTGGGTCCAACAAAACAGGTCAG GCACCCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCTGGTGGAGGAACCAAACTGACTGTCTCTA
125	CD33 B10 HL x l2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYFTFTYGMNWVKQAPGQGLEWMGWINTYTGEPTYADKFKQG RVMTTDTSTSTAYMEIRNLRSDDTAVYYCARWSWSDGYVYFDYWQGTTVTVSSGGSGSGSGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSLDSSNNKNSLAWYQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTIDGLQPEDSATYYCQSAHFPITFQGGTRLEIKSGGGSEVQLVESG GGLVQPGGSLKLSAASGFTFNKYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSVKDRFTISR DSDKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSSGGSGSGSGSGSGGS QTAVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
126	CD33 B10 HL x I2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGTGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATGAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTTCAGGGA CGCGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCAGAAAT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGGCACTACGGTCACCGTCTCTCAGGTGGTGGTCTTGCGGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGGCGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCAACAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCCTCTAAATTAATCTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTAGTGGCAGCGGTTCTGGGACAGATTTCACTCTCACTATTGACGGC CTGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTCGAGTCTGGA GGAGGATTGGTGACAGCTGGGTCGCGCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AAGTACGCCATGAATGATGCAACATATTATGCCGATTCACTGAAAGACAGGTTCACTCTCCAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTCACTGAAAGACAGGTTCACTCTCCAGA GATGATTCAAAAAACACTGCTTATCAAAATGAACAATTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGGCGCGGCTCCGGTGGTGGTGGTCTT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCAACTACCCAACTGGGTCCAACAAAAACAGGTGAG GCACCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCCGGTACTCTGCGCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCCGTGGAGGAACCAAACTGACTGTCTCTA
127	CD33 VH of E11	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWKQAPGQGLEWMGWINTYTGPTYADKFFQ RVTMTTDTSTSTAYMEIRNLGGDDTAVYICARWSWSGYYVYFDYWGGTSVTVSS
128	CD33 HCDR1 of E11	artificial	aa	NYGMN
129	CD33 HCDR2 of E11	artificial	aa	WINTYTGPTYADKFFQ
130	CD33 HCDR3 of E11	artificial	aa	WSWSDGYVYFDY

(continued)

SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
131	CD33 VH of E11	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTCCAGGGA CGGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCGGAGGT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTTGAC TACTGGGGCCAAAGCACTTCGGTCACCGTCTCCTCA
132	CD33 VL of E11	artificial	aa	DIVMTQSPDSLTVSLGERTTINCKSSQSVDLSSTNKNLSLAWYQQKPGQPPKLLLSWASTRESGIPD RFGSGSGTDFTLTIDSPQPEDSATYYCQQSAHFPIITFGQGRLEIK
133	CD33 LCDR1 of E11	artificial	aa	KSSQSVLDSSTNKNLSLA
134	CD33 LCDR2 of E11	artificial	aa	WASTRES
135	CD33 LCDR3 of E11	artificial	aa	QQSAHFPIIT
136	CD33 VL of E11	artificial	nt	GACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGGCGAGAGGACCACCATCAAC TGCAAGTCCAGCCAGAGTGTTTTAGACAGCTCCACGAATAAGAACTCCTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAATTACTCTTCTCTGGGCATCTACGCGGAATCCGGGATCCCTGAC CGATTGAGTGGCAGCGGCTCTGGACAGATTTCACTCTCACTATTGACAGCCCGCAGCCTGAAGAT TCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCCGATCACCTTTGGCCCAAGGGACACGACTG GAGATTAAA
137	CD33 HL of E11	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGEPTYADKFAQ RVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWQQGTSVTVSSGGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVDLSSTNKNLSLAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTITIDSPQPEDSATYYCQQSAHFPIITFGQGRLEIK
138	CD33 HL of E11	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTCCAGGGA CGGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCGGAGGT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGTTACTACGTTTACTTTTGAC TACTGGGGCCAAAGCACTTCGGTCACCGTCTCTCAGGTGGTGGTGGTCTTGGCGGCGGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGGCGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTTAGACAGCTCCACGAATAAGAACTCCTTA

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
				GCTTGGTACCAGAGAAACCAGGACAGCCTCCTAAATTACTCCTTTCTGGGCATCTACGCGGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CCGCAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCCACTTCCCCGATCACCTTTGGC CAAGGGACACGACTGGAGATTAAA
139	CD33 E11 HL x H2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTGEPTYADKFAQ RVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWGGTSVTVSSGGGGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNSLAWYQQKPGQPPKLLLSWASTRE SGI PDRFSGSGGTFTLTIDSPQEDSATYQCQSAHFPITFGQGRLEIKSGGGSEVQLVESG GGLVQPGGSLKLSAASGFTFNKYAMNWVRQAPGKLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQGTLTVTVSSGGGGGGGGGGGS QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
140	CD33 E11 HL x H2C HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAAGCCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATATGAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACTATGCTGATAAGTTCAGGGA CGCGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCGAGGT GATGACACGGCTGTATATTACTGTGCGCTGAGTTGGAGTGGAGTATGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTTCGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGGCGGCGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGGCGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCCTCTAAATTAATTAATTAATTAATTAATTAATTAATTAAT TCCGGGATCCCTGACCGATTAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CCGAGCCTGAAAGATTCTGCAACTTACTATTGTCAACAGTCTCCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGACAGCTGGAGGTCAATGAACTCTCATGTGCAGCTCTGGATTCACTTCAAT AAGTACCCCATGAACTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTGGTCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTAGTGAAGACAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGCTCCGGTGGTGGTGGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTACATCTGGCTACTACCAAACTGGGTCCAACAAAAACAGGTCAAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTCGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGCTCTATGGTACAGCAACCGCTGGGTGTTCCGTGGAGGAACCAAACTGACTGTCTCTA
141	CD33 E11 HL x F12Q HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSCKASGYTFITNYGMNWVQAPGQGLEWMGWINTYTGPTIADKFKQG RVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWQGTSTVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNLSAWYQKPGQPPKLLLSWASTRE SGIPDRFSGSGGTDFLTITIDSPQPEDSATYYCQQAHPITFTGQGRLEIKSGGGGSEVQLVESG
				GGLVQPGGSLKLSAASGFTFNSYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSVKGRFTISR DDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYVSWWAYWQGTLTITVSSGGSGGGSGGGGS QTAVTQEPSTLTVSPGGTITLTCSSTGAVTSGNYPNWWQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGTGKLTIVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
142	CD33 E11 HL x F12Q HL	artificial	nt	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAACCTGGAGAGTCAGTCAAGGTCCTCTGC AAGGTAGCGGGTATACCTTCAAAACTATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTCCAGGGA CGCTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCGAGGT GATGACACGGCTGTATATTACTGTGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGCACTTCGGTCACCGTCTCTCAGGTGGTGGTGTCTGGCGCGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTACAGACTCCACGAATAAGAACTCCTTA GCTTGGTACCAGCAGAAACAGGACAGCTCTCTAAATTACTCTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGTCTGGACAGATTTCACTCTCACTATTGACAGC CCGAGCTTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCAGTCACTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGACGCTGGAGGTCACTGAAACTCTCATGTGCAGCTCTGGATTCACTTCAAT AGTACGCCATGAACTGGTCCGCCAGGTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAAATTATGCAACATATTATCCGATTCACTGAAAGCAGGTTCACTCTCCAGA GATGATTCAAAAACACTGCTTATCAAAATGAACAACTTGAACACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGTACGTTTCTGTGGCTTACTGGGCGCAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGTCTGGCGCGCGGCTCCGGTGGTGGTGTCT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTACATCTGGCAACTACCCAACTGGGTCCAACAAAAACAGGTCA GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTCGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGTGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCCGTGGAGGAACCAAACTGACTGTCTCTA
143	CD33 E11 HL x I2C HL	artificial	aa	QVQLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWINTYTYEPTYADKFFQ RVTTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDYWQGTSTVTVSSGGSGGGGS GGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNLSAWYQQKPGQPPKLLLSWASTRE SGIPDRFSGSGSTDFLTIDSPQPEDSATYYCQSAHFPITFFGQGRLEIKSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPKGLEWVARIRSKYNNYATYYADSVKDRFTISR DDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWQGTLTVTSSGGSGGGSGGGGS QTVVTQEPSTVSPGGTVTLTCSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGTGKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
144	CD33 E11 HL x I2C HL	artificial	nt	CAGGTGCAGCTGGTGCACTCTGGAGCTGAGGTGAAGAACCTGGAGAGTCAGTCAAGGTCCTCTGC AAGGTAGCGGGTATACCTTCAAAAATGGAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACTATGCTGATAAGTCCAGGGA CGCGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCGGAGGT GATGACACGGCTGTATATTACTGTGCGCGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGGCACCTTCGGTCACCGTCTCTCAGGTGGTGGTTCTGGCGGCGGGCTCC GGTGGTGGTGGTTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGGCGAG AGGACCAACCATCAACTGCAAGTCCAGCCAGAGTGTTTATAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACAGCAGAAAACAGGACAGCTCTCTAAATTACTCTTCTTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CCGAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGTGGTGGTCCGAGTGCAGTGGTCGAGTCTGGA GGAGATTGGTGAGCCTGGAGGTCATTGAACTCTCATGTGCAGCTCTGGATTCACCTTCAAT AAGTACGCCATGAACTGGTCCGCCAGGCTCCAGGAAAGGTTTGAATGGTTGCTCGCATAGA AGTAAATATAATAATTATGCAACATATTATGCCGATTCACTGAAAGACAGGTTCAACATCTCCAGA GATGATTCAAAAAACACTGCCCTATCTACAAATGAACAACTTGAAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGGCTTACTGGGGCCAAAGGG ACTCTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGGCTCCGGTGGTGGTGGTTCT CAGACTGTTGTGACTCAGGAACTTCACTCACCGTATCACCTGGTGGAAACAGTCACACTCACTTGT GGCTCCTCGACTGGGGCTGTTACATCTGGCAACTACCAAACCTGGGTCCAAACAAAAACAGGT GCACCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCGGTACTCCTGCCAGATTCTCAGGC TCCCTGCTTGGAGGCAAGGCTGCCCTCACCTCTCAGGGGTACAGCCAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCCGGTGGAGGAACCAAACTGACTGTCTTA

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
145	CD33	human	nt	ATGGGATGGAGCTGTATCATCCTCTTCTTTGGTAGCAACAGCTACAGGTGTACACTCCGATCCAAAT TTCTGGTGCAAGTGCAAGAGTCAGTGACGGTACAGGAGGTTTGTGCGTCTCGTGCCCTGCACCT TTCTTCCATCCCATACCTTACTACGACAAGAACTCCCCAGTTTCATGGTTACTGGTTCGGGAAGGA GCCATTATATCCGGGACTCTCCAGTGCCCAACAAGCTAGATCAAGAAGTACAGGAGGAGACT CAGGGCAGATTCGGCCTCCTTGGGATCCAGTAGGAACAACCTGCTCCCTGAGCATCGTAGACGCC AGGAGGAGGATAATGGTTTCATCTTCTTTCGGATGGAGAGGAAAGTACCAAAATACAGTTACAAA TCTCCCCAGCTCTGTGCATGTACAGACTTGACCCACAGGCCCAAAATCCTCATCCCTGGCACT CTAGAAACCCGGCCACTCCAAAAACCTGACCTGCTGTGTCTGGCCCTGTGAGCAGGGAACACCC CCGATCTTCTCCTGGTTGTGAGCTGCCCCACCTCCCTGGGCCCCAGGACTACTCACTCCTCGGTG CTCATAATCACCCACGGCCACAGGACCAAGGCAACCACTGACCTGTGAGGTGAAGTTTCGCTGGA GCTGGTGTGACTACGGAGAGAACCATCCAGCTCAACGTCACTATGTTCCACAGAACCCCAACAACT GGTATCTTTCCAGGAGATGGCTCAGGGAACAAGAGACCAAGCAGGAGTGGTTTCATGGGGCCATT GGAGAGCTGGTTACAGCCCTGCTCGCTCTTTGTCTCTGCCTCATCTTCTTCATAGTGAAGACC CACAGGAGAAAGCAGCCAGGACAGCAGTGGCAGGAATGACACCCACCTACACAGGTCAGCC TCCCCGAAACACAGAGAAAGTCCAAGTTACATGGCCCCACTGAAACCTCAAGCTGTTCAGGTGCC GCCCCTACTGTGGAGATGGATGAGGAGCTGCATTATGCTTCCCTCAACTTTCATGGGATGAATCCT TCCAAGGACACCTCCACCGAATACTCAGAGGTCAGGACCCAGTCCGGGCATCATCACCATCATCAT TGA
146	CD33	human	aa	MGWSCIILFLVATATGVHSDPNFWLQVQESVTVQEGLCVLVPCTFPHPIPYDKNSPVHGWFREG AII SGDSPVATNKL DQEVQEETQGRFRL LGDPSRNNCSLSIVDARRDNGSYFFRMERGSTKYSYK
				SPQLSVHVTDLTHRPKILIPGTLEPGHSHKILTCVSWACEQGTPIFSWLSAAPTSLGPRTHSSV LIITPRPDHGTNLTQVKFAGAGVTTERTIQLNVTYVPQNPTTGI FPGDGSQKQETRAGVVHGAI GGAGVTALLALCLCLIFFIVKTHRRKAARTAVGRNDTHPTTGSASPKHQKSKLHGPTETSSCSGA APTVMDEELHYASLNFHGMNPSKDTSTEYSEVRTQSGHHHHHH

