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Description

[0001] This invention relates to antibodies that bind to the B cell surface antigen BCMA. The invention also relates to the use of these antibodies to detect, deplete, and otherwise manipulate various B cell subtypes.

[0002] B cells are lymphocytes that play major roles in adaptive humoral immunity and production of antibodies that specifically recognize antigens. Three subclasses of B cells are naïve B cells, memory B cells, and plasma cells. The processes of VDJ recombination, in which two or three segments of DNA are chosen from a genomic library and recombined to generate a combinatorial array of antibody variable domains, and hypermutation, by which the variable domains encoded by different lineages of B cells are further varied, result in up to 10^9 distinct B cell lineages that produce antibodies with specificity for distinct targets. A B cell is said to be specific for an antigen that binds the antibodies made by that B cell. B cells in general are stimulated by exposure to their specific antigen (Ag). Naïve B cells have not yet been exposed to their specific antigen. Such exposure (e.g., during an infection) results in proliferation of B cells and generation of sister clones. Sister clones can develop into plasma cells, which produce high amounts of antibody. Plasma cells may either be short lived, or may migrate into bone marrow, where they can persist for an extended period of time. A sister clone of an Ag-exposed B cell may also develop into a memory B cell that is quiescent until reexposed to the specific antigen. Memory B cells respond rapidly to reexposure to antigen by dividing to produce both plasma cells and additional memory B cells. Memory B cells include switched memory B cells ($CD19^+CD27^{high}CD38^{low}IgD^-$), unswitched memory B cells ($CD19^+CD27^{high}CD38^{low}IgD^+$), and double negative memory B cells ($CD19^+CD27^-CD38^{low}IgD^-$).

[0003] Several significant diseases involve B cells. Malignant transformation of B cells leads to cancers, including some lymphomas such as, for example, multiple myeloma and Hodgkins' Lymphoma. Some autoimmune diseases, including systemic lupus erythematosus (SLE), also involve B cells. Both cancer and autoimmune diseases that involve B cells may be considered gain of function conditions, in that the B cells overgrow and/or attack parts of the body inappropriately. A possible strategy to control such diseases is to use antibodies that target the pathological B cells.

[0004] The B cell maturation antigen (BCMA, also known as TNFRSF17 and CD269) is a protein that has been shown to be expressed on the surface of plasmablasts (i.e., plasma cell precursors) and plasma cells, and is believed to stimulate survival. It therefore represents a potential target for B cell-related diseases. BCMA is a member of the TNF receptor family and binds the TNF family ligands BAFF and APRIL (reviewed in Kalled et al. (2005), Curr Dir Autoimmun 8:206-242). BCMA is a type III membrane protein, as it lacks the signal peptide associated with type I membrane proteins found in most TNF receptor family members.

[0005] BCMA RNA has been detected in the spleen, lymph nodes, thymus, adrenals and liver, and analysis of a number of B cell lines indicated that BCMA mRNA levels increased upon maturation. Human BCMA protein has been detected on various subtypes of $CD38^+$ B cells, particularly plasma cells (Zhang et al. (2005), Int Immunol 17:779-788; Darce et al. (2007), J Immunol 179:7276-7286; Sims et al. (2005), Blood 105:4390-4398; Avery et al. (2003), J Clin Invest 112:286-297). Independent laboratories have examined blood and/or tonsil B cell subsets and found that BCMA expression could not be detected on naïve or memory B cells (Zhang et al. (2005), Int Immunol 17:779-788; Darce et al. (2007), J Immunol 179:7276-7286; Chiu et al. (2007), Blood 109:729-739). Attempts to detect BCMA protein on the surface of germinal center B cells have had inconsistent results (Zhang et al. (2005), Int Immunol 17:779-788; Chiu et al. (2007), Blood 109:729-739).

[0006] The mechanism of action of BCMA is not fully understood. Mice that have been genetically altered to lack a functional gene for BCMA have normal lymphoid organs and cell populations, and a nearly normal functioning immune system (Xu and Lam (2001), Mol Cell Biol 21:4067-4074; Schiemann et al. (2001), Science 293:2111-2114). The only defect defined to date in these mice is a diminished survival of long-lived bone marrow (BM) plasma cells (O'Connor et al. (2004), J Exp Med 199:91-98). Therefore, it may be that BCMA, at least in the murine system, provides a survival signal to BM-resident plasma cells that is either BAFF or APRIL-mediated, or both. Indeed, signalling through BCMA activates the NF-κB pathway (Hatzoglou et al. (2000), J Immunol 165:1322-1330) which is involved in B cell survival, proliferation and maturation (Litinskiy et al. (2002) Nat Immunol 3:822-829; Pomerantz and Baltimore (2002) Mol Cell 10:693-695; Huang et al. (2004) Proc Natl Acad Sci U S A 101:17789-17794; He et al. (2004) J Immunol 172:3268-3279). Results with malignant human cells are generally consistent with a link between BCMA and cell survival. Primary multiple myeloma (MM) cells, MM cell lines (Novak et al. (2004) Blood 103:689-694), and Hodgkin and Reed-Sternberg (HRS) cells from Hodgkin lymphomas (Chiu et al. (2007), Blood 109:729-739; Novak et al. (2004), Blood 104:2247-2253) have been shown to express BCMA. Addition of BAFF and/or APRIL has further been shown to provide a survival signal for these malignant cells, although it is not clear that BCMA is predominantly responsible for this effect.

[0007] Ryan et al. reports on BCMA antibodies that can act on multiple myeloma cell lines through multiple mechanisms that include inhibition of APRIL-dependent NF-κB activation, promotion of tumor cell lysis by natural killer cell-mediated antibody-dependent cellular cytotoxicity, and induction of cytotoxicity by antibody-drug conjugates (Ryan et al. (2007), Mol Cancer Ther; 6 (11)).

[0008] WO 02/066516 discloses antibodies that bind two tumor necrosis factor receptor family members: the transmembrane activator and calcium modulator and cyclophilin ligand-interactor (TACI) receptor, and the B-cell maturation

(BCMA) receptor.

[0009] WO 03/072713 relates to B-cell maturation antigen (BCMA), a receptor for APRIL and BAFF, and its use as an immunoregulatory agent in treatment of immunological disorders such as multiple sclerosis. The disclosure provides methods and compositions for treating neurodegenerative immunological disorders in mammals by administering soluble BCMA, an antibody against BCMA, or an antibody against a BCMA ligand, e.g., APRIL or BAFF.

[0010] Because different B cell subsets are implicated in different B cell related conditions, there exists a need for agents that specifically target one or more B cell subsets. The expression of BCMA on the surface of some B cells provides a marker by which those cells may be specifically targeted. To take advantage of BCMA as a marker of one or more B cell subsets, there is a need for agents that specifically bind to BCMA and for a determination of which B cell subsets are bound by those BCMA-specific agents. The invention provides antibodies that specifically bind to BCMA. The antibodies of the invention may be used to target one or more of the following B cell subsets: plasma cells, memory B cells, and naïve B cells.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

Figure 1 depicts binding of anti-human BCMA mAbs on BCMA-transfected CHO cells. Binding of biotin-conjugated anti-human BCMA mAbs, visualized with Streptavidin-PE, was measured by flow cytometry on a BCMA-CHO stable cell line (A) and control, non-transfected CHO cells (B). The shaded area represents staining of cells with an isotype control mAb.

Figure 2 depicts anti-BCMA binding to B cell subsets. B cell subsets in human peripheral blood were assessed by flow cytometry for reactivity to anti-BCMA mAbs. Visualization was as in Figure 1. The shaded area represents staining with an isotype control Ab. B cell subsets were plasma cells ($CD19^+CD27^{high}CD38^{high}IgD^-$) (A), switched memory B cells ($CD19^+CD27^{high}CD38^{low}IgD^-$) (B), unswitched memory B cells ($CD19^+CD27^{high}CD38^{low}IgD^+$) (C), double negative memory B cells ($CD19^+CD27^-CD38^{low}IgD^-$) (D), and naïve B cells ($CD19^+CD27^-IgD^+$) (E).

Figure 3 depicts anti-BCMA binding to B cell subsets isolated from healthy and SLE-afflicted individuals. B cell subsets in human peripheral blood from a healthy volunteer and an SLE patient were assessed by flow cytometry for reactivity to the anti-BCMA mAbs C12A3.2 and A7D12.2. B cell subsets were as in Figure 2. Visualization was as in Figure 1.

Figure 4 depicts flow cytometric staining of human plasma cells within the human $CD45^+$ splenocyte compartment isolated from HSC/NSG mice. Splenic plasma cells were stained with anti-BCMA antibodies A7D12.2 (left panel; bold line) and C12A3.2 (right panel; bold line) or an isoytpe control mouse IgG2b or IgG1 Ab, respectively (thin line in both panels).

Figure 5 depicts flow cytometric staining for plasma cells (PCs) within the human $CD45^+$ splenocyte compartment isolated from HSC/NSG mice treated with anti-BCMA antibody (chC12A3.2 or chC13F12.1) or human IgG1 control. Mice were injected i.p. with anti-BCMA Ab or HIgG1 control twice weekly for 2 weeks. ** $p<0.0001$; * $p=0.0066$.

Figure 6 depicts flow cytometric staining for plasma cells (PCs) within the human $CD45^+$ splenocyte compartment isolated from HSC/NSG mice treated with anti-BCMA antibody (chC11D5.1 or chA7D12.2) or human IgG1 control. Mice were injected i.p. with anti-BCMA Ab or HIgG1 control twice weekly for 2 weeks.

Table 1. Brief Description of the Sequences

SEQ ID NO	Description of sequence
1	A7D12.2 mature heavy chain variable domain protein sequence
2	A7D12.2 mature light chain variable domain protein sequence
3	C11D5.3 mature heavy chain variable domain protein sequence
4	C11D5.3 mature light chain variable domain protein sequence A
5	C12A3.2 mature heavy chain variable domain protein sequence
6	C12A3.2 mature light chain variable domain protein sequence
7	C13F12.1 mature heavy chain variable domain protein sequence
8	C13F12.1 mature light chain variable domain protein sequence
9	BCMA protein sequence

(continued)

SEQ ID NO	Description of sequence
10	huBCMA-huFc (as defined by N-terminal sequence analysis)
11	C11D5.3 mature light chain variable domain protein sequence B
12	C11D5.3 mature light chain variable domain protein sequence C
13	chA7D12.2 chimeric mature heavy chain protein sequence
14	chA7D12.2 chimeric mature light chain protein sequence
15	chC11D5.3 chimeric mature heavy chain protein sequence
16	chC11D5.3 chimeric mature light chain protein sequence A
17	chC11D5.3 chimeric mature light chain protein sequence C
18	chC12A3.2 chimeric mature heavy chain protein sequence
19	chC12A3.2 chimeric mature light chain protein sequence
20	chC13F12.1 chimeric mature heavy chain protein sequence
21	chC13F12.1 chimeric mature light chain protein sequence
22	huC11D5.3L1 humanized mature light chain variable domain sequence
23	huC11D5.3L2 humanized mature light chain variable domain sequence
24	huC11D5.3L3 humanized mature light chain variable domain sequence
25	huC11D5.3H0 humanized mature heavy chain variable domain sequence
26	huC11D5.3H1 humanized mature heavy chain variable domain sequence
27	huC11D5.3H2 humanized mature heavy chain variable domain sequence
28	huC11D5.3H3 humanized mature heavy chain variable domain sequence
29	huC11D5.3H4 humanized mature heavy chain variable domain sequence
30	huC12A3.2L0 humanized mature light chain variable domain sequence
31	huC12A3.2L1 humanized mature light chain variable domain sequence
32	huC12A3.2L2 humanized mature light chain variable domain sequence
33	huC12A3.2L3 humanized mature light chain variable domain sequence
34	huC12A3.2H0 humanized mature heavy chain variable domain sequence
35	huC12A3.2H1 humanized mature heavy chain variable domain sequence
36	huC12A3.2H2 humanized mature heavy chain variable domain sequence
37	huC12A3.2H3 humanized mature heavy chain variable domain sequence
38	huC12A3.2H4 humanized mature heavy chain variable domain sequence
39	huC13F12.1L0 humanized mature light chain variable domain sequence
40	huC13F12.1L1 humanized mature light chain variable domain sequence
41	huC13F12.1L2 humanized mature light chain variable domain sequence
42	huC13F12.1 L3 humanized mature light chain variable domain sequence
43	huC13F12.1H0 humanized mature heavy chain variable domain sequence
44	huC13F12.1H1 humanized mature heavy chain variable domain sequence
45	huC13F12.1H2 humanized mature heavy chain variable domain sequence
46	huC13F12.1H3 humanized mature heavy chain variable domain sequences
47	huC13F12.1H4 humanized mature heavy chain variable domain sequence

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0012] The invention relates to an isolated antibody or antigen-binding fragment thereof that binds to the polypeptide of SEQ ID NO:9, wherein the antibody or antigen-binding fragment comprises:

a) a heavy chain variable domain comprising a CDR1 region that comprises amino acids 31-35 of SEQ ID NO: 3, a CDR2 region that comprises amino acids 50-66 of SEQ ID NO: 3, and a CDR3 region that comprises amino acids 99-106 of SEQ ID NO: 3; and a light chain variable domain comprising a CDR1 region that comprises amino acids 24-38 of any one of SEQ ID NOs: 4, 11, or 12, a CDR2 region that comprises amino acids 54-60 of any one of SEQ ID NOs: 4, 11, or 12, and a CDR3 region that comprises amino acids 93-101 of any one of SEQ ID NOs: 4, 11 or 12;

b) a heavy chain variable domain comprising a CDR1 region that comprises amino acids 31-35 of SEQ ID NO: 5, a CDR2 region that comprises amino acids 50-66 of SEQ ID NO: 5, and a CDR3 region that comprises amino acids 99-106 of SEQ ID NO: 5; and a light chain variable domain comprising a CDR1 region that comprises amino acids 24-38 of SEQ ID NO: 6, a CDR2 region that comprises amino acids 54-60 of SEQ ID NO: 6, and a CDR3 region that comprises amino acids 93-101 of SEQ ID NO: 6; or

c) a heavy chain variable domain comprising a CDR1 region that comprises amino acids 31-35 of SEQ ID NO: 7, a CDR2 region that comprises amino acids 50-66 of SEQ ID NO: 7, and a CDR3 region that comprises amino acids 99-106 of SEQ ID NO: 7; and a light chain variable domain comprising a CDR1 region that comprises amino acids 24-38 of SEQ ID NO: 8, a CDR2 region that comprises amino acids 54-60 of SEQ ID NO: 8, and a CDR3 region that comprises amino acids 93-101 of SEQ ID NO: 8.

[0013] The invention provides antibodies that bind to BCMA and certain epitopes thereof. In some embodiments, the antibodies of the invention bind to one or more subsets of B cells, such as plasma cells, memory B cells, and naïve B cells. The invention also provides antibodies for use in depleting B cells or subclasses of B cells, including plasma cells, memory B cells, and naïve B cells. In one embodiment, the invention provides an isolated antibody that binds to SEQ ID NO:9 and binds to plasma cells. In one embodiment, the invention provides an isolated antibody that binds to SEQ ID NO:9 and binds to memory B cells. In another embodiment, the invention provides an isolated antibody that binds to SEQ ID NO:9 and binds to naïve B cells.

[0014] Certain anti-BCMA mAbs, including clone C4E2.2 (hamster IgG) generated at Legacy Biogen (6); clone VICKY-1 (rat IgG1) (Alexis Biochemicals, Lausen, Switzerland, also sold as 6D10 by Santa Cruz Biotechnology, Santa Cruz, CA); and clone 335004 (rat IgG2a) (R&D Systems, Inc., Minneapolis, MN), are outside the scope of this invention.

A. Antibodies

[0015] The invention provides antibodies that bind specifically to SEQ ID NO:9. The invention also provides to antibodies that bind to the surface of B cells or subclasses thereof, including plasma cells, memory B cells (including switched, unswitched, and double negative), and/or naïve B cells. The term "antibody" as used herein, includes both full-length immunoglobulins and antibody fragments that bind to the same antigens. The antibodies can be, e.g., a monoclonal, polyclonal, chimeric, humanized, or single chain antibody. In some embodiments, the antibody fragments are Fab fragments or F(ab')2 fragments and retain the ability to specifically bind the protein of SEQ ID NO: 9.

[0016] In part, the invention provides the antibodies C11D5.3, C12A3.2, and C13F12.1. Each of these is a murine monoclonal antibody. A7D12.2, a further antibody described herein, has a murine "miscellaneous" subgroup heavy chain, a heavy chain variable domain sequence that is SEQ ID NO:1, a subgroup I kappa light chain, and a light chain variable domain sequence that is SEQ ID NO:2.

[0017] C11D5.3 has a subgroup II(A) heavy chain, a heavy chain variable domain sequence that is SEQ ID NO:3, a murine subgroup III kappa light chain, and a light chain variable domain sequence that is selected from SEQ ID NO:4, SEQ ID NO:11, and SEQ ID NO:12. In some embodiments, the light chain variable domain sequence of C11D5.3 is SEQ ID NO:12.

[0018] C12A3.2 has a subgroup II(A) heavy chain, a heavy chain variable domain sequence that is SEQ ID NO:5, a murine subgroup III kappa light chain, and a light chain variable domain sequence that is SEQ ID NO:6.

[0019] C13F12.1 has a subgroup II(A) heavy chain, a heavy chain variable domain sequence that is SEQ ID NO:7, a murine subgroup III kappa light chain, and a light chain variable domain sequence that is SEQ ID NO:8.

[0020] Techniques for producing single-chain antibodies specific to the protein of SEQ ID NO: 9 can be adapted from e.g., those described in U.S. Patent 4,946,778. In addition, methods can be adapted for the construction of Fab expression libraries (see e.g., Huse et al. (1989) Science 246:1275-1281) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for a BCMA protein or derivatives, fragments, analogs or homologs thereof.

Numerous techniques for humanizing non-human antibodies are well known in the art. See e.g., U.S. Patent 5,225,539, 6,632,927, or 5,648,237. Antibody fragments that contain the idiotypes to a BCMA protein may be produced by any of a variety of techniques, including, but not limited to: (i) an F(ab')2 fragment produced by pepsin digestion of an antibody molecule; (ii) an Fab fragment generated by reducing the disulfide bridges of an F(ab')2 fragment; (iii) a Fab fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) Fv fragments.

[0021] Additionally, recombinant anti-BCMA antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques such as, for example, the methods described in U.S. Patent No. 7,112,421; Better et al. (1988) Science 240:1041-1043; or Liu et ai. (1987) Proc. Natl. Acad. Sci. USA 84:3439-3443.