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
147	CD33	macaque	nt	ATGCCGCTGCTGCTACTGCTGCCCCCTGCTGTGGGCAGGGGCCCTGGCTATGGATCCAAGAGTCAAG CTGGAAGTGCAGGAGTCAGTGACAGTACAGGAGGGTTGTGCGTCTTGTGCCCTGCACCTTCTTTC CATCCCGTACCTACACACAGGAATTTCCACAGTTCATGGTTACTGGTTCGGGAAGAGCCATT GTATCCTTGGACTCTCCAGTGGCCACAAACAAGCTAGATCAAGAAGTACAGGAGGAGACCCAGGGC CGATTCGGCCTCCTTGGGATCCAGTAGGAACAACCTGCTCCTGAGCATCGTAGATGCCAGGAGG AGGATAACGGTTCACTACTTCTTTCGGATGGAGAAAGGAAGTACCAAAATACAGTTACAAATCTACC CAGCTCTGTGCATGTGACAGACTTGACCCACAGGCCCCCAATCCTCATCCCTGGAGCCCTAGAC CCTGACCACCTCCAAAAACCTGACCTGCTGTGCCCCCTGGCCCTGTGAGCAGGGAACACCTCCAATC TTCTCCTGGATGTGAGTGTGCCCCACCTCCCTGGCCCTCAGGACCACCTCACTCCTCGGTGCTCATA ATCACCCACGGCCCCAGGACACAGGACCAACCTCACCTGTGAGGTGAAGTTCCCTGGAGCTGGC GTGACCACGGAGAGAACCATCCAGCTCAATGTCTCTATCTTACAGAACCCAGAACTGATATC TTTCTAGGAGACGGCTCAGGGAACAAGGAGTGGTTCAGGGAGCCATCGGGGAGCTGGTGTACACA GTCTGCTCGCTCTTGTCTCTGCCTCATCTTCTTACAGTGAAGACTCACAGGAGGAAGCAGCC AGGACAGAGTGGCAGGATCGACACCCACCCGACAGGCCCAACATCCTCGAAACACACAGAAG AAGTCCAAGTTACATGGCGCCACTGAAACCTCAGGCTGTTCAGGTACCACTTACTGTGGAGATG GATGAGGAGTGCACCTACGCTTCCCTCAACTTTCATGGGATGAATCCTTCTGAGGACACCTCCACC GAATACTCAGAGGTCAGGACCCAGTGA
148	CD33 UD H2C HL x AF5 HL	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISYWAYWQGTLVTVSSGGGSGG GGSGGGGQTVVTQEPSTVSPGGTVTLTCSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTFKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYICALWYSNRWVFGGGTKLTVLSGGGGSQVQLVQSGA EVKKPGASVKVSKASGYFTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKGRVTMTSDTS TSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWQGQTTVTVSS9999s9999sDIVM TQSPDSLTVSLGERTTINCKSSQSVLDSKNKNSLAWYQQKPGQPPKLLLSWASTRESGIPDRFSG SGSGTDFTLTIDSLQPEDSATYYCQQAHPFITFGQTRLEIK
149	CD33 UD H2C HL x AF5 HL	artificial	nt	GAGGTGCAGCTGGTCGAGTCTGGAGGAGGATTGGTGCAGCCTGGAGGGTCATTGAAACTCTCATGT GCAGCCTCTGGATTACCTTCAATAAGTACGCCATGAACCTGGTCCGCCAGGCTCCAGGAAAGGGT TTTGAATGGGTTGCTCGCATAGAAGTAATAATAATAATATGCAACATATATGCCGATTCAGTG AAAGACAGGTTACCATCTCCAGAGATGATTCAAAAAACACTGCCTATCTACAAATGAACAACTTG AAAACTGAGGACACTGCCGTGTACTACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCC TACTGGGCTTACTGGGGCCAAGGACTCTGGTCACCGTCTCCTCAGGTGGTGGTGTCTGGCGGC GGCGGCTCCGGTGGTGGTGTCTCAGACTGTTGTGACTCAGGAACCTTCACTACCGTATCACCT GGTGGAACAGTCACACTGCTTGTGGCTCCTCGACTGGGCTGTTACATCTGGCTACTACCCAAAC TGGGTCCAACAAAAACCAGGTGAGGCACCCCGTGGTCTAATAGGTGGGACTAAGTTCTCGCCCCC

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
				GGTACTCCTGCCAGATTCTCAGGCTCCCTGCTTGAGGCAAGGCTGCCCTCACCCCTCTCAGGGGTA CAGCCAGAGGATGAGGCAGAAATATTACTGTGCTCTATGGTACAGCAACCGTGGTGTTCGGTGA GGAACCAAACTGACTGTCTATCCGGAGGTGGTGGCTCCAGGTGCAGTGGTCCAGTCTGGAGCT GAGGTGAAGAAGCCTGGAGCGTCAGTCAAGGTCTCTGCAAGGTAGCGGTATACCTTCACAAAC TATGGAATGAACGGTGAAGCAGGCTCCAGGACAGGTTTAAAGTGGATGGCTGGATAAACACC TACACTGGAGAGCCAAACATATGCTGATGACTTCAAGGACGGTTACCATGACTTCGGATACCTCT ACCAGCACTGCCTATTTGGAACCTCACAACTCAGAAGTGATGACACGGCTGTATATTACTGTGCG CGCTGGAGTTGGAGTGATGGTTACTTACGTTTACTTGTGACTTGGGGCCAAGGCACTACGGTCACC GTCTCCTCAGGTGGTGGTGGTTCTGGCGCGGGCTCCGGTGGTGGTCTGACATCGTGATG ACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGAGAGGACCACTCAACTGCAAGTCCAGC CAGAGTGTCTTAGACAGCTCCAAGAAATAAGAACTCCTTAGCTTGGTACAGCAGAAACCAAGGACAG CCTCCTAAATTACTCCTTCTGGGCATCTACGGGGAATCCGGGATCCCTGACCGATTCTCAGTGGC AGCGGTCTGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGATTCTGCAACTTAC TATTGTCAACAGTCTGCCCACTTCCCGATCACCTTTGGCCAAGGACACGACTGGAGATTAAA
150	CD33 UD F12Q HL x AF5 HL	artificial	aa	EVQLVESGGGLVQPGLSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNLLKTEDTAVYCVRHGNFGNSYVSWWAYWGQGLVTVSSGGGSGG GGSGGGSQTAVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWWVQQKPGQAPRGLIGGTFKFLAP GTPARFSGSLLGKAAALTLSGVQPEDEAEYCVLWYSNRWVFGGGLKLTLSGGGGSQVQLVQSGA EVKKPGASVKVSKASGYTFNIGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKGRVTMTSDTS TSTAYLELHNLRSDDTAVYYCARWSWSDGYVYFDYWQQGTTTVTVSSggsgsgsgsgsgsgsDIVM TQSPDSLTVSLGERTTINCKSSQSVLDSKNKNSLAWYQQKPGQPPKLLLSWASTRESGI PDRFSG SGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGTREIK

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
151	CD33 UD F12Q HL x AF5 HL	artificial	nt	GAGGTGCAGTGGTGCAGTCTGGAGGAGGATTGGTGCAGCCTGGAGGGTCATTGAAACTCTCATGT GCAGCCTCTGGATTACCTTCAATAGCTACGCCATGAAGTGGTCCGCCAGGCTCCAGGAAAGGT TTGGAATGGTTGCTCGCATAGAAGTAATATAATAATATGCAACATATTATGCCGATTTCAGTG AAAGGCAGGTTACCATCTCCAGAGATGATTCAAAAACACTGCCTATCTACAAATGAACAACTTG AAAACTGAGGACACTGCCGTGTACTGTGTGAGACATGGAACCTTCCTCAGGTGGTGGTCTTGCGGC TGGTGGGCTTACTGGGCCCAAGGACTCTGGTCACCGTCTCCTCAGGTGGTGGTCTTGCGGC GGCGGCTCCGGTGGTGGTCTCAGACTGTTGTGACTCAGGAACCTTCACCTCACCGTATCACCT GGTGGAACAGTCACACTCACCTTGTGGCTCCTCGACTGGGGCTGTTACATCTGGCAACTACCCAAAC TGGGTCCAAACAAAAACAGGTGAGGCACCCCGTGGTCTAATAGTGGACTAAGTTCCTCGCCCCC GGTACTCTCTGCCAGATTCTCAGGCTCCCTGTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTA CAGCCAGAGGATGAGGCAGAAATATTACTGTGTTCTATGGTACAGCAACCGTGGTGTTCGGTGA GGAACCAACTGACTGTCTATCCGGAGGTGGTGGTCCCAGGTGCAGTGGTCCAGTCTGGAGCT GAGGTGAAGAAGCCTGGAGCTCAGTCAAGTCTCCTGCAAGGTAGCGGTATACCTTCACAAAC TATGGAATGAAGTGGTGAAGCAGGCTCCAGGACAGGTTTAAAGTGGATGGCTGGATAAACACC TACACTGGAGGCCAACATATGCTGATGACTTCAAGGACGGGTACCATGACTTCGGATACCTCT ACCAGCACTGCCTATTTGGAACCTCCACAACTCAGAACTGATGACACGGCTGTATATTACTGTGCG CGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGACTACTGGGCCAAGGCACCTACGGTCACC GTCTCCTCAGGTGGTGGTGGTCTGGCGCGCGGCTCCGGTGGTGGTGGTCTTGACATCGTGATG ACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAGAGGACCACCATCAACTGCAAGTCCAGC CAGAGTGTCTTAGACAGCTCCAAGAAATAAGAACTCCTTAGCTTGGTACCAGCAAGAACCCAGGACAG CCTCCTAAATTAATCCTTCTGGGCATCTACGCGGGAATCCGGGATCCCTGACCGATTTCAGTGGC AGCGGTCTGGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGATTCTGCAACTTAC TATTGTCAACAGTCTGCCCCTTCCCGATCACCTTTGGCCAAAGGACACGACTGGAGATTAAA EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFNSYISYWAYWGQGLVTVSSGGGSGG GGSGGGGQTAVTQEPSLTVSPGGTVTLTCSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTFKFLAP GTPARFSGSLLGKKAALTLSGVQPEDEAEYICVLWYSNRWVFGGQGLKLTLSGGGGSQVLVQSGA EVKKPGASVKVSKASGYFTFNIGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKGRVTMTSDTS TSTAYLELHNLRDSDTAVYYCARWSWSDGYVYFDYWGGQTTVTVSSGGGSGGGGSDIVM TQSPDSLTVSLGERTTINCKSSQSVLDSKNKNSLAWYQQKPGQPPLKLLLSWASTRESGIPDRFSG SGSGTDFTLTIDSLQPEDSATYYCQQSAHFPIITFGQGRLEIK
152	CD33 UD I2C HL x AF5 HL	artificial	aa	

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
153	CD33 UD I2C HL x AF5 HL	artificial	nt	GAGGTGCAGTGGTCGAGTCTGGAGGAGGATTGGTGCAGCCTGGAGGGTCATTGAAACTCTCATGT GCAGCCTCTGGATTCACTTCAATAAGTACGCCATGAAGTGGTCCGCCAGGCTCCAGGAAAGGT TTGGAATGGTTGCTCGCATAGAAGTAAATATAATAATTATGCAACATATTATGCCGATTCACTG AAAGACAGGTTCAACATCTCCAGAGATGATTCAAAAACACTGCCTATCTACAAATGAACAACTTG AAAACTGAGGACACTGCCGTGTACTACTGTGTGAGACATGGAACTTCCCTCAGGTGGTGGTCTTGGCGGC TACTGGGCTTACTGGGCGCAAGGACTCTGGTCAACCTCTCCTCAGGTGGTGGTCTTGGCGGC GGCGCTCCGGTGGTGGTCTCAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCT GGTGAACAGTCACACTCACTTGTGGCTCCTCGACTGGGCTGTTACATCTGGCAACTACCCAAAC TGGGTCCAACAAAAACAGGTCAAGCACCCCTGGTCTAATAGGTGGACTAAGTTCTTCGCCCCC GGTACTCTGCCAGATTCTCAGGCTCCCTGTGGAGGCAAGGTGCCCTCACCTCTCAGGGGTA CAGCCAGAGGATGAGGCAGAAATATTACTGTGTTCTATGGTACAGCAACCGCTGGTGGTCTCGGTGGA GGAACCAAACTGACTGTCTATCCGGAGGTGGTGGTCCCAGGTGCAGTGGTCCAGTCTGGAGCT GAGGTGAAGAAGCCTGGAGCTCAGTCAAGTCTCCTGCAAGGTAGCGGTATACCTTCACAAAC TATGGAATGAAGTGGTGAAGCAGGCTCCAGGACAGGTTTAAAGTGGATGGCTGGATAAACACC TACACTGGAGAGCCAAACATATCTGATGACTTCAAGGACAGGTTACCATGACTTCGGATACCTCT ACCAGCACTGCCATTTGGAACCTCCAAACCTCAGAACTGATGACAGGCTGTATATTACTGTGG CGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGACTACTGGGCGCAAGGCACTACGGTCACC GTCTCCTCAGGTGGTGGTCTTGGCGCGCGGCTCCGGTGGTGGTCTTGACATCGTGATG ACACAGTCTCCAGACTCCCTGACTGTGTCTCTGGCGGAGAGGACCAACCATCAAGTCCAGC CAGAGTGTCTTAGACAGCTCCAAGAAATAAGAACTCCTTAGCTTGGTACAGCAAGAACCAAGGACAG CCTCCTAAATTAATCCTTCTGGGCATCTACGCGGGAATCCGGGATCCCTGACCGATTCAAGTGGC
				AGCGGCTCTGGGACAGATTTCACTCTCACTATTGACAGCCTGCAGCCTGAAGATTCTGCAACTTAC TATTGTCAACAGTCTGCCACTTCCCAGTACCTTTGGCCAAAGGACACGACTGGAGATTAAA
154	VL of F6A	artificial	aa	QTAVTQEPSLTVSPGGTVTLTTCGSSTGAVTSGYYPNWVQKPGQAPRGLIGGTFKFLAPGTPARFSG SLLGKKAALTLSGVQPEDEAEYYCALWYSNRWVFGGTTKLTVL
155	VH of F6A	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNIYAMNWVRQAPKGLEWVARI RSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNLLKTEDTAVYICVRHGNFGNSYVSFFAYWGQGLTVTVSS
156	VH-VL of F6A	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNIYAMNWVRQAPKGLEWVARI RSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNLLKTEDTAVYICVRHGNFGNSYVSFFAYWGQGLTVTVSSGGGSGG GGSGGGSQTAVTQEPSLTVSPGGTVTLTTCGSSTGAVTSGYYPNWVQKPGQAPRGLIGGTFKFLAP GTPARFSGSLLGKKAALTLSGVQPEDEAEYYCALWYSNRWVFGGTTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
157	VL-P of F6A	artificial	aa	ELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
158	VH-P of F6A	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNIYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSFFAYWGQGLTVTVSS
159	VH-VL-P of F6A	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNIYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSFFAYWGQGLTVTVSSGGGSGG GGSGGSELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
160	VL of H2C	artificial	aa	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
161	VH of H2C	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSS
162	VH-VL of H2C	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSSGGGSGG GGSGGGSQTAVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
163	VL-P of H2C	artificial	aa	ELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
164	VH-P of H2C	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSS
165	VH-VL-P of H2C	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNKYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGLTVTVSSGGGSGG GGSGGSELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
166	VL of H1E	artificial	aa	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
167	VH of H1E	artificial	aa	EVQLVESGGGLEQPGGSLKLSCAASGFTFNSYAMNWRQAPGKGLEWVARIRSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYLSFWAYWGQGLTVTVSS

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
168	VH-VL of H1E	artificial	aa	EVQLVESGGGLEQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSSGGGGSGG GGSGGGGQTVVTTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
169	VL-P of H1E	artificial	aa	ELAVTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
170	VH-P of H1E	artificial	aa	EVQLVESGGGLEQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSS
171	VH-VL-P of H1E	artificial	aa	EVQLVESGGGLEQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSSGGGGSGG GGSGGGSELAVTTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
172	VL of G4H	artificial	aa	QTVVTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
173	VH of G4H	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNRYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSS
174	VH-VL of G4H	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNRYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSSGGGGSGG GGSGGGGQTVVTTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
175	VL-P of G4H	artificial	aa	ELAVTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
176	VH-P of G4H	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNRYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSS
177	VH-VL-P of G4H	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNRYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSV KGRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNGFNSYLSFYAYWGQGTLLTVTVSSGGGGSGG GGSGGGSELAVTTQEPSTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
178	VL of A2J	artificial	aa	QTVVTQEP SLTVSPGGT VTLTCSRSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPSGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
179	VH of A2J	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNVIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYLSWWAYWGQGLTVTVSS
180	VH-VL of A2J	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNVIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYLSWWAYWGQGLTVTVSSGGGGSGG GGGGGSGTAVTQEP SLTVSPGGT VTLTCSRSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPS GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
181	VL-P of A2J	artificial	aa	ELAVTQEP SLTVSPGGT VTLTCSRSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPSGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
182	VH-P of A2J	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNVIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYLSWWAYWGQGLTVTVSS
183	VH-VL-P of A2J	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNVIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYLSWWAYWGQGLTVTVSSGGGGSGG GGGGGSELAVTQEP SLTVSPGGT VTLTCSRSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPS GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
184	VL of E1L	artificial	aa	QTVVTQEP SLTVSPGGT VTLTCSGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
185	VH of E1L	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYTSYYAYWGQGLTVTVSS
186	VH-VL of E1L	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYTSYYAYWGQGLTVTVSSGGGGSGG GGGGGSGTAVTQEP SLTVSPGGT VTLTCSGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
187	VL-P of E1L	artificial	aa	ELAVTQEP SLTVSPGGT VTLTCSGSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
188	VH-P of E1L	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNKIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNILKTEDTAVYYCVRHGNFGNSYTSYYAYWGQGLTVTVSS

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
189	VH-VL-P of E1L	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KSRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGFNGNSYTSYAYWGQGTLLTVSSGGGGSGG GGSGGGSELVVTQEPSLTVSPGGTVTLTSCGSTGAVTSGYYPNWVQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
190	VL of E2M	artificial	aa	QTVVTQEPSLTVSPGGTVTLTCSRSTGAVTSGYYPNWVQKPGQAPRGLIGATDMRPSGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
191	VH of E2M	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KERFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHRNFGNSYLSWFAYWGQGTLLTVSS
192	VH-VL of E2M	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KERFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHRNFGNSYLSWFAYWGQGTLLTVSSGGGGSGG GGSGGGQTVVTQEPSLTVSPGGTVTLTCSRSTGAVTSGYYPNWVQKPGQAPRGLIGATDMRPS GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
193	VL-P of E2M	artificial	aa	ELVVTQEPSLTVSPGGTVTLTCSRSTGAVTSGYYPNWVQKPGQAPRGLIGATDMRPSGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
194	VH-P of E2M	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KERFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHRNFGNSYLSWFAYWGQGTLLTVSS
195	VH-VL-P of E2M	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KERFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHRNFGNSYLSWFAYWGQGTLLTVSSGGGGSGG GGSGGGSELVVTQEPSLTVSPGGTVTLTCSRSTGAVTSGYYPNWVQKPGQAPRGLIGATDMRPS GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
196	VL of F7O	artificial	aa	QTVVTQEPSLTVSPGGTVTLTSCGSTGAVTSGYYPNWVQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
197	VH of F7O	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGFNGNSYISWMAIWGQGTLLTVSS
198	VH-VL of F7O	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGFNGNSYISWMAIWGQGTLLTVSSGGGGSGG GGSGGGQTVVTQEPSLTVSPGGTVTLTSCGSTGAVTSGYYPNWVQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
199	VL-P of F7O	artificial	aa	ELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
200	VH-P of F7O	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNVYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSS
201	VH-VL-P of F7O	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNVYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSSGGGGGG GGSGGGSELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
202	VL of F12Q	artificial	aa	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
203	VH of F12Q	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSS
204	VH-VL of F12Q	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSSGGGGGG GGSGGGGQTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
205	VL-P of F12Q	artificial	aa	ELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
206	VH-P of F12Q	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSS
207	VH-VL-P of F12Q	artificial	aa	EVQLLESGGGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSSGGGGGG GGSGGGSELVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
208	VL of I2C	artificial	aa	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
209	VH of I2C	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KKRFTISRDDSKNTAYLQMNLLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGLTVTVSS

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
210	VH-VL of I2C	artificial	aa	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLLTVSSGGGGSGG GGSGGGSQTVVTQEPSTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAP
				GTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
211	VL-P of I2C	artificial	aa	ELVVTQEPSTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSG SLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
212	VH-P of I2C	artificial	aa	EVQLLESVGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLLTVSS
213	VH-VL-P of I2C	artificial	aa	EVQLLESVGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSV KDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLLTVSSGGGGSGG GGSGGGSELVVTQEPSTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAP GTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
214	SA21-CD33 E11 HL x I2C HL (His Tag)		nt	CGCCTGATTGAAGATATTTGCCTGCCGCGCTGGGGCTGCCTGTGGGAAGATGAT CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGAGAGTCAGTCAAGGTCTCCTGC AAGCTAGCGGGTATACCTTCAAAAATATGAAATGAACTGGTGAAGCAGGCTCCAGGACAGGGT TTAGAGTGGATGGCTGGATAAACACCTACACTGGAGAGCCAACCTATGCTGATAAGTTCCAGGA CGGTTACCATGACTACGGATACCTCTACCAGCACTGCCTATATGAAATCCGCAACCTCGGAGGT GATGACACGGCTGTATATTACTGTGCGGCTGGAGTTGGAGTGATGGTTACTACGTTTACTTTGAC TACTGGGGCCAAAGGCACTTCGGTCACCGTCTCTCAGGTGGTGGTGGTCTGGCGGCGGCTCC GGTGGTGGTGGTCTGACATCGTGATGACACAGTCTCCAGACTCCCTGACTGTCTCTGGGCGAG AGGACCACCATCAACTGCAAGTCCAGCCAGAGTGTCTTAGACAGCTCCACGAATAAGAACTCCTTA GCTTGGTACACAGAGAAAACAGGACAGCTCTAAATTAATCTCTTCTCTGGGCATCTACGCGGAA TCCGGGATCCCTGACCGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACTATTGACAGC CCGAGCCTGAAGATTCTGCAACTTACTATTGTCAACAGTCTGCCACTTCCCGATCACCTTTGGC CAAGGACACGACTGGAGATTAAATCCGGAGGTGGTGGTCCGAGGTGCAGTGGTGCAGTCTGGA GGAGATTGGTGAGCTGGAGGTCACTGAAACTCTCATGTGAGCCTCTGGATTCACTTCAAT AAGTACGCCATGAACTGGTCCGCCAGGCTCCAGGAAAGGTTTGGAAATGGTTGCTCGCATAAGA AGTAAATATAAATATGCAACATATTATGCCGATTCACTGAAAGACAGGTTCACTATCTCCAGA GATGATTCAAAAACACTGCCTATCTACAAATGAACAACTTGAAACTGAGGACACTGCCGTGTAC TACTGTGTGAGACATGGAACTTCGGTAATAGCTACATATCTACTGGGCTTACTGGGCGCAAGGG ACTTGGTCACCGTCTCCTCAGGTGGTGGTGGTCTGGCGGCGGCTCCGGTGGTGGTGGTCTT CAGACTGTTGTGACTCAGGAACCTTCACTCACCGTATCACCTGGTGGAAACAGTCACACTCACTTGT GGTCTCTCGACTGGGGCTGTACATCTGGCAACTACCAAACTGGGTCCAACAAAAACAGGTCAAG GCACCCGTGGTCTAATAGGTGGACTAAGTTCTCGCCCCGGTACTCTCGCCAGATTCTCAGGC TCCCTGCTTGGAGCAAGGTGCCCTCACCTCTCAGGGGTACAGCCAGAGGATGAGGCAGAAATAT TACTGTGTTCTATGGTACAGCAACCGCTGGGTGTTCTGGTGGAGGAACCAAACTGACTGTCTTA CATCACCATCACCATCAC
215	SA21-CD33 E11 HL x I2C HL H6		aa	RLIEDICLPRWGCLWEDDQVLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPQGLEWM GWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYCARWSWSDGYVYFDYWGQ GTSVTVSSGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNLSLAWYQ QKPGQPPLKLLLSWASTRESGIPDRFSGSGSGTDFLTIDSPQEDSATYQCQSAHFPIITFGQGR LEIKSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPKGLEWVARIRSKYN
				NYATYYADSVKDRFTTISRDDSKNTAYLQMNLLKTEDTAVYCVRHGNFGNSYISYWAYWGQGTLLVT VSSGGSGGGSGGGSGGGSQTVVTQEPSTLTVSPGGTVTTLTCSSTGAVTSGNYPNWVQKPGQAPRG LIGGTFKFLAPGTPARFSGSLGGKAAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVLHHHHH H

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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217	SA25-CD33 E11 HL x I2C HL H6		aa	EDICLPWGLWEDQVLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWIN TYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYICARWSWSDGYVYFYDWGQTSV TVSSGGGSGGGSGGGSDIVMTQSPDLTVSLGERTTINCKSSQSVLDSSTNKNLSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGGTDFLTITIDSPQEDSATYYCQSAHFPIITFGQGTREIK SGGGSEVQLVESGGGLVQPPGSLKLSCAASGFTFNKYAMNWNVRQAPKGLEWVARIRSKYNNYAT YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYICVRHGNFGNSYISYWAYWGQGTLLTVSSG GGSGGGSGGGSGGTQTVVTQEPSTVSPGGTTLTCSSTGAVTSGNYPNWWQKPGQAPRGLIGG TKFLAPGTPARFSGSLGGKAAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVLHHHHHH

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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219	SA08-CD33 E11 HL x I2C HL H6		aa	QGLIGDICI LPRWGCLMGDSVKQVLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGL EWMGWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDY WGQGTSVTVSSGGGSGGGSGGGSDIVMTQSPDSLTVSLGRTTINCKSSQSVLDSSTNKNLSLA WYQKPGQPPKLLLSWASTRESGIPDRFSGSGSGTDFTLTIDSPQEDSATYYCQQSAPHFPIITFGQ GTRLEIKSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRS KYNRYATYYADSVKDRFTISRDDSKNTAYLQMNILKTEDTAVYCVRHGNGFNSYISYWAYWGQGT LVTVSSGGGSGGGSGGGSGGQTAVTQEPSTLTVSPGGTTLTTCGSSTGAVTSGNYPNWVQKPGQA PRGLIGGTKFLAPGTPARFSGSLIGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVLHH HHHH

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221	SA21-CD33 E11 HL x I2C HL		aa	RLIEDICLPWGCLWEDDQVLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWM GWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYCARWSWSDGYVYFDYWGQ GTSVTVSSGGGSGGGSGGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNLSLAWYQ QKPGQPPLLLSWASTRESGIPDRFSGSGSTDFTLTIDSPQEDSATYCYQSAHFPITTFGQGR LEIKSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYN NYATYYADSVKDRFTISRDDSKNTAYLQMNLLKTEDAVYYCVRHGNFGNSYISYWAYWGQGLVT VSSGGGSGGGSGGGSGQTVVTQEPSTVSPGGTVTTLTCSSTGAVTSGNYPNWVQQKPGQAPRG LIIGTKFLAPGTPARFSGSLLGKKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGTGKLTVL

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SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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223	SA25-CD33 E11 HL x I2C HL		aa	EDICLPWGLWEDQVLVQSGAEVKKPGESVKVSKASGYTFTNYGMNWVKQAPGQGLEWMGWIN TYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYICARWSWSDGYVYFDYWGQTSV TVSSGGSGSGSGGSDIVMTQSPDSLTVSLGERTTINCKSSQSVLDSSTNKNLSLAWYQQKPG QPPKLLLSWASTRESGIPDRFSGSGGTFTLTIDSPQEDSATYCCQSAHFPITFGQGRLEIK SGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPKGLEWVARIRSKYNNYAT YYADSVKDRFTISRDDSKNTAYLQMNLLKTEDTAVYICVRHGNFGNSYISYWAYWGQGLTVTVSSG GGSGGGSGSGSGSQTVVTQEPSTVSPGGTFTLTCSGSTGAVTSGNYPNWVQQKPGQAPRGLIGG TKFLAPGTPARFSGSLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

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225	SA08-CD33 E11 HL x I2C HL		aa	QGLIGDICIPLRWGLWGDVVKQVLQVSGAEVKKPGESVKVSKASGYFTFTNYGMNWVKQAPGQGL EWMGWINTYTGEPTYADKFQGRVTMTTDTSTSTAYMEIRNLGGDDTAVYYCARWSWSDGYVYFDY WGQTSVTVSSGGSGGGGGSDIVMTQSPDSLTVSLGERTTINCKSSQS SVLDSSTNKNLSLA WYQKPQPPKLLLSWASTRESGIPDRFSGSGGTDFLTIDSPQEDSATYCCQSAHFPIITFGQ GTRLEIKSGGGSEVQLVSGGGLVQPGGSLKLSCAASGTFNKYAMNWRQAPKGLEWVARIRS KYNNTATYYADSVKDRFTISRDDSKNTAYLQMNLLKTEDTAVYCVRHGNGFNSYISYWAYWGQT LVTVSSGGSGGGGGSGGTSQTVTQEPSTVSPGGTTLTCSGSTGAVTSGNYPNWVQKPGQA PRGLIGGTFKFLAPGTPARFSGSLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

SEQ ID NO.	DESIGNATION	SOURCE	TYPE	SEQUENCE
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SEQUENCE LISTING

[0242]

5 <110> Amgen Research (Munich) GmbH
Amgen Inc.