[0022] Some of the antibodies of the invention are chimeric forms of murine monoclonal antibodies C11D5.3, C12A3.2, and C13F12.1. As described herein, a chimeric form of A7D12.2 comprises a heavy chain comprising SEQ ID NO:13 and a light chain comprising SEQ ID NO:14. In some embodiments, a chimeric form of C11D5.3 comprises a heavy chain comprising SEQ ID NO:15 and a light chain comprising a sequence selected from SEQ ID NO:16 and SEQ ID NO:17, preferably SEQ ID NO:17. In some embodiments, a chimeric form of C12A3.2 comprises a heavy chain comprising SEQ ID NO:18 and a light chain comprising SEQ ID NO:19. In some embodiments, a chimeric form of C13F12.1 comprises a heavy chain comprising SEQ ID NO:20 and a light chain comprising SEQ ID NO:21.

[0023] Some of the antibodies of the invention are humanized forms of murine monoclonal antibodies C11D5.3, C12A3.2, and C13F12.1. In some embodiments, a humanized form of C11D5.3 comprises a light chain variable domain comprising a sequence that is at least 95%, or 100% identical to a sequence selected from SEQ ID NOs 22-24 and a heavy chain variable domain sequence comprising a sequence that is at least 95%, or 100% identical to a sequence selected from SEQ ID NOs 25-29. In some embodiments, a humanized form of C12A3.2 comprises a light chain variable domain comprising a sequence that is at least 95%, or 100% identical to a sequence selected from SEQ ID NOs 30-33 and a heavy chain variable domain sequence comprising a sequence that is at least 95%, or 100% identical to a sequence selected from SEQ ID NOs 34-38. In some embodiments, a humanized form of C13F12.1 comprises a light chain variable domain comprising a sequence that is at least 95%, or 100% identical to a sequence selected from SEQ ID NOs 39-42 and a heavy chain variable domain sequence comprising a sequence that is at least 95%, or 100% identical to a sequence selected from SEQ ID NOs 43-47.

B. Antibody variable domain sequence

[0024] The antibodies of the invention may comprise the heavy chain variable domain sequences of SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7. The heavy chain variable domain sequences may consist essentially of SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

[0025] The antibodies of the invention may comprise the light chain variable domain sequences of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, or SEQ ID NO:12. The light chain variable domain sequences may consist essentially of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, or SEQ ID NO:12.

[0026] Also described herein is a variable domain sequence comprising a sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, and SEQ ID NO:7. Also described herein is a variable domain sequence comprising a sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence selected from SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, and SEQ ID NO:12. Also described herein are antibodies comprising a heavy chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:1 and a light chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:2. Also described herein are antibodies comprising a heavy chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:3 and a light chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO: 4, SEQ ID NO:11, or SEQ ID N0:12. Also described herein are antibodies comprising a heavy chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:5 and a light chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:6. Also described herein are antibodies comprising a heavy chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:7 and a light chain variable domain sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to SEQ ID NO:8.

[0027] The invention also provides antibodies with particular complementarity determining regions (CDR). Table 2 defines the amino acid coordinates of CDR1, CDR2, and CDR3 of SEQ ID NOs:1 through 8, 11, and 12.

Table 2. CDR Amino Acid Coordinates

SEQ ID NO	Description			
3	C11D5.3 V_H	31-35	50-66	99-106
4	C11D5.3 V_L A	24-38	54-60	93-101
	C12A3.2 V_H	31-35	50-66	99-106
6	C12A3.2 V_L	24-38	54-60	93-101
7	C13F12.1 V_H	31-35	50-66	99-106
8	C13F12.1 V_L	24-38	54-60	93-101
11	C11D5.3 V_L B	24-38	54-60	93-101
12	C11D5.3 V_L C	24-38	54-60	93-101

[0028] CDRs are designated using the Kabat definitions (Johnson and Wu (2000), Nucleic Acids Res 28:214-218). As used herein, the "corresponding CDR" means the CDR in the most similar position within the variable domain amino acid sequence.

[0029] The heavy chain variable domain of antibodies of the invention may comprise CDRs such that one, two, or three of the CDRs are identical to the corresponding CDRs of SEQ ID NO:3; identical to the corresponding CDRs of SEQ ID NO:5; or identical to the corresponding CDRs of SEQ ID NO:7. The light chain variable domain of antibodies of the invention may comprise CDRs such that one, two, or three of the CDRs are identical to the corresponding CDRs of SEQ ID NO:4; identical to the corresponding CDRs of SEQ ID NO:6; identical to the corresponding CDRs of SEQ ID NO:8; identical to the corresponding CDRs of SEQ ID NO:11; or identical to the corresponding CDRs of SEQ ID NO:12.

[0030] The heavy chain variable domain may comprise CDRs identical to each of the corresponding CDRs of one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7 except that one or more amino acid substitutions have been made in said CDR regions. CDRs of the heavy chain variable domain may have up to a total of 12 amino acid substitutions relative to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7. The heavy chain variable domain CDRs of the antibodies described herein may have up to 10, up to 8, up to 5, or up to 3 substitutions relative to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7. The heavy chain variable domain CDRs of the antibodies described herein may be at least 80%, at least 85%, at least 90%, or at least 95% identical to the heavy chain variable domain CDRs of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

[0031] CDR2 of SEQ ID NO:7 may be replaced by CDR2 (i.e., amino acids 50-66) of SEQ ID NO:46. For example, the heavy chain variable domain of an antibody described herein may comprise CDR1 and CDR3 of SEQ ID NO:7 and CDR2 of SEQ ID NO:46. The heavy chain variable domain of an antibody described herein may also comprise CDR1, CDR2, and CDR3 regions that are together at least 80%, at least 85%, at least 90%, or at least 95% identical to CDR1 and CDR3 of SEQ ID NO:7 and CDR2 of SEQ ID NO:46

[0032] The light chain variable domain may comprise CDRs identical to the corresponding CDRs of one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, or SEQ ID NO:12, except for one or more amino acid substitutions in said CDR regions. The antibodies described herein may comprise CDRs that are identical to the corresponding CDRs of one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, or SEQ ID NO:12, except for up to 12, up to 10, up to 8, up to 5, or up to 3 amino acid substitutions in said CDR regions. The light chain variable domain CDRs of the antibodies described herein may be at least 80%, at least 85%, at least 90%, or at least 95% identical to the light chain variable domain CDRs of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, or SEQ ID NO:12.

[0033] The substitutions in the CDR regions may be conservative substitutions.

C. Epitopes; antibody binding specificity

[0034] The invention also provides antibodies that bind particular epitopes. Whether a pair of antibodies binds the same epitope is determined based on cross-blocking experiments, as described in Example 4. Cross-blocking profiles are defined for seven antibodies in Table 3. For the purposes of this disclosure, two antibodies are considered to bind to the same epitope if each one reduces the other's binding to BCMA (i.e., they mutually cross-block) by at least 90% according to the procedure described in Example 4. Similarly, antibodies that do not reduce each other's binding by at least 90% as described in Example 4 are considered to bind to distinct epitopes. The cross-blocking profiles of antibodies with certain variable domains are listed in Table 3. Pairs of antibodies that bind to distinct epitopes (as defined above) are noted with a "d".

Table 3. Cross-Blocking Profiles

Heavy chain var. domain SEQ ID NO	Light chain var. domain SEQ ID NO	Example	Distinct (d) from epitope bound by:						
			C12A3.2	C11D5.3	C13F12.1	335004	C4E2	A7D12.2	VICKY-1
1	2	A7D12.2	d	d	d	d	d	-	d
3	12	C11D5.3	-	-	-	d	d	d	d
5	6	C12A3.2	-	-	-	d	d	d	d
7	8	C13F12.1	-	-	-	d	d	d	d

[0035] Further herein described are antibodies that bind to the same epitope as antibodies A7D12.2, C11D5.3, C12A3.2, or C13F12.1. Also described are antibodies that have cross-blocking profiles that match the profiles of A7D12.2, C11D5.3, C12A3.2, or C13F12.1. For example, following the definitions provided above, an antibody that has the same profile as C11D5.3 binds to the same epitope as compared to C12A3.2 and C13F12.1 but binds to a distinct epitope as compared to A7D12.2, 335004, C4E2, and Vicky-1. The antibodies described herein may mutually cross-block one or more of A7D12.2, C11D5.3, C12A3.2, or C13F12.1 from binding the protein of SEQ ID NO: 9 by at least 80%, 85%, 90%, or 95%. The extent of cross-blocking is measured according to the procedure described in Example 4.

[0036] In some embodiments, the antibodies and antibody fragments of the invention bind to the extracellular domain of BCMA. In particular embodiments, the antibodies bind to amino acids 1-52, 1-51, 1-41, or 8-41 of SEQ ID NO:9.

[0037] The invention also provides anti-BCMA antibodies that bind to one or more particular types of cell. The antibodies or antibody fragments of the invention may bind one or more of the following: plasma cells, memory B cells, naïve B cells, or cells that express BCMA (SEQ ID NO:9), a protein similar thereto, the extracellular domain thereof, or a polypeptide similar to the extracellular domain thereof.

D. Methods

[0038] The invention provides an antibody for use in depleting various types of cells. The medical uses comprise administering the antibodies of the invention, as described above. Types of cells that may be depleted by the antibodies of the invention include, without limitation, plasma cells, naïve B cells, memory B cells (including switched, unswitched, and double negative), lymphoma cells derived from B cells, and cells that express BCMA, a protein similar thereto, the extracellular domain thereof, or a polypeptide similar to the extracellular domain thereof. A cell may be in more than one of the foregoing categories. For an example of antibody-mediated cell depletion methods, see "Depletion of B Cells In Vivo by a Chimeric Mouse Human Monoclonal Antibody to CD20", Mitchell E. Reff, Blood, vol. 83, pp. 435-445, Jan. 15, 1994.