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myeloid leukemia

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 5 ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gccaacatat 180
 gctgatgact tcaagggacg ggttaccatg tcttcggata cctctaccag cactgcctat 240
 ttggaaatca acagcctcag aagtgatgac acggctatat attactgtgc gcgctggagt 300
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 <223> CD33 VL of AH3
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 Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60
 40 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 45 Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
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<223> CD33 LCDR1 of AH3

<400> 7

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<211> 7

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Gln Gln Ser Ala His Phe Pro Ile Thr
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<223> CD33 VL of AH3

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<400> 10

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15

20

25

30

35

40

45

50

55

	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr	
				20					25					30			
5	Gly	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35				40						45				
10	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
		50					55					60					
15	Lys	Gly	Arg	Val	Thr	Met	Ser	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
20	Leu	Glu	Ile	Asn	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
				85					90						95		
25	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
30	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	
			115					120					125				
35	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
		130					135					140					
40	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
	145					150					155					160	
45	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	
				165					170						175		
50	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
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60	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
		210					215					220					
65	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
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<212> DNA
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<400> 12

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15      gctgatgact tcaagggacg ggttaccatg tcttcggata cctctaccag cactgcctat      240
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      tggagtgatg gttactacgt ttactttgac tactggggcc aaggcactac ggtcaccgtc      360
20      tcctcagggtg gtggtgggtc tggcggcggc ggctccggtg gtggtgggtc tgacatcgtg      420
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      aagtccagcc agagtgtttt agacagctcc aagaataaga actccttagc ttggtaccag      540
25      cagaaaccag gacagcctcc taaattactc ctttcctggg catctacgcg ggaatccggg      600
      atccctgacc gattcagtgg cagcgggtct gggacagatt tcactctcac tattgacagc      660
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<210> 13
 <211> 505
 <212> PRT
 <213> artificial

<220>
 <223> CD33 AH3 HL x H2C HL

<400> 13

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				20					25					30		
10	Gly	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe
	50						55					60				
20	Lys	Gly	Arg	Val	Thr	Met	Ser	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75					80
25																
30																
35																
40																
45																
50																
55																

	Leu	Glu	Ile	Asn	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
					85					90					95		
5	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
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20	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
	145					150					155					160	
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				165						170					175		
30	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
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40	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
		210					215					220					
45	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
	225					230					235					240	
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				260					265					270			
60	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
			275					280					285				
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70	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
	305					310					315					320	
75	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
				325						330					335		

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
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5 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

10 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
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Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

15 Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

20 Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
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25 Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

30 Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
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<210> 14

<211> 1515

<212> DNA

<213> artificial

<220>

<223> CD33 AH3 HL x H2C HL

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ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gccaacatat 180

gctgatgact tcaagggacg ggttaccatg tcttcggata cctctaccag cactgcctat 240

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 5 tcctcaggtg gtggtggttc tggcggcggc ggctccggtg gtggtggttc tgacatcgtg 420
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<210> 15

<211> 505

<212> PRT

<213> artificial

<220>

<223> CD33 AH3 HL x F12Q HL

<400> 15

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			35					40					45				
5	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
		50					55					60					
	Lys	Gly	Arg	Val	Thr	Met	Ser	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
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	Leu	Glu	Ile	Asn	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
					85					90					95		
15	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	
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25		130					135					140					
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		145				150					155					160	
30	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	
					165					170					175		
	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
35				180					185					190			
	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
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		210					215					220					
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				260					265					270			
55	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr	
			275					280					285				

	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
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5	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
	305					310					315					320	
10	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
					325					330					335		
15	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
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	385					390					395					400	
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				420					425					430			
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	450						455					460					
55	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	465				470						475					480	
60	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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<211> 1515

<212> DNA

<213> artificial

<220>

<223> CD33 AH3 HL x F12Q HL

<400> 16

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	tggagtgatg gttactacgt ttactttgac tactggggcc aaggcactac ggtcaccgtc	360
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20	aagtccagcc agagtgtttt agacagctcc aagaataaga actccttagc ttggtaccag	540
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30	gtcgagtctg gaggaggatt ggtgcagcct ggagggtcat tgaaactctc atgtgcagcc	840
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	atgaacaact tgaaaactga ggacactgcc gtgtactact gtgtgagaca tgggaacttc	1080
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<210> 17

<211> 505

<212> PRT

<213> artificial

<220>

<223> CD33 AH3 HL x I2C HL

<400> 17

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45

50

55

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5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr	
				20					25					30			
10	Gly	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
		50					55					60					
20	Lys	Gly	Arg	Val	Thr	Met	Ser	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
		65				70					75					80	
25	Leu	Glu	Ile	Asn	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
					85					90					95		
30	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
35	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	
			115					120					125				
40	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
		130					135					140					
45	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
		145				150					155					160	
50	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	
					165					170					175		
55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
60	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
			195					200					205				
65	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
		210					215					220					
70	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
		225				230					235					240	

	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser	245	250	255
5	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	260	265	270
10	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr	275	280	285
	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	290	295	300
15	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp	305	310	315
20	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	325	330	335
	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr	340	345	350
25	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp	355	360	365
30	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly	370	375	380
35	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val	385	390	395
	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu	405	410	415
40	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn	420	425	430
45	Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly	435	440	445
	Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu	450	455	460
50	Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp	465	470	475
55	Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe	485	490	495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

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 <212> DNA
 <213> artificial

10 <220>
 <223> CD33 AH3 HL x I2C HL

<400> 18

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	ttggaaatca	acagcctcag	aagtgatgac	acggctatat	attactgtgc	gcgctggagt	300
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<400> 19

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 1 5 10 15

 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 10
 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45

 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60
 15
 Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 20
 Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 25
 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110
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 Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

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<213> artificial

<220>

<223> CD33 HCDR1 of AF5

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<400> 20

Asn Tyr Gly Met Asn
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<211> 17

<212> PRT

<213> artificial

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<220>

<223> CD33 HCDR2 of AF5

<400> 21

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Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
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5 Gly

<210> 22

<211> 13

<212> PRT

10 <213> artificial

<220>

<223> CD33 HCDR3 of AF5

15 <400> 22

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
 1 5 10

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<211> 366

<212> DNA

<213> artificial

25 <220>

<223> CD33 VH of AF5

<400> 23

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35 ccaggacagg gtttaaagtg gatgggctgg ataaacacct aactggaga gccaacatat 180

gctgatgact tcaagggacg ggttaccatg acttcggata cctctaccag cactgcctat 240

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tcctca 366

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50 <223> CD33 VL of AF5

<400> 24

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 Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
 20 25 30
 10
 Ser Lys Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60
 15
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 20
 Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
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 Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
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 Lys
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 <400> 26
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 1 5
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 15
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 20
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5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr	
				20					25					30			
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Lys	Trp	Met	
			35					40					45				
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
	50						55					60					
20	Lys	Gly	Arg	Val	Thr	Met	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
25	Leu	Glu	Leu	His	Asn	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85						90					95		
30	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
35	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	
			115					120					125				
40	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
	130						135					140					
45	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
	145					150					155					160	
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				165						170					175		
55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
60	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
			195					200					205				
65	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
	210						215					220					
70	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
	225					230					235					240	
75	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys							
				245						250							

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 10 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 15 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 20 Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 25 Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 30 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 35 Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 40
 45
 50
 55

	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
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	145					150					155					160	
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15	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
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30	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
	225					230					235					240	
35	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser	
					245					250					255		
40	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
				260					265					270			
45	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
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60	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
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65	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
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10	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
				420					425					430			
15	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
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		450					455					460					
25	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	465					470					475					480	
30	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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10

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			20					25					30		

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

15

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

20

Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
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Leu Glu Leu His Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys

25

30

35

40

45

50

55

	85	90	95
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15	Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser 130 135 140		
20	Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys 145 150 155 160		
25	Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu 165 170 175		
30	Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser 180 185 190		
35	Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 195 200 205		
40	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu 210 215 220		
45	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr 225 230 235 240		
50	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser 245 250 255		
55	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 260 265 270		
60	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr 275 280 285		
65	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 290 295 300		
70	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 305 310 315 320		
75	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 325 330 335		

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

5 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
355 360 365

10 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

15 Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

20 Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
420 425 430

25 Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

30 Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

35 Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
40 500 505

<210> 34

<211> 1515

<212> DNA

<213> artificial

<220>

<223> CD33 AF5 HL x F12Q HL

<400> 34

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5	ccaggacagg	gtttaaagtg	gatgggctgg	ataaacacct	acactggaga	gccaacatat	180
	gctgatgact	tcaagggacg	ggttaccatg	acttcggata	cctctaccag	cactgcctat	240
10	ttggaactcc	acaacctcag	aagtgatgac	acggctgtat	attactgtgc	gcgctggagt	300
	tggagtgatg	gttactacgt	ttactttgac	tactggggcc	aaggcactac	ggtcaccgtc	360
	tcctcagggtg	gtggtgggtc	tggcggcggc	ggctccgggtg	gtggtgggtc	tgacatcgtg	420
15	atgacacagt	ctccagactc	cctgactgtg	tctctgggcg	agaggaccac	catcaactgc	480
	aagtccagcc	agagtgtttt	agacagctcc	aagaataaga	actccttagc	ttggtaccag	540
20	cagaaaccag	gacagcctcc	taaattactc	ctttcctggg	catctacgcg	ggaatccggg	600
	atccctgacc	gattcagtgg	cagcgggtct	gggacagatt	tcactctcac	tattgacagc	660
	ctgcagcctg	aagattctgc	aacttactat	tgtcaacagt	ctgcccactt	cccgatcacc	720
25	tttggccaag	ggacacgact	ggagattaaa	tccggagggtg	gtggctccga	ggtgcagctg	780
	gtcgagtctg	gaggaggatt	ggtgcagcct	ggagggtcat	tgaaactctc	atgtgcagcc	840
	tctggattca	ccttcaatag	ctacgccatg	aactgggtcc	gccaggctcc	aggaaaggg	900
30	ttggaatggg	ttgctcgcat	aagaagtaaa	tataataatt	atgcaacata	ttatgccgat	960
	tcagtgaag	gcaggttcac	catctccaga	gatgattcaa	aaaacactgc	ctatctacaa	1020
	atgaacaact	tgaaaactga	ggacactgcc	gtgtactact	gtgtgagaca	tgggaacttc	1080
35	ggtaatagct	acgtttcctg	gtgggcttac	tggggccaag	ggactctggt	caccgtctcc	1140
	tcagggtggtg	gtggttctgg	cggcggcggc	tccggtggtg	gtggttctca	gactgttgtg	1200
40	actcaggaac	cttcactcac	cgtatcacct	ggtggaacag	tcacactcac	ttgtggctcc	1260
	tcgactgggg	ctgttacatc	tggcaactac	ccaaactggg	tccaacaaaa	accaggtcag	1320
	gcaccccggtg	gtctaataag	tgggactaag	ttcctcgccc	ccggtactcc	tgccagattc	1380
45	tcaggctccc	tgcttggagg	caaggctgcc	ctcaccctct	caggggtaca	gccagaggat	1440
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50	aaactgactg	tccta					1515
	<210> 35						
	<211> 505						
	<212> PRT						
	<213> artificial						
55	<220>						
	<223> CD33 AF5 HL x I2C HL						

<400> 35

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	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
				20					25					30		
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Lys	Trp	Met
			35					40					45			
15																
20																
25																
30																
35																
40																
45																
50																
55																

	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
	50						55					60					
5	Lys	Gly	Arg	Val	Thr	Met	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
10	Leu	Glu	Leu	His	Asn	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85						90					95		
15	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
20	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	
			115					120					125				
25	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
	130						135					140					
30	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
	145					150					155					160	
35	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	
				165						170					175		
40	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
45	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
			195					200					205				
50	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
	210						215					220					
55	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
	225					230					235					240	
60	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser	
				245						250					255		
65	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
				260					265					270			
70	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
		275						280					285				
75	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	

	290		295		300											
5	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp
	305					310					315					320
	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
10					325					330					335	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
				340					345					350		
15	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp
			355					360					365			
	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
20		370					375					380				
	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val
25	385					390					395					400
	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu
					405					410					415	
30	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn
				420					425					430		
	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly
35			435					440					445			
	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu
40		450					455					460				
	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp
	465					470					475					480
45	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe
					485					490					495	
50	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu							
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<210> 36

<211> 1515

<212> DNA

<213> artificial

<220>

<223> CD33 AF5 HL x I2C HL

<400> 36

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	ccaggacagg	gtttaaagtg	gatgggctgg	ataaacacct	acactggaga	gccaacatat	180
	gctgatgact	tcaagggacg	ggttaccatg	acttcggata	cctctaccag	cactgcctat	240
10	ttggaactcc	acaacctcag	aagtgatgac	acggctgtat	attactgtgc	gcgctggagt	300
	tggagtgatg	gttactacgt	ttactttgac	tactggggcc	aaggcactac	ggtcaccgtc	360
15	tcctcagggtg	gtgggtgggtc	tggcggcggc	ggctccgggtg	gtgggtgggtc	tgacatcggtg	420
	atgacacagt	ctccagactc	cctgactgtg	tctctgggcg	agaggaccac	catcaactgc	480
	aagtccagcc	agagtgtttt	agacagctcc	aagaataaga	actccttagc	ttgggtaccag	540
20	cagaaaccag	gacagcctcc	taaattactc	ctttcctggg	catctacgcg	ggaatccggg	600
	atccctgacc	gattcagtg	cagcgggtct	gggacagatt	tcactctcac	tattgacagc	660
	ctgcagcctg	aagattctgc	aacttactat	tgtcaacagt	ctgcccactt	cccgatcacc	720
25	tttggccaag	ggacacgact	ggagattaaa	tccggagggtg	gtggctccga	ggtgcagctg	780
	gtcgagtctg	gaggaggatt	ggtgcagcct	ggagggtcat	tgaaactctc	atgtgcagcc	840
30	tctggattca	ccttcaataa	gtacgccatg	aactgggtcc	gccaggctcc	aggaaaggg	900
	ttggaatggg	ttgctcgcat	aagaagtaaa	tataataatt	atgcaacata	ttatgccgat	960
	tcagtgaaag	acaggttcac	catctccaga	gatgattcaa	aaaacactgc	ctatctacaa	1020
35	atgaacaact	tgaaaactga	ggacactgcc	gtgtactact	gtgtgagaca	tgggaacttc	1080
	ggtaatagct	acatatccta	ctgggcttac	tggggccaag	ggactctgg	caccgtctcc	1140
	tcagggtggtg	gtggttctg	cggcggcggc	tccgggtggtg	gtggttctca	gactgttgtg	1200
40	actcaggaac	cttcactcac	cgtatcacct	ggtggaacag	tcacactcac	ttgtggctcc	1260
	tcgactgggg	ctgttacatc	tggcaactac	ccaaactggg	tccaacaaaa	accaggtcag	1320
45	gcaccccggtg	gtctaataag	tgggactaag	ttcctcgccc	ccggtactcc	tgccagattc	1380
	tcaggctccc	tgcttgagg	caaggctgcc	ctcaccctct	caggggtaca	gccagaggat	1440
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<210> 37

<211> 122

<212> PRT

55 <213> artificial

<220>

<223> CD33 VH of AC8

<400> 37

5 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 10
 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45

 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60
 15
 Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 20
 Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 25
 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110
 30
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 38

<211> 5

<212> PRT

<213> artificial

<220>

<223> CD33 HCDR1 of AC8

40

<400> 38

Asn Tyr Gly Met Asn
 1 5

45

<210> 39

<211> 17

<212> PRT

<213> artificial

50

<220>

<223> CD33 HCDR2 of AC8

<400> 39

55

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
 1 5 10 15

5 Gly

<210> 40

<211> 13

<212> PRT

10 <213> artificial

<220>

<223> CD33 HCDR3 of AC8

15 <400> 40

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
 1 5 10

20 <210> 41

<211> 366

<212> DNA

<213> artificial

25 <220>

<223> CD33 VH of AC8

<400> 41

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35 ccaggacagg gtttaaagtg gatgggctgg ataaacacct aactggaga gccaacatat 180

gctgatgact tcaagggacg ggttaccatg actacggata cctctaccag cactgcctat 240

atggaaatcc gcaacctcag aaatgatgac acggctgtat attactgtgc gcgctggagt 300

40 tggagtgatg gttactacgt ttactttgac tactggggcc aaggcactac ggtcaccgtc 360

tcctca 366

<210> 42

45 <211> 113

<212> PRT

<213> artificial

<220>

50 <223> CD33 VL of AC8

<400> 42

55

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Thr Val Ser Leu Gly
 1 5 10 15
 5
 Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
 20 25 30
 10
 Ser Lys Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 15
 50 55 60
 20
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
 85 90 95
 25
 Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
 100 105 110
 30
 Lys
 <210> 43
 <211> 17
 <212> PRT
 35 <213> artificial
 <220>
 <223> CD33 LCDR1 of AC8
 40 <400> 43
 Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
 1 5 10 15
 45
 Ala
 <210> 44
 <211> 7
 50 <212> PRT
 <213> artificial
 <220>
 <223> CD33 LCDR2 of AC8
 55 <400> 44

Trp Ala Ser Thr Arg Glu Ser
1 5

5 <210> 45
<211> 9
<212> PRT
<213> artificial

10 <220>
<223> CD33 LCDR3 of AC8

<400> 45

15 Gln Gln Ser Ala His Phe Pro Ile Thr
1 5

20 <210> 46
<211> 339
<212> DNA
<213> artificial

<220>
<223> CD33 VL of AC8

25 <400> 46

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tggtaccagc agaaaccagg acagcctcct aaattactcc tttcctgggc atctacgcgg 180
gaatccggga tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcact 240
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ccgatcacct ttggccaagg gacacgactg gagattaata 339

40 <210> 47
<211> 250
<212> PRT
<213> artificial

45 <220>
<223> CD33 HL of AC8

<400> 47

50

55

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
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 5 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 10 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45
 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60
 15 Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 20 Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 25 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 30
 35
 40
 45
 50
 55

	115	120	125
5	Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser 130 135 140		
10	Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys 145 150 155 160		
15	Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu 165 170 175		
20	Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser 180 185 190		
25	Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 195 200 205		
30	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu 210 215 220		
35	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr 225 230 235 240		
40	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys 245 250		

<210> 48

<211> 750

<212> DNA

<213> artificial

<220>

<223> CD33 HL of AC8

<400> 48

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	tcctgcaagg ctagcgggta taccttcaca aactatggaa tgaactgggt gaagcaggct	120
5	ccaggacagg gtttaaagtg gatgggctgg ataaacacct aactggaga gccaacatat	180
	gctgatgact tcaagggacg ggttaccatg actacggata cctctaccag cactgcctat	240
	atggaaatcc gcaacctcag aaatgatgac acggctgtat attactgtgc gcgctggagt	300
10	tggagtgatg gttactacgt ttactttgac tactggggcc aaggcactac ggtcaccgtc	360
	tcctcaggtg gtggtggttc tggcggcggc ggctccggtg gtggtggttc tgacatcgtg	420
	atgacacagt ctccagactc cctgactgtg tctctgggcg agaggaccac catcaactgc	480
15	aagtccagcc agagtgtttt agacagctcc aagaataaga actccttagc ttggtaccag	540
	cagaaaccag gacagcctcc taaattactc ctttcctggg catctacgcg ggaatccggg	600
20	atccctgacc gattcagtgg cagcgggtct gggacagatt tcactctcac tattgacagc	660
	ctgcagcctg aagattctgc aacttactat tgtcaacagt ctgcccactt cccgatcacc	720
25	tttggccaag ggacacgact ggagattaaa	750

<210> 49

<211> 505

<212> PRT

<213> artificial

30

<220>

<223> CD33 AC8 HL x H2C HL

35

<400> 49

40

45

50

55

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 5 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 10 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
 35 40 45
 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60
 15 Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 20 Met Glu Ile Arg Asn Leu Arg Asn Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 25 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125
 30 Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140
 35 Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160
 40 Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu
 165 170 175
 Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser

	180	185	190
5	Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 195 200 205		
10	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu 210 215 220		
15	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr 225 230 235 240		
20	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser 245 250 255		
25	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 260 265 270		
30	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr 275 280 285		
35	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 290 295 300		
40	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 305 310 315 320		
45	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 325 330 335		
50	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr 340 345 350		
55	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp 355 360 365		
	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly 370 375 380		
	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val 385 390 395 400		
	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu 405 410 415		
	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn 420 425 430		

	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly
			435					440					445			
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 Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
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5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr	
				20					25					30			
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Lys	Trp	Met	
			35					40					45				
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
		50					55					60					
20	Lys	Gly	Arg	Val	Thr	Met	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
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25	Met	Glu	Ile	Ser	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
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30	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
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			115					120					125				
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		130					135					140					
45	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
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50	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	
					165					170					175		
55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
60	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
			195					200					205				
65	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
		210					215					220					
70	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
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<400> 66

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 <212> PRT
 <213> artificial

<220>
 <223> CD33 AH11 HL x H2C HL

<400> 67

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				20					25					30			
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Lys	Trp	Met	
			35					40					45				
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	
	50						55					60					
20	Lys	Gly	Arg	Val	Thr	Met	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
25	Met	Glu	Ile	Ser	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
					85					90					95		
30	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
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35	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	
			115					120					125				
40	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
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45	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
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55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
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60	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
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		210					215					220					
70	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
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15	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
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20	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
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30	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
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35	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
			355					360					365				
40	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
		370					375					380					
45	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
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50	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
					405					410					415		
55	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
				420					425					430			
60	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
			435					440					445				
65	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
		450					455					460					
70	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
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75	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	

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490

495

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<210> 68

<211> 1515

<212> DNA

10 <213> artificial

<220>

<223> CD33 AH11 HL x H2C HL

15 <400> 68

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5	ccaggacagg gtttaaagtg gatgggctgg ataaacacct aactggaga gccaacatat	180
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<210> 69

<211> 505

<212> PRT

<213> artificial

<220>

<223> CD33 AH11 HL x F12Q HL

<400> 69

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20	Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe	50 55 60
25	Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr	65 70 75 80
30	Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys	85 90 95
35	Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp	100 105 110
40	Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly	115 120 125
45	Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser	130 135 140
50	Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys	145 150 155 160
55	Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu	165 170 175
	Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser	180 185 190

	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
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	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser	
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15	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
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	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr	
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	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
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30	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
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	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
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			355					360					365				
40	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
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	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
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	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	
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	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
	450						455					460					
5	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	465					470					475					480	
10	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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<211> 505

<212> PRT

20 <213> artificial

<220>

<223> CD33 AH11 HL x I2C HL

25 <400> 71

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 35 40 45
 40 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
 50 55 60
 Lys Gly Arg Val Thr Met Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 45 Met Glu Ile Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 50 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
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 55 Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

	Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys	
	145	150 155 160
5	Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Lys Asn Lys Asn Ser Leu	
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10	Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser	
		180 185 190
15	Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser	
		195 200 205
20	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu	
		210 215 220
25	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr	
		225 230 235 240
30	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser	
		245 250 255
35	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	
		260 265 270
40	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr	
		275 280 285
45	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
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50	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp	
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55	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
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60	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr	
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65	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp	
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70	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly	
		370 375 380
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				420					425					430			
10	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
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20	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
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25	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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 35 40 45

 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
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 Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
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 20 Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
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50 <213> artificial

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55 <400> 75

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10 <213> artificial

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15 <400> 76

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25 <220>

<223> CD33 VH of B3

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35 ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gacaaactat 180

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tcctca 366

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10 Ser Thr Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60

15 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

20 Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
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 1 5 10 15

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 <400> 80

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				20					25					30			
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
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		50					55					60					
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	65					70					75					80	
25	Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
					85					90					95		
30	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
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				165						170					175		
55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
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			195					200					205				
65	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
		210					215					220					
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35

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<220>
 <223> CD33 B3 HL x H2C HL

<400> 85

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
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50

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
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55

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10	Gln	Gly	Arg	Val	Thr	Phe	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
15	Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
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<212> DNA

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<220>

<223> CD33 B3 HL x H2C HL

<400> 86

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<211> 505

<212> PRT

<213> artificial

<220>

<223> CD33 B3 HL x F12Q HL

<400> 87

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20

25

30

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70	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
	225					230					235					240	

	Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys Ser Gly Gly Gly Gly Ser	245	250	255
5	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	260	265	270
10	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr	275	280	285
	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	290	295	300
15	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp	305	310	315
20	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	325	330	335
	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr	340	345	350
25	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp	355	360	365
30	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly	370	375	380
35	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val	385	390	395
	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu	405	410	415
40	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn	420	425	430
45	Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly	435	440	445
	Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu	450	455	460
50	Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp	465	470	475
55	Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe	485	490	495

Gly Gly Gly Thr Lys Leu Thr Val Leu
500 505

5 <210> 88
 <211> 1515
 <212> DNA
 <213> artificial

10 <220>
 <223> CD33 B3 HL x F12Q HL

<400> 88

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5	ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gacaaactat	180
	gctgataagt tccagggacg cgttaccttc acttcggata cctctaccag cactgcctat	240
	atggaactcc gcaacctcaa aagtgatgac acggctgtat attactgtgc gcgctggagt	300
10	tggagtgatg gttactacgt ttactttgac tactggggcc aaggcactac ggtcaccgtc	360
	tcctcaggtg gtggtggttc tggcggcggc ggctccggtg gtggtggttc tgacatcgtg	420
	atgacacagt ctccagactc catgactgtg tctctgggcg agaggaccac catcaactgc	480
15	aagtccagcc agagtgtttt agacagctcc acgaataaga actccttagc ttggtaccag	540
	cagaaaccag gacagcctcc taaattactc ctttcctggg catctacgcg ggaatccggg	600
20	atccctgacc gattcagtgg cagcgggtct gggacagatt tcactctcac tattgacagc	660
	ctgcagcctg aagattctgc aacttactat tgtcaacagt ctgccactt cccgatcacc	720
	tttgccaag ggacacgact ggacattaaa tccggagggtg gtggctccga ggtgcagctg	780
25	gtcgagtctg gaggaggatt ggtgcagcct ggagggtcat tgaaactctc atgtgcagcc	840
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	atgaacaact tgaaaactga ggacactgcc gtgtactact gtgtgagaca tgggaacttc	1080
35	ggtaatagct acgtttcctg gtgggcttac tggggccaag ggactctggt caccgtctcc	1140
	tcagggtggtg gtggttctg cggcggcggc tccggtggtg gtggttctca gactgttgtg	1200
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40	tcgactgggg ctgttacatc tggcaactac ccaaactggg tccaacaaaa accaggtcag	1320
	gcaccccggtg gtctaataag tgggactaag ttctctgccc ccggtactcc tgccagattc	1380
	tcaggctccc tgcttgagg caaggctgcc ctcaccctct caggggtaca gccagaggat	1440
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<400> 89

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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

 10 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
 50 55 60

 Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

 20 Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

 Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125

 Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

 35 Pro Asp Ser Met Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
 145 150 155 160

 Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 165 170 175

 Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
 180 185 190

 Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser

50

55

	195	200	205
5	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu 210 215 220		
10	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr 225 230 235 240		
15	Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys Ser Gly Gly Gly Gly Ser 245 250 255		
20	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 260 265 270		
25	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr 275 280 285		
30	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 290 295 300		
35	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 305 310 315 320		
40	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 325 330 335		
45	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr 340 345 350		
50	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp 355 360 365		
55	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly 370 375 380		
	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val 385 390 395 400		
	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu 405 410 415		
	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn 420 425 430		
	Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly 435 440 445		

	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
	450						455					460					
5	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	465					470					475					480	
	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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				500					505								
15																	
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	<211> 1515																
	<212> DNA																
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20																	
	<220>																
	<223> CD33 B3 HL x I2C HL																
	<400> 90																
25																	
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35																	
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5	ccaggacagg	gtttagagt	gatgggctgg	ataaacacct	acactggaga	gacaaactat	180
	gctgataagt	tccagggacg	cgttaccttc	acttcggata	cctctaccag	cactgcctat	240
	atggaactcc	gcaacctcaa	aagtgatgac	acggctgtat	attactgtgc	gcgctggagt	300
10	tggagtgatg	gttactacgt	ttactttgac	tactggggcc	aaggcactac	ggtcaccgtc	360
	tcctcagggtg	gtgggtggttc	tggcggcggc	ggctccgggtg	gtgggtggttc	tgacatcgtg	420
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	tctggattca	ccttcaataa	gtacgccatg	aactgggtcc	gccaggctcc	aggaaaggg	900
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	tcagtgaaag	acaggttcac	catctccaga	gatgattcaa	aaaacactgc	ctatctacaa	1020
	atgaacaact	tgaaaactga	ggacactgcc	gtgtactact	gtgtgagaca	tgggaacttc	1080
35	ggtaatagct	acatatccta	ctgggcttac	tggggccaag	ggactctggt	caccgtctcc	1140
	tcagggtggtg	gtggttctgg	cggcggcggc	tccggtggtg	gtggttctca	gactgttgtg	1200
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45	tcaggctccc	tgcttgagg	caaggctgcc	ctcaccctct	caggggtaca	gccagaggat	1440
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	aaactgactg	tccta					1515
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	<211> 122						
	<212> PRT						
	<213> artificial						
55	<220>						
	<223> CD33 VH of F2						

<400> 91

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 1 5 10 15

 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 10 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe
 50 55 60

 Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 20 Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110

 Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120
 30

<210> 92

<211> 5

35 <212> PRT

<213> artificial

<220>

<223> CD33 HCDR1 of F2

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<400> 92

Asn Tyr Gly Met Asn
 1 5

45

<210> 93

<211> 17

<212> PRT

<213> artificial

50

<220>

<223> CD33 HCDR2 of F2

<400> 93

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Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe Gln
 1 5 10 15

5 Gly

<210> 94

<211> 13

<212> PRT

10 <213> artificial

<220>

<223> CD33 HCDR3 of F2

15 <400> 94

Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr
 1 5 10

20 <210> 95

<211> 366

<212> DNA

<213> artificial

25 <220>

<223> CD33 VH of F2

<400> 95

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tcctgcaagg ctagcgggta taccttcaca aactatggaa tgaactgggt gaagcaggct 120

35 ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gacaaactat 180

gctgataaagt tccagggacg cgttaccttc acttcggata cctctaccag cactgcctat 240

atggaactcc gcaacctcaa aagtgatgac acggctgtat attactgtgc gcgctggagt 300

40 tggagtgatg gttactacgt ttactttgac tactggggcc aaggcactac ggtcaccgtc 360

tcctca 366

<210> 96

45 <211> 113

<212> PRT

<213> artificial

<220>

50 <223> CD33 VL of F2

<400> 96

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Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ser Val Ser Leu Gly
 1 5 10 15

5 Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
 20 25 30

10 Ser Thr Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60

15 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

20 Ile Asp Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
 85 90 95

25 Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
 100 105 110

Lys

30 <210> 97
 <211> 17
 <212> PRT
 <213> artificial

35 <220>
 <223> CD33 LCDR1 of F2
 <400> 97

40 Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu
 1 5 10 15

Ala

45 <210> 98
 <211> 7
 <212> PRT
 <213> artificial

50 <220>
 <223> CD33 LCDR2 of F2
 <400> 98

55 Trp Ala Ser Thr Arg Glu Ser
 1 5

<210> 99
 <211> 9
 <212> PRT
 <213> artificial
 5
 <220>
 <223> CD33 LCDR3 of F2
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 <400> 99
 Gln Gln Ser Ala His Phe Pro Ile Thr
 1 5
 <210> 100
 <211> 339
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 30 gaatccggga tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcact 240
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 <210> 101
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 <212> PRT
 <213> artificial
 40
 <220>
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 <400> 101
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 1 5 10 15
 50 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 55