[0039] In some embodiments, medical use of an antibody of the invention reduces the number of one or more of the above-listed cell types by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, and least 85%, at least 90%, or at least 95%. In some embodiments, medical use of an antibody of the invention reduces the number of plasma cells by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. In some embodiments, medical use of an antibody of the invention reduces the number of switched memory B cells by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 60%. In some embodiments, medical use of an antibody of the invention reduces the number of unswitched memory B cells by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 60%. In some embodiments, medical use of an antibody of the invention reduces the number of double negative memory B cells by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 60%. In some embodiments, medical use of an antibody of the invention reduces the number of naive B cells by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 60%.

[0040] The invention also provides an antibody for use in reducing serum immunoglobulin levels comprising administering an antibody of the invention. In some embodiments, such medical uses reduce serum IgM levels. In particular embodiments, medical use of an antibody of the invention reduces serum IgM levels by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or at least 65%. In some embodiments,

such medical uses reduce serum IgG levels. In some embodiments, such medical uses reduce the levels of one or both of IgG2 and IgG3. In some embodiments, such medical uses reduce the levels of IgG2 by at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 65%, or at least 70%. In some embodiments, such medical uses reduce the levels of IgG3 by at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, or at least 80%. In some embodiments, such medical uses reduce IgG2, IgG3, and IgM levels.

[0041] The invention also provides an antibody for use in reducing the level of at least one autoantibody comprising administering an antibody of the invention. In some embodiments, such medical uses reduce the level of one or more autoantibodies by at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, and least 85%, at least 90%, or at least 95%.

[0042] In a still further aspect, the invention provides antibodies for use in treating or preventing or delaying a B-cell mediated condition disorder. The medical use includes administering to a subject in which such treatment or prevention or delay is desired, an antibody of the invention in an amount sufficient to treat, prevent, or delay a tumorigenic or immunoregulatory condition in the subject. In some embodiments, the subject is a human. In other embodiments, the subject is a non-human mammal. In some embodiments, administration of the antibody of the invention blocks BCMA-mediated signalling in the subject, which may result in one or more of cell death, inhibition, reduction, or cessation of cell proliferation.

[0043] In some embodiments, the antibodies or antibody fragments of the invention use BCMA to "target" B cell lymphomas. In essence, such targeting can be generalized as follows: antibodies or antibody fragments of the invention specific to the BCMA surface antigen of B cells are, e.g., injected into a subject and specifically bind to the BCMA cell surface antigen of (ostensibly) both normal and malignant B cells; this binding leads to the destruction and/or depletion of neoplastic B cells. Additionally, chemical agents or radioactive labels having the potential to destroy cancer cells and/or tumors can be conjugated to the antibodies or antibody fragments of the invention such that the agent is specifically "delivered" to the targeted B cells, such as, e.g., neoplastic B cells. In some embodiments, the medical uses of the invention comprise administering an antibody or antibody fragment that is not conjugated to a chemical agent or radioactive label. In some embodiments, the medical uses of the invention comprise administering an antibody or antibody fragment that is not conjugated to a cytotoxic agent.

[0044] B cell-related disorders include, without limitation, autoimmune diseases involving inappropriate B cell activity and B cell lymphomas. B cell lymphomas include, without limitation, multiple myeloma, plasmacytoma, Hodgkins' lymphoma, follicular lymphomas, small non-cleaved cell lymphomas, endemic Burkitt's lymphoma, sporadic Burkitt's lymphoma, marginal zone lymphoma, extranodal mucosa-associated lymphoid tissue lymphoma, nodal monocytoid B cell lymphoma, splenic lymphoma, mantle cell lymphoma, large cell lymphoma, diffuse mixed cell lymphoma, immunoblastic lymphoma, primary mediastinal B cell lymphoma, pulmonary B cell angiocentric lymphoma, and small lymphocytic lymphoma. The antibodies or antibody fragments of the invention may also be used to treat cancers in which the cancer cells express BCMA. The B cell-related disorders additionally include B cell proliferations of uncertain malignant potential, such as, for example, lymphomatoid granulomatosis and post-transplant lymphoproliferative disorder.

[0045] The conditions diagnosed, treated, prevented or delayed using the antibodies or antibody fragments of the invention can additionally be an immunoregulatory disorder. These disorders include those that are autoimmune in nature such as, for example, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, autoimmune hemolytic anemia, idiopathic thrombocytopenia purpura, anti-phospholipid syndrome, Chagas' disease, Grave's disease, Wegener's granulomatosis, poly-arteritis nodosa, Sjogren's syndrome, pemphigus vulgaris, scleroderma, multiple sclerosis, anti-phospholipid syndrome, ANCA associated vasculitis, Goodpasture's disease, Kawasaki disease, and rapidly progressive glomerulonephritis. The antibodies or antibody fragments of the invention may also have application in plasma cell disorders such as heavy-chain disease, primary or immunocyte-associated amyloidosis, and monoclonal gammopathy of undetermined significance (MGUS).

[0046] Compositions and medical uses of the antibodies or antibody fragments of the invention can be used with any condition associated with undesired BCMA-expressing cell proliferation.

[0047] The antibodies of the invention may also be administered in conjunction with antibody C2B8 of US Patent 5,736,137, also known as RITUXAN™. In some embodiments, such combined administration depletes or inhibits the proliferation of multiple B cell subtypes.

[0048] The antibodies provided herein may be used to assay B cell phenotypes, such as determination of the presence, absence, or amount of a marker on the surface of a B cell or B cell subtype. For example, the antibodies of the invention may be used to measure the presence of a marker associated with SLE or another B cell-related condition on the surface of naïve B cells, memory B cells, IgD+ memory B cells, IgD- memory B cells, or double negative memory B cells.

E. Pharmaceutical Compositions

[0049] The antibodies of the invention can be incorporated into pharmaceutical compositions suitable for administration.

Such compositions typically comprise antibodies and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, diluents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the antibodies, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0050] A pharmaceutical composition comprising antibodies of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0051] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0052] Sterile injectable solutions can be prepared by incorporating antibodies of the invention in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the antibodies into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the antibodies plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0053] In one embodiment, the antibodies are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. Additionally, the antibodies or antibody fragments of the invention may be used to target liposomal suspensions to B cells or subclasses thereof to which the particular antibody binds. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0054] Parenteral compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of antibody calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0055] The pharmaceutical compositions comprising an antibody of the invention can be included in a container, pack, or dispenser together with instructions for administration.

Example 1. Generation and biotin conjugation of anti-human BCMA monoclonal antibodies

[0056] Anti-BCMA monoclonal antibodies (mAbs) were generated by immunizing female RBF mice with BCMA-Fc/KLH conjugate protein i.p. in CFA, followed by additional immunizations at regular intervals with IFA, except that the last boost used RIBI instead of IFA, prior to splenocyte fusion to the FL653 myeloma cell line after the method of Harlow and Lane (1998), Using Antibodies: A Laboratory Manual: Portable Protocol No. I, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. Briefly, splenocytes isolated from a mouse 3 days after the final boost were washed twice and mixed in a 7:1 ratio with twice-washed log phase FL653 myeloma cells. The cell mixture was split four ways, pelleted, and incubated in 37°C PEG for 1 min during which time cells were gently resuspended, followed by careful addition of 10 ml ice-cold DMEM. Cells were mixed, pelleted, and resuspended in AAT hybridoma growth selection media. Cell supernatants were screened for BCMA-specific reactivity by ELISA and flow cytometry. Clones that scored positive for BCMA and negative for Fc-specificity in an ELISA format, positive on BCMA-transfected cells, and negative on mock-transfected cells were expanded and subcloned. Four BCMA-specific clones were selected for further evaluation: C11D5.3 (IgG1), C12A3.2 (IgG1), C13F12.1 (IgG1) and A7D12.2 (IgG2b). Anti-BCMA mAbs were biotin-conjugated for use in ELISA and FACS experiments described below using a kit according to the manufacturer's recommendations (Molecular Probes, Eugene, OR).

Example 2. Cloning of murine anti-human BCMA mAb variable regions

[0057] Total cellular RNA from murine hybridoma cells was prepared using a Qiagen RNeasy mini kit following the manufacturer's recommended protocol. cDNAs encoding the variable regions of the heavy and light chains were cloned by RT-PCR from total cellular RNA, using random hexamers for priming of first strand cDNA. For PCR amplification of the murine immunoglobulin variable domains with intact signal sequences, a cocktail of degenerate forward primers hybridizing to multiple murine immunoglobulin gene family signal sequences and a single back primer specific for the 5' end of the murine constant domain were used. PCR was performed using Clontech Advantage 2 Polymerase mix following the manufacturer's recommended protocol. The PCR products were gel-purified and subcloned into Invitrogen's pCR2.1TOPO vector using their TOPO cloning kit following the manufacturer's recommended protocol. Inserts from multiple independent subclones were sequenced to establish a consensus sequence. Deduced mature immunoglobulin N-termini were consistent with those determined by Edman degradation from the hybridoma. Assignment to specific subgroups was based upon BLAST analysis using consensus immunoglobulin variable domain sequences from the Kabat database (Johnson and Wu (2000), Nucleic Acids Res 28:214-218). CDRs were designated using the Kabat definitions (Johnson and Wu (2000), Nucleic Acids Res 28:214-218).