	20	25	30
5	Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45		
10	Gly Trp Ile Asn Thr Tyr Thr Gly Glu Thr Asn Tyr Ala Asp Lys Phe 50 55 60		
15	Gln Gly Arg Val Thr Phe Thr Ser Asp Thr Ser Thr Ser Thr Ala Tyr 65 70 75 80		
20	Met Glu Leu Arg Asn Leu Lys Ser Asp Asp Thr Ala Val Tyr Tyr Cys 85 90 95		
25	Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp 100 105 110		
30	Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly 115 120 125		
35	Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser 130 135 140		
40	Pro Asp Ser Leu Ser Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys 145 150 155 160		
45	Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu 165 170 175		
50	Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser 180 185 190		
55	Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 195 200 205		
	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu 210 215 220		
	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr 225 230 235 240		
	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys 245 250		

<210> 102
 <211> 750
 <212> DNA

<213> artificial

<220>

<223> CD33 HL of F2

5

<400> 102

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15	gctgataagt tccagggacg cgttaccttc acttcggata cctctaccag cactgcctat	240
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20	tcctcagggtg gtggtgggtc tggcggcggc ggctccggtg gtggtgggtc tgacatcgtg	420
	atgacacagt ctccagactc cctgtctgtg tctctgggcg agaggaccac catcaactgc	480
	aagtccagcc agagtgtttt agacagctcc acgaataaga actccttagc ttggtaccag	540
25	cagaaaccag gacagcctcc taaattactc ctttcctggg catctacgcg ggaatccggg	600
	atccctgacc gattcagtgg cagcgggtct gggacagatt tcactctcac tattgacagc	660
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<210> 103

<211> 505

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<212> PRT

<213> artificial

<220>

<223> CD33 F2 HL x H2C HL

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<400> 103

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50

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	1				5					10					15	
5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
				20					25					30		
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Thr	Asn	Tyr	Ala	Asp	Lys	Phe
	50						55					60				
20	Gln	Gly	Arg	Val	Thr	Phe	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75				80	
25	Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
30																
35																
40																
45																
50																
55																

	85	90	95
5	Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp 100 105 110		
10	Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly 115 120 125		
15	Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser 130 135 140		
20	Pro Asp Ser Leu Ser Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys 145 150 155 160		
25	Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Thr Asn Lys Asn Ser Leu 165 170 175		
30	Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser 180 185 190		
35	Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 195 200 205		
40	Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu 210 215 220		
45	Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr 225 230 235 240		
50	Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser 245 250 255		
55	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 260 265 270		
60	Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr 275 280 285		
65	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 290 295 300		
70	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 305 310 315 320		
75	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 325 330 335		

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
340 345 350

5 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
355 360 365

10 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
385 390 395 400

15 Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
405 410 415

20 Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
420 425 430

25 Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
435 440 445

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
450 455 460

30 Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
465 470 475 480

35 Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
485 490 495

Gly Gly Gly Thr Lys Leu Thr Val Leu
40 500 505

<210> 104

<211> 1515

<212> DNA

45 <213> artificial

<220>

<223> CD33 F2 HL x H2C HL

50 <400> 104

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10	atggaactcc	gcaacctcaa	aagtgatgac	acggctgtat	attactgtgc	gcgctggagt	300
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	atccctgacc	gattcagtg	cagcgggtct	gggacagatt	tcactctcac	tattgacagc	660
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<400> 105

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10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
15																
20																
25																
30																
35																
40																
45																
50																
55																

	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Thr	Asn	Tyr	Ala	Asp	Lys	Phe	
	50						55					60					
5	Gln	Gly	Arg	Val	Thr	Phe	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
10	Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
					85					90					95		
15	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
				100					105					110			
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			115					120					125				
25	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	
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40	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
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70	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr	
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	305					310					315					320
	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
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	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
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15	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Val	Ser	Trp	Trp
			355					360					365			
	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
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	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val
25	385					390					395					400
	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu
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	465					470					475					480
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<211> 1515

<212> DNA

55 <213> artificial

<220>

<223> CD33 F2 HL x F12Q HL

<400> 106

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	atggaactcc	gcaacctcaa	aagtgatgac	acggctgtat	attactgtgc	gcgctggagt	300
	tggagtgatg	gttactacgt	ttactttgac	tactggggcc	aaggcactac	ggtcaccgtc	360
15	tcctcagggtg	gtgggtgggtc	tggcggcggc	ggctccgggtg	gtgggtgggtc	tgacatcggtg	420
	atgacacagt	ctccagactc	cctgtctgtg	tctctgggcg	agaggaccac	catcaactgc	480
	aagtccagcc	agagtgtttt	agacagctcc	acgaataaga	actccttagc	ttggtaggag	540
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40	actcaggaac	cttcactcac	cgtatcacct	ggtggaacag	tcacactcac	ttgtggctcc	1260
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<211> 505

<212> PRT

55 <213> artificial

<220>

<223> CD33 F2 HL x I2C HL

<400> 107

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10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
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15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Thr	Asn	Tyr	Ala	Asp	Lys	Phe	
	50					55					60						
20	Gln	Gly	Arg	Val	Thr	Phe	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
25	Met	Glu	Leu	Arg	Asn	Leu	Lys	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
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55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
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65	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	
	210						215					220					
70	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	
	225					230					235					240	
75	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser	
					245					250					255		

	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	260	265	270
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10	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	290	295	300
15	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp	305	310	315
	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	325	330	335
20	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr	340	345	350
25	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp	355	360	365
30	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly	370	375	380
	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val	385	390	395
35	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu	405	410	415
40	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn	420	425	430
	Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly	435	440	445
45	Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu	450	455	460
50	Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp	465	470	475
	Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe	485	490	495
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10 <220>
 <223> CD33 F2 HL x I2C HL

 <400> 108

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 15 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
 20 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
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 55 Asn Tyr Gly Met Asn
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<400> 112

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ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gccaacctat 180

30

gctgataagt tccagggacg cgttaccatg actacggata cctctaccag cactgcctat 240

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tcctca 366

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<220>
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<400> 114

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55

Glu Arg Thr Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Asp Ser
 20 25 30

5 Ser Asn Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

10 Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60

15 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Asp Gly Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
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20 Ser Ala His Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
 100 105 110

25 Lys

30 <210> 115
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35 <220>
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Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Asn Asn Lys Asn Ser Leu
 1 5 10 15

40 Ala

45 <210> 116
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<220>
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50 <400> 116

Trp Ala Ser Thr Arg Glu Ser
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<210> 118

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<223> CD33 VL of B10

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25

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<212> PRT

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<223> CD33 HL of B10

<400> 119

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
50 55 60

55

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Ile Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

5 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
100 105 110

10 Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
130 135 140

15 Pro Asp Ser Leu Thr Val Ser Leu Gly Glu Arg Thr Thr Ile Asn Cys
145 150 155 160

20 Lys Ser Ser Gln Ser Val Leu Asp Ser Ser Asn Asn Lys Asn Ser Leu
165 170 175

25 Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Leu Ser
180 185 190

Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

30 Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Gly Leu Gln Pro Glu
210 215 220

35 Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Ala His Phe Pro Ile Thr
225 230 235 240

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
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<210> 120

<211> 750

<212> DNA

45 <213> artificial

<220>

<223> CD33 HL of B10

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ccaggacagg gtttagagtg gatgggctgg ataaacacct aactggaga gccaacctat 180

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25 Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
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45	tcaggctccc tgcttgagg caaggctgcc ctccacctct caggggtaca gccagaggat	1440
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<400> 127

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 10 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 15 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
 50 55 60
 20 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 25 Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
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 30 Gly Gln Gly Thr Ser Val Thr Val Ser Ser
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40 <220>
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<400> 128

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50 <210> 129
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55 <220>
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<400> 129

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15 <400> 130

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<211> 366

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25 <220>

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<400> 131

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10 Ser Thr Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Leu Ser Trp Ala Ser Thr Arg Glu Ser Gly Ile
 50 55 60

15 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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Ala

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 20 25 30
 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 10 35 40 45
 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
 50 55 60
 15
 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 20
 Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 25 100 105 110
 Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125
 30
 35
 40
 45
 50
 55

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	145					150					155					160	
10	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Thr	Asn	Lys	Asn	Ser	Leu	
					165					170					175		
15	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
				180					185					190			
20	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	
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25	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Pro	Gln	Pro	Glu	
	210						215					220					
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<210> 139

<211> 505

<212> PRT

30 <213> artificial

<220>

<223> CD33 E11 HL x H2C HL

35 <400> 139

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				20					25					30			
10	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
15	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Lys	Phe	
	50						55					60					
20	Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	
	65					70					75					80	
25	Met	Glu	Ile	Arg	Asn	Leu	Gly	Gly	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
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30	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	
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			115					120					125				
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	130						135					140					
45	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	
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55	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	
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		210					215					220					
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					245					250					255		
15	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
				260					265					270			
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	305					310					315					320	
30	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
					325					330					335		
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
35				340					345					350			
	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
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40	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
		370					375					380					
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				420					425					430			
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
			435					440					445				

	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
	450						455					460					
5	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	465					470					475					480	
10	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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	<212> DNA																
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	<223> CD33 E11 HL x H2C HL																
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<211> 505

<212> PRT

20 <213> artificial

<220>

<223> CD33 E11 HL x F12Q HL

25 <400> 141

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 20 25 30
 35 Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 40 Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 45 Met Glu Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 50 Ala Arg Trp Ser Trp Ser Asp Gly Tyr Tyr Val Tyr Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125
 55 Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
 130 135 140

	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	145	150	155	160
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	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	195	200	205	
15	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Pro	Gln	Pro	Glu	210	215	220	
20	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	225	230	235	240
25	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly	Gly	Ser	245	250	255	
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40	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	305	310	315	320
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	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	370	375	380	
55	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	385	390	395	400

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5	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn
				420					425					430		
10	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly
			435					440					445			
15	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu
		450					455					460				
20	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp
	465					470					475					480
25	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe
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30	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu							
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<210> 142

<211> 1515

<212> DNA

<213> artificial

<220>

<223> CD33 E11 HL x F12Q HL

<400> 142

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<400> 143

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<223> CD33 UD H2C HL x AF5 HL

<400> 148

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25

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35

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45

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55

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<223> CD33 UD H2C HL x AF5 HL

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40	gactccctga ctgtgtctct gggcgagagg accaccatca actgcaagtc cagccagagt	1260
	gttttagaca gctccaagaa taagaactcc ttagcttggt accagcagaa accaggacag	1320
45	cctcctaaat tactcctttc ctgggcatct acgcgggaat ccgggatccc tgaccgattc	1380
	agtggcagcg ggtctgggac agatttcact ctactattg acagcctgca gcctgaagat	1440
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<211> 505

<212> PRT

55 <213> artificial

<220>

<223> CD33 UD F12Q HL x AF5 HL

<400> 150

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				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
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20	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
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					85					90					95		
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				100					105					110			
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			115					120					125				
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		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
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50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	
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		210					215					220					
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15	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	Lys	
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30	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	Gly	
			355					360					365				
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		370					375					380					
40	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	
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45	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	Lys	
				405						410					415		
50	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	Ala	
				420					425					430			
55	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	Trp	
			435					440					445				
60	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	
		450					455					460					
65	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Leu	Gln	Pro	Glu	Asp	
	465					470					475					480	
70	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro	Ile	Thr	Phe	
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 <212> **DNA**
 <213> artificial

10 <220>
 <223> CD33 UD F12Q HL x AF5 HL

 <400> 151

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5	ccaggaaagg gtttggaatg ggttgctcgc ataagaagta aatataataa ttatgcaaca	180
	tattatgccg attcagtgaa aggcagggtc accatctcca gagatgattc aaaaaaact	240
10	gcctatctac aaatgaacaa cttgaaaact gaggacactg ccgtgtacta ctgtgtgaga	300
	catgggaact tcggtaatag ctacgtttcc tgggtgggctt actggggcca agggactctg	360
	gtcaccgtct cctcagggtg tgggtggttct ggcggcggtg gctccggtg tgggtggttct	420
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25	cagtctggag ctgagggtgaa gaagcctgga gcgtcagtca aggtctcctg caaggctagc	840
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30	aagtggatgg gctggataaa cacctacact ggagagccaa catatgctga tgacttcaag	960
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45	agtggcagcg ggtctgggac agatttcact ctactattg acagcctgca gcctgaagat	1440
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				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
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	50						55					60					
20	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
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					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
				100					105					110			
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				180					185					190			
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			195					200					205				

	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
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	225					230					235					240	
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15	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	Ser	
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20	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr	Gly	
			275					280					285				
25	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Lys	Trp	Met	Gly	
	290						295					300					
30	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe	Lys	
	305					310					315					320	
35	Gly	Arg	Val	Thr	Met	Thr	Ser	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	Leu	
					325					330					335		
40	Glu	Leu	His	Asn	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
				340					345					350			
45	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	Tyr	Trp	Gly	
			355					360					365				
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		370					375					380					
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	385					390					395					400	
60	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	Asn	Cys	Lys	
					405					410					415		
65	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Lys	Asn	Lys	Asn	Ser	Leu	Ala	
				420					425					430			
70	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Leu	Ser	Trp	
			435					440					445				
75	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	
	450						455					460					

Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Glu Asp
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485 490 495

10 Gly Gln Gly Thr Arg Leu Glu Ile Lys
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<211> 1515

<212> DNA

15 <213> artificial

<220>

<223> CD33 UD I2C HL x AF5 HL

20 <400> 153

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	ccaggaaagg	gtttggaatg	ggttgctcgc	ataagaagta	aatataataa	ttatgcaaca	180
	tattatgccg	attcagtga	agacagggtc	accatctcca	gagatgattc	aaaaaacact	240
30	gcctatctac	aaatgaacaa	cttgaaaact	gaggacactg	ccgtgtacta	ctgtgtgaga	300
	catgggaact	tcggtaatag	ctacatatcc	tactgggctt	actggggcca	agggactctg	360
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	cagccagagg	atgaggcaga	atattactgt	gttctatggt	acagcaaccg	ctgggtgttc	720
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	cagtctggag	ctgagggtga	gaagcctgga	gcgtcagtca	aggtctcctg	caaggctagc	840
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50	aagtggatgg	gctggataaa	cacctacact	ggagagccaa	catatgctga	tgacttcaag	960
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55	ctcagaagtg	atgacacggc	tgtatattac	tgtgcgcgct	ggagttggag	tgatggttac	1080
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<220>
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 35 40 45
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 Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60
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 Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
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 50 <211> 125
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 55 <223> VH of F6A
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				20					25					30			
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10			35					40					45				
	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
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	65					70					75					80	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
20					85					90					95		
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		210					215					220					
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<400> 157

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Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
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Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

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Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
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Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
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<210> 158
 <211> 125
 <212> PRT
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<220>
 <223> VH-P of F6A

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<400> 158

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	Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
	1				5					10					15		
5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ile	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Ser	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85				90						95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Val	Ser	Phe	Phe	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
			115					120					125				
40	<210> 159																
	<211> 249																
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<220>
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<400> 160

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
 1 5 10 15

15

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

20

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

30

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

35

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

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 <211> 125
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45

<400> 161

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

50

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
 20 25 30

55

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

	35	40	45
5	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 50 55 60		
10	Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 65 70 75 80		
15	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr 85 90 95		
20	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp 100 105 110		
25	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser 115 120 125		
30	<210> 162 <211> 249 <212> PRT <213> artificial <220> <223> VH-VL of H2C		
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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 100 105 110
 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 115 120 125