Example 3. Stable BCMA-expressing CHO cell line development and assessment of anti-human BCMA mAbs

[0058] To validate specific binding to BCMA, anti-BCMA mAbs were screened on a stable BCMA-expressing CHO cell line. The stable BCMA-expressing CHO cell line was generated using a previously described method (Brezinsky et al. (2003), J Immunol Methods 277:141-155). Briefly, approximately 1.5 million dihydrofolate reductase (DHFR) deficient DG44 Chinese hamster ovary (CHO) cells were transfected with 4 μg PV90 plasmid DNA containing the human BCMA gene using Fugene 6 Transfection Reagent (Roche, Indianapolis, IN). Following transfection, the cells were cultured in 6-well culture dishes. Twenty-four hours post-transfection, the growth medium was changed to alpha minus MEM (Gibco, Rockville, MD), 10% dialyzed serum (Hyclone, Logan, UT), and 2 mM L-glutamine (Gibco, Rockville, MD), and cells were pooled and split into three T-75 tissue culture flasks and allowed to grow to confluence. Seven days post-transfection, the cells were pooled again and split into five T225 tissue culture flasks and allowed to grow to confluence.

[0059] Fourteen days post-transfection, the cells were incubated with the C4E2.2 Ab (6) and sorted for BCMA+ cells. These cells were grown in culture and sorted a second time, with positive cells sorted into 96-well plates. Clones were expanded and assessed for BCMA expression using clone C4E2.2.

[0060] The highest expressing clone was used for assessing new anti-human BCMA mAbs, with untransfected CHO cells as a control. Briefly, BCMA-CHO cells were pretreated with FACS buffer plus 5% normal mouse serum to block non-specific binding sites. Seven anti-BCMA mAbs-C11D5.3, C12A3.2, C13F12.1 and A7D12.2 and the commercially available anti-BCMA mAbs, C4E2.2 (Legacy Biogen), VICKY-1 (Alexis) and 335004 (R&D Systems, inc.)-and isotype control antibodies were incubated separately with cells for 30 minutes on ice at 1 μg/ml, and washed. Biotin-conjugated isotype control Abs were as follows: mouse IgG1, eBioscience cat. no. 13-4714-85; mouse IgG2a, eBioscience, cat. no. 13-4732-85; hamster IgG1, BD Pharmingen cat. no. 553970; rat IgG2a, eBioscience, cat. No. 13-4321-82. To visualize positive staining, Streptavidin-PE (Molecular Probes, Eugene, OR) was added to cells for 30 minutes on ice, after which cells were washed, fixed in 0.8% paraformaldehyde, and run on a FACScalibur flow cytometer (BDbiosciences, San Jose, CA) and analyzed using Flowjo software (Treestar, Ashland, OR). Results are shown in Figure 1.

[0061] All seven antibodies showed specific recognition of the BCMA-expressing cells. C11D5.3 showed a slightly

higher basal binding to the negative control cells than the control mAb; basal binding of the other six antibodies to the negative control cells was similar to that of the control Ab.

Example 4. Analysis of anti-BCMA mAb epitope overlap by cross-blocking ELISA

[0062] The seven anti-BCMA mAbs tested in Example 3 were then assessed in a cross-blocking assay to determine the presence or absence of epitope overlap between each antibody. Corning 96-well flat-bottom plates were incubated overnight at 4°C with 10 μg/ml of mouse anti-human Fc in a 50 mM pH 9.6 sodium bicarbonate solution, washed, incubated with 2 μg/ml human BCMA-Fc (SEQ ID NO:10) at 37°C for 1 hr, washed again, and non-specific binding sites were blocked with blocking buffer (3% BSA in PBS) for 30 min at 37°C. Triplicate wells were then incubated with each unconjugated anti-BCMA mAb clone in blocking buffer at a concentration that was ten times the concentration of the single biotin-conjugated anti-BCMA mAb used in each individual experiment. A single biotin-conjugated anti-BCMA mAb clone in blocking buffer was added to all wells at a concentration pre-determined to give 80% of maximal signal (EC80) and incubated for 1 hr at 37°C, after which wells were washed and incubated with a streptavidin-HRP solution for 30 min, 37°C, washed, and incubated with substrate, TMB, to visualize positive reactivity. Enzymatic reactivity was stopped by adding 2N sulfuric acid, and the absorbance at 450 nm was measured using a plate reader.

[0063] For each species of biotin-conjugated antibody, control readings in which the unconjugated and conjugated antibodies were the same (except for the presence/absence of conjugated biotin) were considered background levels, i.e., the absorbance from this control was subtracted from each experimental reading for that antibody. In some cases, this background subtraction resulted in slightly negative values. Although it is possible that the labeled antibody was blocked slightly more effectively by a different unconjugated antibody than by itself, these slightly negative values might also result from experimental variation. Results were then expressed as a percentage of the positive control value, i.e., the background-adjusted absorbance reading for the biotin-conjugated antibody in the absence of a competing unconjugated antibody.

[0064] Antibodies were considered to bind the same epitope or very closely overlapping epitopes if they each reduced the other's binding (according to the fraction calculated as above) to below 20% of the positive control value. If they did not satisfy this condition, they were considered to have at least partially distinct epitopes. Table 3 shows which antibodies have at least partially distinct epitopes.

Example 5. Flow cytometric analysis of antibody binding to human peripheral blood cells

[0065] Blood was obtained from consenting healthy volunteers and peripheral blood mononuclear cells (PBMCs) were enriched by centrifugation through Ficoll-Paque (GE Healthcare, UK) according to the manufacturer's recommendations. PBMCs were washed extensively in PBS prior to use. Cells were pretreated with FACS buffer containing 5% normal mouse serum to block non-specific binding sites. The following fluorphore-conjugated monoclonal antibodies directed against specific B cell and plasma cell markers were used: anti-CD19-PE-Cy5, anti-IgD-FITC, anti-CD27-APC, anti-CD38-PE-Cy7 (BD Biosciences, San Jose, CA). Streptavidin-PE (Molecular Probes, Eugene, OR) was used to visualize biotin-conjugated anti-BCMA mAbs (10 μg/ml). Binding of an isotype control mAb as in Example 3 was also measured.

[0066] None of the anti-BCMA mAbs stained naïve B cells from healthy volunteers (Fig. 2E), while all stained plasma cells, although with varying intensities (Fig. 2A). Only clone A7D12.2 stained a proportion of all three memory B cell subsets (Fig. 2B-D).

Example 6. Comparison of antibody binding to B cells of healthy and SLE-afflicted individuals

[0067] Blood was obtained from consenting healthy volunteers and SLE patients and processed as in Example 5. Figure 3 shows a comparison between samples from a healthy volunteer and a representative SLE patient. Antibody A7D12.2 bound to plasma cells from both healthy volunteers and SLE patients (Fig. 3A). In the SLE samples but not the healthy samples, the A7D12.2 antibody bound naïve B cells (Fig. 3E). Binding of the A7D12.2 antibody to memory B cells (Fig. 3B-D), particularly double negative memory B cells (Fig. 3D), was increased in SLE samples.

Example 7. Generation of cell lines producing chimeric anti-BCMA mAbs

[0068] CHO-DG44-I, a dhfr-deficient, insulin-independent Chinese hamster ovary cell line, was used to construct anti-BCMA wild type cell lines. The host cells were cultured in CHO-S-SFM II medium with nucleosides prior to transfection.

[0069] Chimeric antibodies were produced by transfecting cells with expression plasmids encoding the mature heavy and light chain sequences listed in Table 4.

Table 4. Mature heavy and light chain sequences of chimeric anti-BCMA antibodies

Chimeric antibody	Mature heavy chain sequence	Mature light chain sequence
chA7D12.2	SEQ ID NO:13	SEQ ID NO:14
chC11D5.3	SEQ ID NO:15	SEQ ID NO:16 (for Example 8) SEQ ID NO:17 (for Example 9)
chC12A3.2	SEQ ID NO:18	SEQ ID NO:19
chC13F12.1	SEQ ID NO:20	SEQ ID NO:20

[0070] Chimeric anti-BCMA expression plasmids were transfected into the CHO host cell line DG44-I using a cationic lipid (Fugene HD) method. Briefly, $1x10^6$ DG44-I cells were seeded in each of two wells of a 6-well plate containing 3 mL of CHO-S-SFMII medium w/nucleosides per well. Four μg of plasmid DNA (2 μg heavy chain, 2 μg light chain) was diluted into 200 μL CHO-S-SFM II (Invitrogen) medium at room temperature. Sixteen μL of Fugene HD (Roche) reagent and allowed to complex with the DNA for approximately 15 minutes. 100 μL of the complexed DNA mixture was added to each well containing the cells. After three days, the transfected cells were combined and transferred to a T-75 flask containing 20 mL CHO-S-SFM II medium w/o nucleosides containing 400 μg/mL geneticin (Invitrogen). Cells were monitored for viability and scaled-up accordingly. As the cells were scaled-up they were adapted to production medium. Clonal cell lines were obtained by FACS sorting individual cells from the stable population.

[0071] CHO-DG44-I cells stably transfected with chimeric heavy and light chains were fermented in CHOM39 media, harvested, and the cells were removed by centrifugation. The pH of the cleared media was adjusted prior to passing through a protein A Fast Flow column. Antibodies were eluted with 100 mM Na-citrate buffer, pH 3.0, neutralized to pH 7.0 using 10% (v/v) of 2M glycine, pH 8.9, and the recovered antibody solution was buffer-exchanged to PBS (pH 7.2) using a Superdex 200 size exclusion chromatography under endotoxin-free conditions. The purified protein was kept at -80°C.

Example 8. Anti-BCMA-mediated killing in vitro

Cells and cell culture

[0072] JJN-3 human plasmacytoma cells (DSMZ ACC 541) were cultured in culture medium consisting of 40% Dulbecco's MEM, 40% Iscove's MDM, 20% FBS, 100 units/mL penicillin and 100 μg/mL streptomycin. U266 human plasmacytoma cells (ATCC TIB 196) were cultured in culture medium consisting of RPMI 1640, 15% FBS, 20 mM HEPES, 100 units/mL penicillin and 100 μg/mL streptomycin. All cells were cultured at 37 °C in a 5% CO2 atmosphere. Peripheral blood mononuclear cells were isolated from a consented normal healthy donor by density centrifugation through Ficoll-Paque PLUS (GE Healthcare, Uppsala, Sweden).

In vitro antibody-dependent cellular cytotoxicity (ADCC) assay

[0073] Assay diluent was RPMI 1640, 1% BSA, 20 mM HEPES, 100 units/mL penicillin and 100 μg/mL streptomycin. Human plasmacytoma cell lines JJN-3 and U266 were washed and resuspended in assay diluent to 0.4 x 10^6 cells per mL. 50 μL of each cell suspension was plated into a 96-well U bottom microtiter plate in triplicates. 50 μL of serially diluted chimeric anti-BCMA antibodies (chC12A3.2, chC13F12.1, chC11D5.3, and chA7D12.2, as described in Example 7) and control human IgG1 (HIgG1; Protos Immunoresearch, Burlingame, CA) were added to wells containing the cell lines and incubated for 30 minutes at 37 °C. For an effector:target ratio of 25:1, 50 μL of PBMCs (500,000) were added and incubated for an additional four hours at 37 °C in a 5% CO2 atmosphere. Plates were centrifuged at 1200 rpm for 5 minutes, and 100 μL of supernatant was transferred to a 96-flat-bottom microwell plate. The level of cell lysis was determined by measuring the amount of lactate dehydrogenase (Cytotoxicity Detection Kit (LDH), #11 644 793 001 Roche) released from lysed cells. 100 μL of LDH kit reaction mixture was added to 100 μL of supernatant for up to 30 minutes as followed by manufacturer instructions. Absorbance was measured at 490 nm. Controls included target cells alone (spontaneous LDH release), target cells alone with 2% Triton X-100 in assay diluent (maximum LDH release), effector cells with and without target cells, and human IgG1 isotype control.

Results

[0074] The human BCMA+ plasmacytoma cell line, U266, was utilized to test the ability of chimeric anti-BCMA anti-

bodies to kill via ADCC. Human peripheral blood mononuclear cells (PBMCs) were used as effector cells. As shown in Table 5, chimeric mAbs C12A3.2 and C13F12.1 demonstrated marked ADCC activity relative to HIgG1 controls. Chimeric clones A7D12.2 and C11D5.3 also mediated ADCC, although to a lesser degree than C12A3.2 and C13F12.1.

Table 5. ADCC of U266 cells by anti-human BCMA mAbs

mAb Clone	% Killing at 1 nM	% Maximal Killing (mAb concentration, nM)
chC12A3.2	32	35 (4)
chC13F12.1	20	20 (0.4)
chA7D12.2	10	24 (100)
chC11D5.3	18	≥42 (≥100)[1]
[1]Maximum killing determination is incomplete		

[0075] ADCC assays were also performed using a second BCMA+ plasmacytoma cell line, JJN-3, as the target cells. As shown in Table 6, chimeric C12A3.2, C13F12.1, and A7D12.2 also mediated ADCC of JJN-3 cells.

Table 6. ADCC of JJN-3 cells by anti-human BCMA mAbs

mAb Clone	% Killing at 1 nM	% Maximal Killing (mAb concentration, nM)
chC12A3.2	5	14 (100)
chC13F12.1	3	≥14(≥100)[1]
chA7D12.2	20	37 (100)
[1]Maximum killing determination is incomplete		

[0076] Using enriched human NK cells as effector cells did not result in improved killing for chC12A3.2, chC13F12.1 or chA7D12.2. Rather, percent killing by NKs was diminished relative to PBMCs, indicating that NK cells are not the effector cells for chC12A3.2, chC13F12.1, or chA7D12.2 in the ADCC assays with U266 and JJN3 as target cells (data not shown). Generation of afucosyl variants of chC12A3.2, chC13F12.1, or chA7D12.2 did not improve activity of these mAbs (data not shown).

Example 9. Anti-BCMA-mediated cell depletion in vivo

Establishment of humanized (HSC/NSG) mice

[0077] HSC/NSG mice provide a useful tool for testing in vivo biologic reagents specific for human protein targets since their immune system consists of functioning human cell types (Brehm et al. (2010), Clin Immunol [Epub ahead of print]). Humanized mice were generated as previously described (Pearson et al. (2008), Curr Protoc Immunol Chapter 15:Unit 15.21.PMID: 18491294). NOD/SCID/common gamma chain-deficient mice (NSG mice) were purchased from Jackson Laboratories (Bar Harbor, ME). Mice were maintained and bred under specific-pathogen-free conditions in isolator cages. Breeding pairs were established and dams were monitored for pregnancy and delivery. Pups ranging in age from 2-6 days old were used to create humanized mice. Pups were lightly irradiated, receiving a dose of 1 Gy (100 rad) from a 137Cs irradiator. Pups were immediately injected intra-orbitally with approximately 50,000 CD34+CD3- human stem cells (HSC) derived from umbilical cord blood (All Cell LLC, purchased from StemCell Technologies Inc., Vancouver, BC, Canada), then returned to the dam. Pups were weaned at 21 days and caged with littermates according to gender. Starting at 3 months of age mice were bled via the facial vein into heparinized tubes and the whole blood was analyzed by flow cytometry for the presence of human cells. In brief, 100 μl whole blood was stained with a cocktail of mAbs, anti-human CD45-FITC, anti-human CD3-PE, anti-human CD19-PerCp, and anti-mouse CD45-APC (BD Biosciences, San Jose, California). Mice were considered successfully humanized if they had at least 20% human CD45+ cells in whole blood of which 10% or more were human CD3+, the remainder being human B cells and other human hematopoietic cells. Mice were occasionally bled and analyzed to ensure that the humanization was stable, and were routinely analyzed 2 weeks prior to study enrollment.

Flow cytometry

[0078] To identify plasma cells (PC) in human stem cell humanized NSG (HSC/NSG) mice, collagenase-digested spleens were subjected to flow cytometric analysis. Cells were incubated with a cocktail of mAbs directed to human cell lineage and to human B cell markers. The panel consisted of anti-human CD45, anti-human CD19, anti-human CD27, anti-human IgD, and anti-human CD38. Two markers used to exclude specific cell populations were anti-mouse CD45 and anti-human CD3. Cells identified as PC were human CD45+, human CD19+, human CD3-, human CD27+, human IgD- and human CD38bright. To identify BCMA+ cells the biotin-conjugated anti-human BCMA mAbs, C12A3.2 and A7D12.2, were used.

In vivo cell depletion assay

[0079] 5-6 month-old HSC/NSG mice received chimeric anti-BCMA mAb i.p. Human IgG1 with no known reactivity (Protos Immunoresearch) was used as a negative control. Blood was collected to prepare serum for analysis of human Ig isoform levels. At the study terminus the spleen was harvested, a single cell suspension was prepared, RBCs were lysed and cells were washed 3x with PBS/5% FCS and the cell number was determined. Cells were assessed by flow cytometry for T lineage cells, B lineage cells, and plasma cells.

Assessment of serum human Ig isotypes

[0080] Serum levels of human IgM and IgG were determined using an ELISA format (Bethyl Laboratories Inc., Montgomery, TX) and a human immunoglobulin isotyping kit (Millipore, Billerica, MA), respectively, according to the manufacturer's protocol.

Results

[0081] Analysis of HSC/NSG mice aged 5-6 months revealed that among the diverse cell subsets assessed BCMA+ cells were only found in the B cell lineage. Within the B cell lineage, BCMA was found only on splenic PCs (human CD19+, human CD27+, IgD-, CD38 bright) (Figure 4), and not on naïve B cells (human CD19+, human CD27-, IgD+), unswitched memory B cells (human CD19+, human CD27+, human IgD+), or switched memory B cells (human CD19+, human CD27+, human IgD-) (data not shown).

[0082] To assess the ability of chimeric anti-human BCMA mAbs to deplete human PC, HSC/NSG mice received various amounts of chimeric anti-human BCMA clones chAC11D5.3, chC12A3.2, chC13F12.1, and chA7D12.2 (Example 7) twice weekly i.p. for 2 weeks, after which the presence of splenic PCs was determined. Splenic PCs from the HIgG1-treated control group were analyzed for expression of BCMA using the A7D12.2 and C12A3.2 clones and were confirmed to express cell surface BCMA (data not shown). PCs were identified using the flow cytometric parameters described above, and total cell numbers were determined from the flow cytometric dot plots (calculated as a percentage of the total human cell number). The numbers of naïve human B cells, unswitched memory human B cells, and switched memory human B cells were also determined.

[0083] Treatment with chC12A3.2 (N=5) resulted in a statistically significant decline, 93% and 95%, in the number of splenic PCs at the 200 μg and 20 μg dose levels, respectively, when compared with control HIgG-treated mice (N=5) while the 2 μg dose also showed a marked decline (32%), although it was not statistically significant. Treatment with chC13F12.1 (N=5) resulted in a statistically significant decline, 88% and 51%, in the number of splenic PCs at the 200 μg and 20 μg dose levels, respectively (Figure 5). No impact on the number of other B cell subsets or T cells was observed with chC12A3.2 and chC13F12.1 (data not shown).