	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
	130						135					140					
5	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
10	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
15	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
20	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
25	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	210						215					220					
30	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
35	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
					245												
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	1				5					10					15		
60	Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	
				20					25					30			
65	Tyr	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	
			35					40					45				
70	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	
	50						55					60					
75	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	
	65					70					75					80	

	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn
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5	Arg	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu			
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	1				5					10					15	
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				20					25					30		
25																
	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35					40					45			
30	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp
	50						55					60				
	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
35	65					70				75					80	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
				85						90					95	
40																
	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp
				100					105					110		
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	<210> 165															
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	Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
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				20					25					30			
	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
10			35					40					45				
	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
15	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
20					85						90				95		
	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
25				100					105					110			
	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
30	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
35	145					150					155					160	
	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
40					165					170					175		
	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
45	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
50		210					215					220					
	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
 1 5 10 15

15

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

20

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

30

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

35

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 167
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 <212> PRT
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45

<400> 167

50

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Glu Gln Pro Gly Gly
 1 5 10 15
 5 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 20 25 30
 10 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 15 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 20 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 25 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 30 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Phe Trp
 100 105 110
 35 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Phe	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
50																	
55																	

	145		150		155		160									
5	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn
				165						170					175	
10	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly
				180					185					190		
15	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu
			195					200					205			
20	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp
		210					215					220				
25	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe
	225					230					235					240
30	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu							
					245											
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	Glu	Leu	Val	Val	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	
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5	Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	
				20				25						30			
10	Tyr	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	
			35					40					45				
15	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	
	50						55					60					
20	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	
	65					70					75				80		
25	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	
				85						90					95		
30	Arg	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
				100					105								
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Glu Gln Pro Gly Gly
 1 5 10 15
 5 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 20 25 30
 10 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 15 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 20 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 25 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 30 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Phe Trp
 100 105 110
 35 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
 40 <210> 171
 <211> 249
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 50 <400> 171

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Glu Gln Pro Gly Gly
 1 5 10 15
 45 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 20 25 30
 50 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

55

	35	40	45
5	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 50 55 60		
10	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 65 70 75 80		
15	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr 85 90 95		
20	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Phe Trp 100 105 110		
25	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly 115 120 125		
30	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val 130 135 140		
35	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu 145 150 155 160		
40	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn 165 170 175		
45	Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly 180 185 190		
50	Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu 195 200 205		
55	Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp 210 215 220		
	Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe 225 230 235 240		
	Gly Gly Gly Thr Lys Leu Thr Val Leu 245		

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<400> 172

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 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
 20 25 30
 10
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 15 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60

 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 20
 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 25 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Tyr Phe
 100 105 110

 30 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 173

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35 <212> PRT

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	1				5					10					15		
5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Arg	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75				80		
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85				90						95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Tyr	Phe	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Arg	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Tyr	Phe	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
60	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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75	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
					245												

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<400> 175

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Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

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Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

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Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
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Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
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 5 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
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 10 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 15 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 20 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 25 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 30 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Tyr Phe
 100 105 110
 35 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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 45 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
 20 25 30
 50 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
	50						55					60					
5	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
10					85					90					95		
	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Tyr	Phe	
				100					105					110			
15	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
20	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
25	145					150					155					160	
	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
30	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
35	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
40		210					215					220					
	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
45	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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				20					25					30		
10																
	Tyr	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly
			35					40					45			
15																
	Leu	Ile	Gly	Ala	Thr	Asp	Met	Arg	Pro	Ser	Gly	Thr	Pro	Ala	Arg	Phe
	50						55					60				
20																
	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val
	65					70					75				80	
	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn
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	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
	1				5					10					15		
5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Val	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Lys	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Trp	Trp	
				100					105					110			
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				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Lys	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Trp	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Arg	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Ala	
				180					185					190			
60	Thr	Asp	Met	Arg	Pro	Ser	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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75	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

20

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Ala Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

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Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

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Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Lys Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Trp Trp
 100 105 110
 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
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 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Lys Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80

	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
5	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Trp	Trp	
				100					105					110			
10	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
15	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
20	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
25	Thr	Cys	Arg	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
30	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Ala	
				180					185					190			
35	Thr	Asp	Met	Arg	Pro	Ser	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
40	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
45	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
50	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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55	Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	
				20					25					30			

	Tyr	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	
			35					40					45				
5	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	
		50					55					60					
10	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	
	65					70					75				80		
15	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	
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				20					25					30			
40	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
45	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
50	Ser	Val	Lys	Ser	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75				80		
55	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85				90						95		
	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Thr	Ser	Tyr	Tyr	
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	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
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<400> 186

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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Ser	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Thr	Ser	Tyr	Tyr	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
60	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
75	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
					245												

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Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
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Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
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20

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

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Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

35

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 188
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

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Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr

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	20	25	30
5	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		
	35	40	45
10	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp		
	50	55	60
15	Ser Val Lys Ser Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr		
	65	70	75
20	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr		
	85	90	95
25	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Thr Ser Tyr Tyr		
	100	105	110
30	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser		
	115	120	125
35	<210> 189		
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	Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Ser	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Thr	Ser	Tyr	Tyr	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
60	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
75	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
					245												

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Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
 1 5 10 15

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Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

20

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Ala Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

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Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

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Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

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				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Glu	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85				90						95		
30	Tyr	Cys	Val	Arg	His	Arg	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Trp	Phe	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Gly	Tyr
				20					25					30		
	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
10			35					40					45			
	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp
	50						55					60				
15	Ser	Val	Lys	Glu	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr
	65					70					75					80
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
20					85					90					95	
	Tyr	Cys	Val	Arg	His	Arg	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Trp	Phe
25				100					105					110		
	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
			115					120					125			
30	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val
	130						135					140				
	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu
35	145					150					155					160
	Thr	Cys	Arg	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn
40					165					170					175	
	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Ala
				180					185					190		
45	Thr	Asp	Met	Arg	Pro	Ser	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu
			195					200					205			
	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp
50		210					215					220				
	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe
	225					230					235					240
55	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu							

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      <400> 193

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            1              5              10              15

           Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ser Gly
                20              25              30

           Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
                35              40              45

25          Leu Ile Gly Ala Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe
            50              55              60

           Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
            65              70              75              80

           Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85              90              95

35          Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                100              105

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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Gly	Tyr	
				20					25					30			
	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
10			35					40					45				
	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
15	Ser	Val	Lys	Glu	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
20					85					90					95		
	Tyr	Cys	Val	Arg	His	Arg	Asn	Phe	Gly	Asn	Ser	Tyr	Leu	Ser	Trp	Phe	
25				100					105					110			
	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
			115					120					125				
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Gly Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Glu Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Val Arg His Arg Asn Phe Gly Asn Ser Tyr Leu Ser Trp Phe
 100 105 110
 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val

	130		135		140												
5	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
	Thr	Cys	Arg	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
10					165					170					175		
	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Ala	
				180					185					190			
15	Thr	Asp	Met	Arg	Pro	Ser	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
20	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
	210						215					220					
	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
25	225					230					235					240	
	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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	Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly		
	1				5					10					15			
5		Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	
					20					25					30			
10	Tyr	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly		
			35					40					45					
15	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe		
		50					55					60						
20	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val		
	65					70					75					80		
25	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn		
					85					90					95			
30		Arg	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
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 5 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
 20 25 30
 10 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 15 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 20 Ser Val Lys Lys Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 25 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Trp Trp
 100 105 110
 30 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
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 1 5 10 15
 45 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr

	20	25	30
5	Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45		
10	Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp 50 55 60		
15	Ser Val Lys Lys Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr 65 70 75 80		
20	Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr 85 90 95		
25	Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Trp Trp 100 105 110		
30	Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly 115 120 125		
35	Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val 130 135 140		
40	Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu 145 150 155 160		
45	Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn 165 170 175		
50	Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly 180 185 190		
55	Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu 195 200 205		
	Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp 210 215 220		
	Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe 225 230 235 240		
	Gly Gly Gly Thr Lys Leu Thr Val Leu 245		

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 Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

15 Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

20 Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

 Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
25 65 70 75 80

 Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

30 Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Val	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Lys	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75				80		
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85				90						95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Trp	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Val	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Lys	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
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25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Trp	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Tyr	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
60	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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75	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
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15

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

20

Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

30

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
 85 90 95

35

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 5 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 20 25 30
 10 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 15 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 20 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 25 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 30 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
 100 105 110
 35 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
 40 <210> 204
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 50 <400> 204
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 1 5 10 15
 45 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
 20 25 30
 50 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
	50						55					60					
5	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
10					85					90					95		
	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Val	Ser	Trp	Trp	
				100					105					110			
15	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
20	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr	Val	Val	
		130					135					140					
	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
25	145					150					155					160	
	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	
					165					170					175		
30	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
35	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
40		210					215					220					
	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
45	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
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	Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly
				20					25					30		
10	Asn	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly
			35					40					45			
15	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe
	50						55					60				
	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val
20	65					70					75				80	
	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn
					85					90					95	
25	Arg	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu			
				100					105							
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	Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Val	Ser	Trp	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
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40	<210>	207															
	<211>	249															
	<212>	PRT															
	<213>	artificial															
45	<220>																
	<223>	VH-VL-P of F12Q															
50	<400>	207															

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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Ser	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
	50						55					60					
20	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Val	Ser	Trp	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
60	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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 <211> 109
 <212> PRT
 <213> artificial

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<220>
 <223> VL of I2C

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<400> 208

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
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15

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
 20 25 30

20

Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
 35 40 45

25

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
 50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
 65 70 75 80

30

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
 85 90 95

35

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

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 <211> 125
 <212> PRT
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40

<220>
 <223> VH of I2C

45

<400> 209

50

55

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 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80
 Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
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 Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
 100 105 110
 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
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 <211> 249
 <212> PRT
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 <223> VH-VL of I2C
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 1 5 10 15
 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
 50 55 60
 Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
 65 70 75 80

	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
5	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
				100					105					110			
10	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
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20	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
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25	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	
					165					170					175		
30	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
35	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
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	210						215					220					
45	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
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	<211>	109															
	<212>	PRT															
	<213>	artificial															
	<220>																
	<223>	VL-P of I2C															
55	<400>	211															
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				20					25					30			

	Asn	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	
			35					40					45				
5	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	
		50					55					60					
10	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	
	65					70					75					80	
15	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	
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	<211>	125															
	<212>	PRT															
	<213>	artificial															
25	<220>																
	<223>	VH-P of I2C															
	<400>	212															
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	1				5					10					15		
35	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
				20					25					30			
40	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
45	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
50	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
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55	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
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	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
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	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
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<211> 249
<212> PRT
<213> artificial

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<220>
<223> VH-VL-P of I2C

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<400> 213

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55

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5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	
				20					25					30			
10	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	
		50					55					60					
20	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
	65					70					75					80	
25	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
					85					90					95		
30	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	
				100					105					110			
35	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	
			115					120					125				
40	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Leu	Val	Val	
		130					135					140					
45	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	
	145					150					155					160	
50	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	
					165					170					175		
55	Trp	Val	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	
				180					185					190			
60	Thr	Lys	Phe	Leu	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	
			195					200					205				
65	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	
		210					215					220					
70	Glu	Ala	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	
	225					230					235					240	
75	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu								
					245												

<210> 214
 <211> 1587
 <212> DNA
 <213> artificial

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<220>
 <223> SA21-CD33 E11 HL x I2C HL (His Tag)

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<400> 214

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15	aaggctagcg ggtatacctt cacaaactat ggaatgaact ggggaagca ggctccagga	180
	cagggtttag agtggatggg ctggataaac acctacactg gagagccaac ctatgctgat	240
	aagttccagg gacgcgttac catgactacg gatacctcta ccagcactgc ctatatggaa	300
20	atccgcaacc tcggaggtga tgacacggct gtatattact gtgcgcgctg gagttggagt	360
	gatggttact acgtttactt tgactactgg ggccaaggca cttcggtcac cgtctcctca	420
	gggtgggtggtg gttctggcgg cggcggctcc ggtgggtggtg gttctgacat cgtgatgaca	480
25	cagtctccag actccctgac tgtgtctctg ggcgagagga ccaccatcaa ctgcaagtcc	540
	agccagagtg ttttagacag ctccacgaat aagaactcct tagcttggtg ccagcagaaa	600
30	ccaggacagc ctccctaaatt actcctttcc tgggcatcta cgcgggaatc cgggatccct	660
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35	caagggacac gactggagat taaatccgga ggtgggtggct ccgaggtgca gctgggtcag	840
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40	ttcaccttca ataagtacgc catgaactgg gtccgccagg ctccaggaaa gggtttgga	960
	tgggttgctc gcataagaag taaatataat aattatgcaa catattatgc cgattcagtg	1020
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45	aacttgaaaa ctgaggacac tgccgtgtac tactgtgtga gacatgggaa cttcggtaat	1140
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	gggtgggtggt ctggcggcgg cggctccggt ggtgggtggt ctcagactgt tgtgactcag	1260
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5 ggggctgtta catctggcaa ctacccaaac tgggtccaac aaaaaccagg tcaggcaccc 1380
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<210> 215

<211> 529

<212> PRT

<213> artificial

<220>

<223> SA21-CD33 E11 HL x I2C HL H6

<400> 215

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				20					25					30			
10	Gly	Glu	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	
			35					40					45				
15	Asn	Tyr	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	
	50						55					60					
20	Trp	Met	Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	
	65					70					75					80	
25	Lys	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	
					85					90					95		
30	Ala	Tyr	Met	Glu	Ile	Arg	Asn	Leu	Gly	Gly	Asp	Asp	Thr	Ala	Val	Tyr	
				100					105					110			
35	Tyr	Cys	Ala	Arg	Trp	Ser	Trp	Ser	Asp	Gly	Tyr	Tyr	Val	Tyr	Phe	Asp	
			115					120					125				
40	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	
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45	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	
	145					150					155				160		
50	Gln	Ser	Pro	Asp	Ser	Leu	Thr	Val	Ser	Leu	Gly	Glu	Arg	Thr	Thr	Ile	
					165					170					175		
55																	

	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Val	Leu	Asp	Ser	Ser	Thr	Asn	Lys	Asn
				180					185					190		
5	Ser	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu
			195					200					205			
10	Leu	Ser	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser
		210					215					220				
15	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp	Ser	Pro	Gln
	225					230					235					240
20	Pro	Glu	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	His	Phe	Pro
					245					250					255	
25	Ile	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Ser	Gly	Gly	Gly
				260					265					270		
30	Gly	Ser	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro
			275					280					285			
35	Gly	Gly	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn
		290					295					300				
40	Lys	Tyr	Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu
	305					310					315					320
45	Trp	Val	Ala	Arg	Ile	Arg	Ser	Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr
					325					330					335	
50	Ala	Asp	Ser	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys
				340					345					350		
55	Asn	Thr	Ala	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala
			355					360					365			
60	Val	Tyr	Tyr	Cys	Val	Arg	His	Gly	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser
		370					375					380				
65	Tyr	Trp	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly
	385					390					395					400
70	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Thr
					405					410					415	
75	Val	Val	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val

	420	425	430
5	Thr Leu Thr Cys Gly Ser Ser	Thr Gly Ala Val Thr	Ser Gly Asn Tyr
	435	440	445
10	Pro Asn Trp Val Gln Gln Lys	Pro Gly Gln Ala Pro Arg Gly Leu Ile	
	450	455	460
15	Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr	Pro Ala Arg Phe Ser Gly	
	465	470	475 480
20	Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro		
	485	490	495
25	Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp		
	500	505	510
30	Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu His His His His His		
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35	His		
40	<210> 216		
	<211> 1575		
	<212> DNA		
	<213> artificial		
45	<220>		
	<223> SA25-CD33 E11 HL × I2C HL with His tag		
50	<400> 216		
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	cgcgttacca tgactacgga tacctctacc agcactgcct atatggaaat ccgcaacctc	300
10	ggaggtgatg acacggctgt atattactgt gcgcgctgga gttggagtga tggttactac	360
	gtttactttg actactgggg ccaaggcact tcggtcaccg tctcctcagg tgggtggtggt	420
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15	tccctgactg tgtctctggg cgagaggacc accatcaact gcaagtccag ccagagtgtt	540
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20	cctaaattac tcctttcctg ggcattctacg cgggaatccg ggatccctga ccgattcagt	660
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35	gaggacactg ccgtgtacta ctgtgtgaga catgggaact tcggtaatag ctacatatcc	1140
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40	ggcggcggcg gctccggtgg tgggtggttct cagactgttg tgactcagga accttcactc	1260
	accgtatcac ctggtggaac agtcacactc acttgtggct cctcgactgg ggctgttaca	1320
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<211> 525

55 <212> PRT

<213> artificial

<220>

<223> SA25-CD33 E11 HL × I2C HL H6

<400> 217

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20	Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp	50 55 60
25	Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Lys Phe Gln Gly	65 70 75 80
30	Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu	
35		
40		
45		
50		
55		

	85	90	95
5	Ile Arg Asn Leu Gly Gly Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg 100 105 110		
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	Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met 290 295 300		
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	Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val 325 330 335		

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25	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	Thr	Cys	
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50	Glu	Tyr	Tyr	Cys	Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	Gly	Gly	
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<211> 532

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<213> artificial

<220>

<223> SA08-CD33 E11 HL × I2C HL H6

<400> 219

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10	Thr	Phe	Thr	Asn	Tyr	Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	
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25	Thr	Ser	Thr	Ala	Tyr	Met	Glu	Ile	Arg	Asn	Leu	Gly	Gly	Asp	Asp	Thr	
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					325					330					335		
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His His His His
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<400> 220

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Patentkrav

1. Farmaceutisk sammensætning, som omfatter en CD33-målrettet forbindelse og en epigenetisk faktor, hvor

5 (a) den CD33-målrettede forbindelse er en bispecifik antistofkonstruktion, der omfatter et første bindingsdomæne, der binder specifikt til CD33, og et andet bindingsdomæne, der binder specifikt til CD3; og

(b) den epigenetiske faktor er hydroxyurinstof.

10

2. Farmaceutisk sammensætning ifølge krav 1, hvor

(a) den epigenetiske faktor administreres før administrationen af den CD33-målrettede forbindelse;

(b) den epigenetiske faktor administreres efter

15 administrationen af den CD33-målrettede forbindelse; eller

(c) den epigenetiske faktor og den CD33-målrettede forbindelse administreres samtidig.

3. Farmaceutisk sammensætning ifølge krav 1 eller 2, hvor en

20 første dosis af den epigenetiske faktor administreres før start på administrationen af den CD33-målrettede forbindelse.

4. Farmaceutisk sammensætning ifølge krav 3, hvor administrationen af den epigenetiske faktor fortsættes under

25 administrationen af den CD33-målrettede forbindelse.

5. Farmaceutisk sammensætning ifølge krav 1, hvor den bispecifikke antistofkonstruktion er en bispecifik enkeltkædet antistofkonstruktion.

30

6. Farmaceutisk sammensætning ifølge krav 1 eller 5, hvor den bispecifikke antistofkonstruktion binder til human og cynomolgusabe-CD3 og human og cynomolgusabe-CD33.

7. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1, 5 eller 6, hvor den bispecifikke antistofkonstruktion omfatter

- et første bindingsdomæne, der binder specifikt til CD33 og

omfatter en VL-kæde, der har en aminosyresekvens ifølge SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 og 132, og en VH-kæde, der har en aminosyresekvens ifølge SEQ ID NO: 1, 19, 37, 55, 73, 91, 109 og 127; og

- 5 • et andet bindingsdomæne, der binder specifikt til CD3 og omfatter en VL-kæde, der har en aminosyresekvens ifølge SEQ ID NO: 154, 157, 160, 163, 166, 169 og 172, og en VH-kæde, der har en aminosyresekvens ifølge SEQ ID NO: 155, 158, 161, 164, 167, 170 og 173.

10

8. Farmaceutisk sammensætning ifølge krav 7, hvor den bispecifikke antistofkonstruktion omfatter en aminosyresekvens ifølge en hvilken som helst af SEQ ID NO: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 15 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 og 227.

9. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 8 til anvendelse til behandling af en myeloid leukæmi.

20

10. Farmaceutisk sammensætning til anvendelse ifølge krav 9, hvor den myeloide leukæmi er valgt fra gruppen, der består af akut myeloblastisk leukæmi, kronisk neutrofil leukæmi, myeloid dendritcelleleukæmi, accelereret fase-kronisk myelogen leukæmi, akut myelomonocytisk leukæmi, juvenil myelomonocytisk leukæmi, kronisk myelomonocytisk leukæmi, akut basofil leukæmi, akut eosinofil leukæmi, kronisk eosinofil leukæmi, akut megakaryoblastisk leukæmi, essentiel trombocytose, akut erytroid leukæmi, polycythemia vera, myelodysplastisk syndrom, 25 akut panmyelose, myeloidt sarkom og akut bifænotypisk leukæmi.

30

11. Epigenetisk faktor til anvendelse til bedring og/eller behandling af en myeloid leukæmi, hvor den epigenetiske faktor øger reaktionen hos en patient på en CD33-målrettet forbindelse, hvor

35

(a) den CD33-målrettede forbindelse er en bispecifik antistofkonstruktion, der omfatter et første bindingsdomæne,

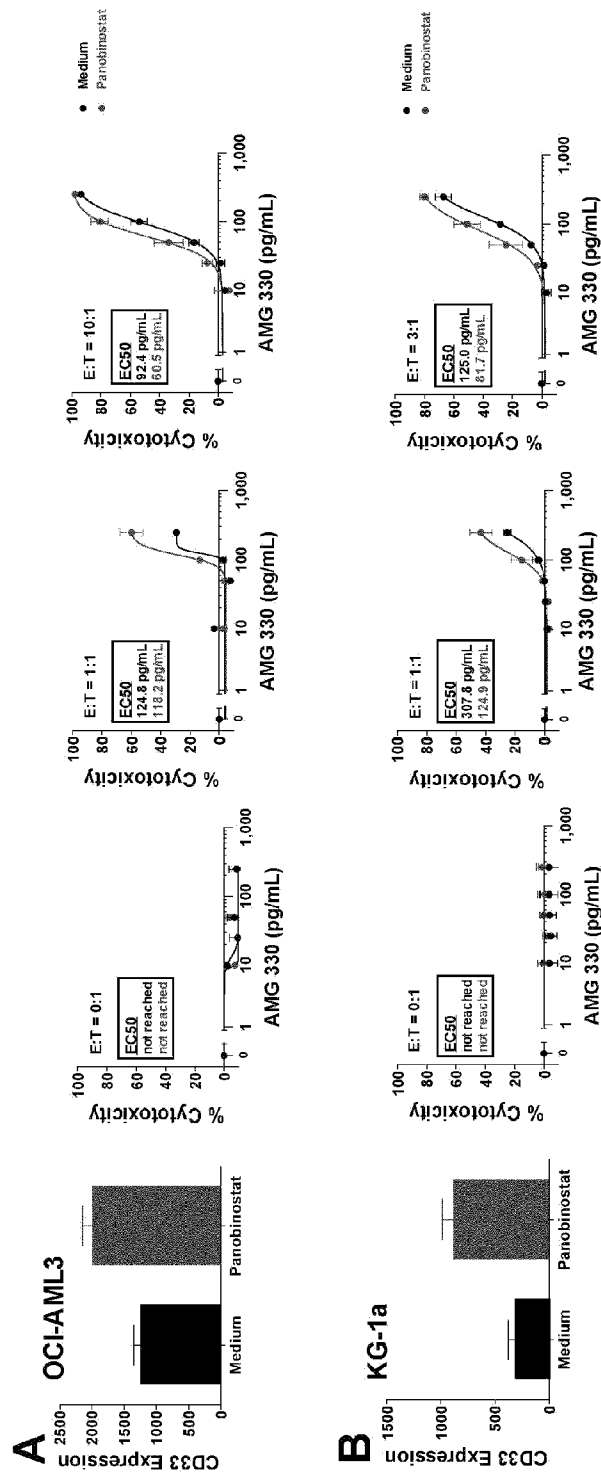
der binder specifikt til CD33, og et andet bindingsdomæne, der binder specifikt til CD3; og

(b) den epigenetiske faktor er hydroxyurinstof.

- 5 12. Kit, som omfatter en farmaceutisk sammensætning ifølge et
hvilket som helst af kravene 1 til 10 eller den epigenetiske
faktor ifølge krav 11 og en bispecifik CD33-målrettet
forbindelse, der omfatter et første bindingsdomæne, der binder
specifikt til CD33, og et andet bindingsdomæne, der binder
10 specifikt til CD3, til anvendelse til bedring og/eller
behandling af en myeloid leukæmi.

DRAWINGS

Figure 1



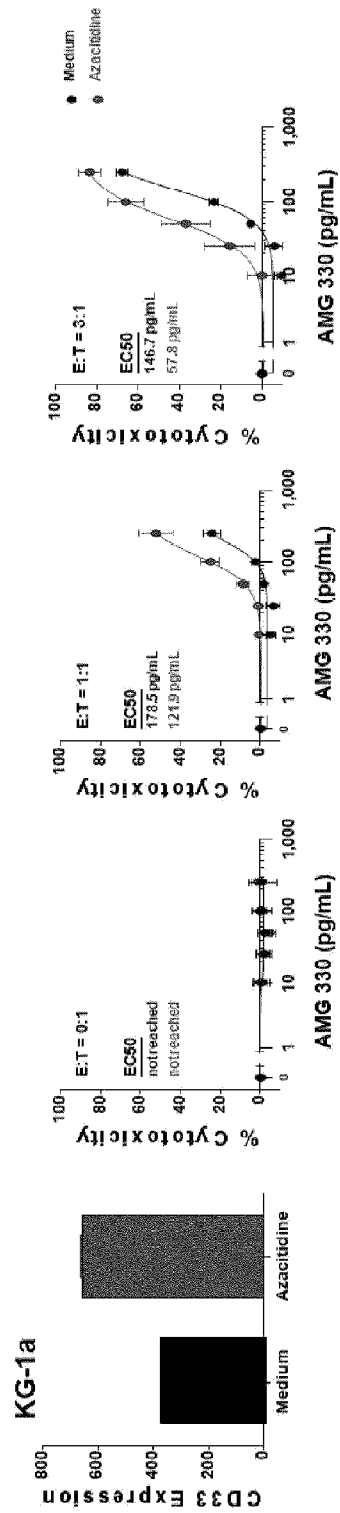


Figure 2

Figure 3

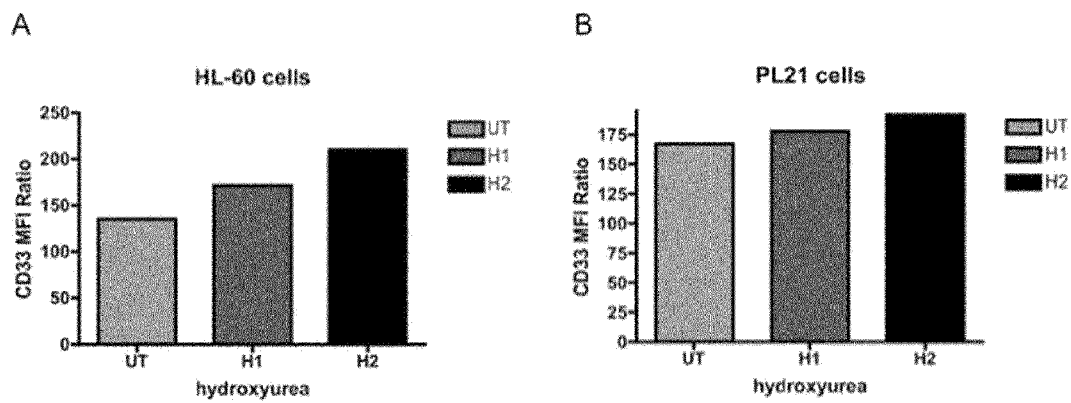


Figure 4

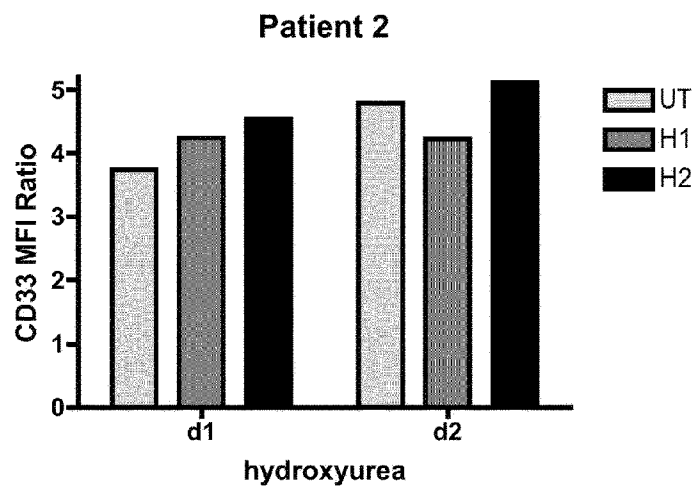


Figure 5

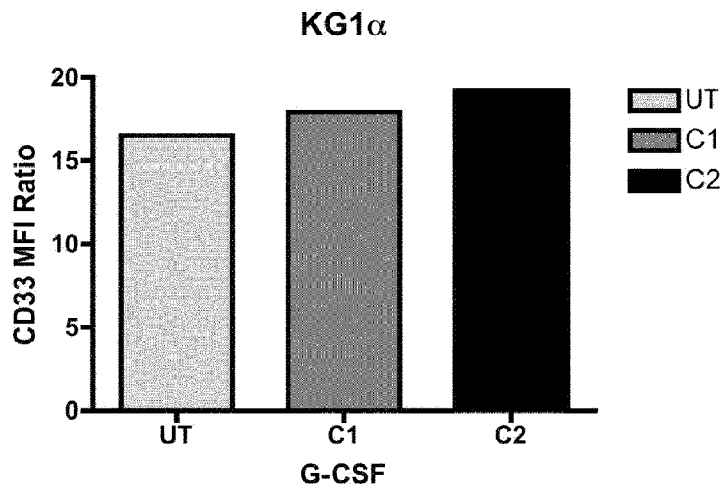


Figure 6