[0084] Treatment with 200 μg of chC11D5.1 (N=2) or chA7D12.2 (N=1) resulted in an 89% and 97% reduction, respectively, in human PCs within the spleen when compared to HIgG-treated control mice (N =5) (Figure 6). Treatment with chA7D12.1 also resulted in a 2.6-fold decline in the number of splenic human switched memory B cells when compared to HIgG-treated mice (575 vs. 217 PCs/10^5 $HuCD45^+$ cells, for HIgG and chA7D12.1, respectively). Although BCMA could not be detected on the surface of switched memory B cells in untreated humanized mice, it appears that while the level of BCMA was below the limit of detection by flow cytometry, it was sufficient to result in Ab-mediated killing.

[0085] To determine the impact of human PC depletion on serum human Ig levels in the HSC/NSG mice described above, human Ig subsets were analyzed. The chimeric anti-BCMA mAbs used in these studies were of the human IgG1 isoform, therefore human IgG1 levels could not be accurately evaluated. In some experimental cohorts, control-treated mice had very little and variable amounts of isotypes IgG1, IgG2, IgA and IgE (data not shown). As shown in Table 7, both chC12A3.2 and chC13F12.1 resulted in marked reductions in serum human IgM, especially at the higher dose levels. Chimeric C12A3.2 resulted in a 63%, 62% and 30% reduction in IgM for the 200, 20 and 2 μg dose levels, respectively. Chimeric C13F12.1 resulted in a 52%, 42% and 32% reduction in IgM for the 200, 20 and 2 μg dose levels,

respectively.

Table 7. Serum human IgM levels (μg/mL)

	Treatment					
Treatment dose (μg)	**chC12A3.2**		**chC13F12.1**		**Human IgG1**	
	Mean	**SD[1]**	**Mean**	**SD**	**Mean**	**SD**
200	70.2[1]	37.4	91.1[3]	26.5	190.6	67.3
20	73.0[2]	32.2	110.3[4]	47.3	ND[5]	
2	134.3	60.1	128.9	112.4	ND	
[1]SD=standard deviation; [2]*p*=0.008; [3]*p*=0.02; [4]*p*=0.05 ; [5]ND=not done						

[0086] In a separate experiment, mice received chC12A3.2 (N=14) or HIgG1 control (N=9), and the control mice had readily detectable IgG2 and IgG3 isotypes as well as IgM. Chimeric C12A3.2-treated mice exhibited a significant depletion of splenic plasma cells, similar to that seen in Figure 5 (data not shown). As shown in Table 8, mice that received chC12A3.2 exhibited significantly reduced serum IgG2 and IgM levels when compared with HIgG-treated control mice. Chimeric C12A3.2-treated mice also had a marked reduction in serum IgG3, although the difference did not reach statistical significance when compared to control mice (Table 8).

Table 8. Serum human immunoolobulin levels

	Serum Immunoglobulin (μg/mL)					
Treatment	**IgG2**		**IgG3**		**IgM**	
	Mean	**SE[1]**	**Mean**	**SE**	**Mean**	**SE**
chC12A3.2	5.4[2]	1.9	1.1	0.7	40.5[3]	12.2
HIgG	19.2	7.6	6.9	4.1	114.3	19.1
[1]SE=standard error; [2]*p*=0.05; [3]*p*=0.003						

[0087] The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material. The citation of any references herein is not an admission that such references are prior art to the present invention.

[0088] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification, including claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless otherwise indicated to the contrary, the numerical parameters are approximations and may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0089] 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 following claims.

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Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly
450

<210> 14
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 14

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Asp Val Val Met Thr Gln Ser His Arg Phe Met Ser Thr Ser Val Gly
1               5                  10                  15

Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

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

Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
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<210> 15
<211> 446
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 15

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

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

Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

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

Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
```

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 16
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 16

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

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

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

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 17
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 17

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

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Ser Val Ile
20 25 30

Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

Pro Val Glu Glu Asp Asp Val Ala Ile Tyr Ser Cys Leu Gln Ser Arg
85 90 95

Ile Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 18
<211> 446
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 18

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

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg His Tyr
20 25 30

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

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Val Ile Asn Asn Leu Lys Asp Glu Asp Thr Ala Ser Tyr Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser

145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 19
<211> 218
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 19

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

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

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

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 20
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 20

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

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

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

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

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Val Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Phe Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Cys Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 21
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 21

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

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

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

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 22
<211> 111
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 22

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

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Ser Val Ile
20 25 30

Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Ala Ala Ile Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Ile Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 23
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 23

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

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Ser Val Ile
            20                  25                  30

Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Thr Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Leu Gln Ala Glu Asp Ala Ala Ile Tyr Ser Cys Leu Gln Ser Arg
                85                  90                  95

Ile Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 24
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 24

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

Glu Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Ser Val Ile
            20                  25                  30

Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Thr Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80
```

Arg Val Gln Ala Glu Asp Ala Ala Ile Tyr Ser Cys Leu Gln Ser Arg
85 90 95

Ile Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 25
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 25

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

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

Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 26
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 26

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

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

Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 27
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: synthetic polypeptide"

<400> 27

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

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

Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys

                85                  90                  95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 28
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 28

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

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

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

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 29
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 29

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

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

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

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 30
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 30

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

Asp Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
            20                  25                  30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Leu Ala Ser Asn Val Gln Thr Gly Ile Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80
```

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 31
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 31

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

Asp Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 32
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 32

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

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 33
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 33

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

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Arg Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 34
<211> 117

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 34

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

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

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

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
    50                  55                  60

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

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

Ala Arg Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> 35
<211> 117
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: synthetic polypeptide"

<400> 35

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

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

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
50 55 60

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

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

Ala Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 36
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 36

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

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

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

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 37
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 37

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

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg His Tyr
20 25 30

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

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
50 55 60

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

Leu Glu Ile Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 38
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 38

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

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg His Tyr

20 25 30

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

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
50 55 60

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

Leu Glu Ile Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 39
<211> 112
<212> PRT
<213> Artificial sequence

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<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 39

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

Asp Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Leu Ala Ser Asn Val Gln Thr Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg

100 105 110

<210> 40
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 40

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

Asp Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 41
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 41

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

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 42
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: Synthetic polypeptide"

<400> 42

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

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Arg Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 43
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 43

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

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

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

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Tyr Leu Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> 44
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 44

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

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

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

Gly Arg Ile Asn Thr Glu Thr Gly Glu Pro Leu Tyr Ala Asp Asp Phe
    50                  55                  60
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Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Asn Asp Tyr Leu Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 45
<211> 117
<212> PRT
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<220>
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<223> /note="Description of Artificial sequence: synthetic polypeptide"

<400> 45

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

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

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

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 46
<211> 117
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46

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

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

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

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Leu Thr Val Ser Ser
        115
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<210> 47
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 47

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

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

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

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

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Leu Thr Val Ser Ser
        115
```

Claims

1. An isolated antibody or antigen-binding fragment thereof that binds to the polypeptide of SEQ ID NO:9, wherein the antibody or antigen-binding fragment comprises:

   a) a heavy chain variable domain comprising a CDR1 region that comprises amino acids 31-35 of SEQ ID NO: 3, a CDR2 region that comprises amino acids 50-66 of SEQ ID NO: 3, and a CDR3 region that comprises amino acids 99-106 of SEQ ID NO: 3; and a light chain variable domain comprising a CDR1 region that comprises amino acids 24-38 of any one of SEQ ID NOs: 4, 11, or 12, a CDR2 region that comprises amino acids 54-60 of any one of SEQ ID NOs: 4, 11, or 12, and a CDR3 region that comprises amino acids 93-101 of any one of SEQ ID NOs: 4, 11 or 12;
   b) a heavy chain variable domain comprising a CDR1 region that comprises amino acids 31-35 of SEQ ID NO: 5, a CDR2 region that comprises amino acids 50-66 of SEQ ID NO: 5, and a CDR3 region that comprises amino acids 99-106 of SEQ ID NO: 5; and a light chain variable domain comprising a CDR1 region that comprises amino acids 24-38 of SEQ ID NO: 6, a CDR2 region that comprises amino acids 54-60 of SEQ ID NO: 6, and a CDR3 region that comprises amino acids 93-101 of SEQ ID NO: 6; or
   c) a heavy chain variable domain comprising a CDR1 region that comprises amino acids 31-35 of SEQ ID NO: 7, a CDR2 region that comprises amino acids 50-66 of SEQ ID NO: 7, and a CDR3 region that comprises amino acids 99-106 of SEQ ID NO: 7; and a light chain variable domain comprising a CDR1 region that comprises amino acids 24-38 of SEQ ID NO: 8, a CDR2 region that comprises amino acids 54-60 of SEQ ID NO: 8, and a CDR3 region that comprises amino acids 93-101 of SEQ ID NO: 8.

2. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises:

   a) a heavy chain variable domain comprising SEQ ID NO: 3 and a light chain variable domain comprising SEQ ID NO: 12;
   b) a heavy chain variable domain comprising SEQ ID NO: 3 and a light chain variable domain comprising SEQ ID NO: 4;
   c) a heavy chain variable domain comprising SEQ ID NO: 3 and a light chain variable domain comprising SEQ ID NO: 11;
   d) a heavy chain variable domain comprising a SEQ ID NO: 5 and a light chain variable domain comprising SEQ ID NO: 6; or
   e) a heavy chain variable domain comprising SEQ ID NO: 7 and a light chain variable domain comprising SEQ ID NO: 8.

3. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises:

   a) a heavy chain comprising SEQ ID NO: 15 and a light chain comprising SEQ ID NO: 16 or SEQ ID NO: 17;
   b) a heavy chain comprising a SEQ ID NO: 18 and a light chain comprising SEQ ID NO: 19; or

c) a heavy chain comprising SEQ ID NO: 20 and a light chain comprising SEQ ID NO: 21.

4. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises:

a) a heavy chain variable domain comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 25-29 and a light chain variable domain comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 22-24;
b) a heavy chain variable domain comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NO: 34-38 and a light chain variable domain comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NO: 30-33; or
c) a heavy chain variable domain comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NO: 43-47 and a light chain variable domain comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NO: 39-42.

5. The antibody or antigen-binding fragment of claim 4, wherein the antibody or antigen-binding fragment comprises:

a) a heavy chain variable domain comprising any one of SEQ ID NOs: 25-29 and a light chain variable domain comprising any one of SEQ ID NOs: 22-24;
b) a heavy chain variable domain comprising SEQ ID NO: 34-38 and a light chain variable domain comprising SEQ ID NO: 30-33; or
c) a heavy chain variable domain comprising a SEQ ID NO: 43-47 and a light chain variable domain comprising SEQ ID NO: 39-42.

6. The antibody of any of claims 1-2, wherein the antibody is a chimeric or single chain antibody.

7. The antibody of claim 1, wherein the antibody is a humanized antibody.

8. A polypeptide that binds to SEQ ID NO:9 and comprises the antigen binding portion, Fab fragment, or F(ab')2 fragment of the antibody of any of claims 1-7.

9. A hybridoma that produces the antibody of any of claims 1-7.

10. A pharmaceutical composition comprising:

a) the antibody or antigen-binding fragment of any of claims 1-7; or
b) the polypeptide of claim 8.

11. The antibody or antigen-binding fragment of any of claims 1-7 for use in treating a B cell related disorder.

12. The antibody or antigen-binding fragment for use as in claim 11, wherein the B-cell related disorder is plasmacytoma, Hodgkins' lymphoma, follicular lymphomas, small non-cleaved cell lymphomas, endemic Burkitt's lymphoma, sporadic Burkitt's lymphoma, marginal zone lymphoma, extranodal mucosa-associated lymphoid tissue lymphoma, nodal monocytoid B cell lymphoma, splenic lymphoma, mantle cell lymphoma, large cell lymphoma, diffuse mixed cell lymphoma, immunoblastic lymphoma, primary mediastinal B cell lymphoma, pulmonary B cell angiocentric lymphoma, small lymphocytic lymphoma, B cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, post-transplant lymphoproliferative disorder, an immunoregulatory disorder, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenia purpura, anti-phospholipid syndrome, Chagas' disease, Grave's disease, Wegener's granulomatosis, poly-arteritis nodosa, Sjogren's syndrome, pemphigus vulgaris, scleroderma, multiple sclerosis, anti-phospholipid syndrome, ANCA associated vasculitis, Goodpasture's disease, Kawasaki disease, autoimmune hemolytic anemia, and rapidly progressive glomerulonephritis, heavy-chain disease, primary or immunocyte-associated amyloidosis, or monoclonal gammopathy of undetermined significance.

13. The antibody or antigen-binding fragment for use as in claim 12, wherein the B cell-related disorder is

a) a B cell malignancy, such as a plasma cell malignancy;
b) an autoimmune disease;
c) idiopathic thrombocytopenia purpura;
d) myasthenia gravis; or

e) autoimmune hemolytic anemia.

14. The antibody or antigen-binding fragment for use as in claim 13, wherein the plasma cell malignancy is multiple myeloma.

15. The antibody or antigen-binding fragment for use as in claim 13, wherein the autoimmune disease is systemic lupus erythematosus or rheumatoid arthritis.

16. The antibody or antigen-binding fragment for use as in claim 11 or 12, wherein the antibody or antigen-binding fragment is administered in conjunction with RITUXAN™.

Patentansprüche

1. Isolierter Antikörper oder Antigen-bindendes Fragment davon, der an das Polypeptid der SEQ ID NO: 9 bindet, wobei der Antikörper oder das Antigen-bindende Fragment Folgendes umfasst:

a) eine variable Domäne der schweren Kette, die eine CDR1-Region umfasst, welche die Aminosäuren 31-35 von SEQ ID NO: 3 umfasst, eine CDR2 Region, welche die Aminosäuren 50-66 von SEQ ID NO: 3 umfasst und eine CDR3-Region, welche die Aminosäuren 99-106 von SEQ ID NO: 3 umfasst; und eine variable Domäne der leichten Kette, die eine CDR1-Region umfasst, welche die Aminosäuren 24-38 von einer der SEQ ID NOs: 4, 11 oder 12 umfasst, eine CDR2 Region, welche die Aminosäuren 54-60 von einer der SEQ ID NOs: 4, 11 oder 12 umfasst und eine CDR3-Region, welche die Aminosäuren 93-101 von einer der SEQ ID NOs: 4, 11 oder 12 umfasst;
b) eine variable Domäne der schweren Kette, die eine CDR1-Region umfasst, welche die Aminosäuren 31-35 von SEQ ID NO: 5 umfasst, eine CDR2 Region, welche die Aminosäuren 50-66 von SEQ ID NO: 5 umfasst und eine CDR3-Region, welche die Aminosäuren 99-106 von SEQ ID NO: 5 umfasst; und eine variable Domäne der leichten Kette, die eine CDR1-Region umfasst, welche die Aminosäuren 24-38 von SEQ ID NO: 6 umfasst, eine CDR2 Region, welche die Aminosäuren 54-60 von SEQ ID NO: 6 umfasst und eine CDR3-Region, welche die Aminosäuren 93-101 von SEQ ID NO: 6 umfasst; oder
(c) eine variable Domäne der schweren Kette, die eine CDR1 Region umfasst, welche die Aminosäuren 31-35 von SEQ ID NO: 7 umfasst, eine CDR2 Region, welche die Aminosäuren 50-66 von SEQ ID NO: 7 umfasst und eine CDR3 Region, welche die Aminosäuren 99-106 von SEQ ID NO: 7 umfasst; und eine variable Domäne der leichten Kette, die eine CDR1 Region umfasst, welche die Aminosäuren 24-38 von SEQ ID NO: 8 umfasst, eine CDR2 Region, welche die Aminosäuren 54-60 von SEQ ID NO: 8, umfasst und eine CDR3 Region, welche die Aminosäuren 93-101 von SEQ ID NO: 8 umfasst.

2. Antikörper oder Antigen-bindendes Fragment nach Anspruch 1, wobei der Antikörper oder das Antigen-bindende Fragment Folgendes umfasst:

a) eine variable Domäne der schweren Kette, welche SEQ ID NO: 3 umfasst und eine variable Domäne der leichten Kette, welche SEQ ID NO: 12 umfasst;
b) eine variable Domäne der schweren Kette, welche SEQ ID NO: 3 umfasst und eine variable Domäne der leichten Kette, welche SEQ ID NO: 4 umfasst;
c) eine variable Domäne der schweren Kette, welche SEQ ID NO: 3 umfasst und eine variable Domäne der leichten Kette, welche SEQ ID NO: 11 umfasst;
d) eine variable Domäne der schweren Kette, welche SEQ ID NO: 5 umfasst und eine variable Domäne der leichten Kette, welche SEQ ID NO: 6 umfasst; oder
e) eine variable Domäne der schweren Kette, welche SEQ ID NO: 7 umfasst und eine variable Domäne der leichten Kette, welche SEQ ID NO: 8 umfasst.

3. Antikörper oder Antigen-bindendes Fragment nach Anspruch 1, wobei der Antikörper oder das Antigen-bindende Fragment Folgendes umfasst:

a) eine schwere Kette, welche SEQ ID NO: 15 umfasst und eine leichte Kette, welche SEQ ID NO: 16 oder SEQ ID NO: 17 umfasst;
b) eine schwere Kette, welche SEQ ID NO: 18 umfasst und eine leichte Kette, welche SEQ ID NO: 19 umfasst; oder

c) eine schwere Kette, welche SEQ ID NO: 20 umfasst und eine leichte Kette, welche SEQ ID NO: 21 umfasst.

4. Antikörper oder Antigen-bindendes Fragment nach Anspruch 1, wobei der Antikörper oder das Antigen-bindende Fragment Folgendes umfasst:

a) eine variable Domäne der schweren Kette, die eine Sequenz umfasst, die mindestens 95% identisch mit einer Sequenz ist, die ausgewählt ist aus SEQ ID NOs: 25-29 und eine variable Domäne der leichten Kette, die eine Sequenz umfasst, die mindestens 95% identisch ist mit einer Sequenz, die ausgewählt ist aus SEQ ID NOs: 22-24;
b) eine variable Domäne der schweren Kette, die eine Sequenz umfasst, die mindestens 95% identisch mit einer Sequenz ist, die ausgewählt ist aus SEQ ID NOs: 34-38 und eine variable Domäne der leichten Kette, die eine Sequenz umfasst, die mindestens 95% identisch ist mit einer Sequenz, die ausgewählt ist aus SEQ ID NOs: 30-33; oder
c) eine variable Domäne der schweren Kette, die eine Sequenz umfasst, die mindestens 95% identisch mit einer Sequenz ist, die ausgewählt ist aus SEQ ID NOs: 43-47 und eine variable Domäne der leichten Kette, die eine Sequenz umfasst, die mindestens 95% identisch ist mit einer Sequenz, die ausgewählt ist aus SEQ ID NOs: 39-42.

5. Antikörper oder Antigen-bindendes Fragment nach Anspruch 4, wobei der Antikörper oder das Antigen-bindende Fragment Folgendes umfasst:

a) eine variable Domäne der schweren Kette, die eine der Aminosäuresequenzen von SEQ ID NOs: 25-29 umfasst und eine variable Domäne der leichten Kette, die eine der Aminosäuresequenzen von SEQ ID NOs: 22-24 umfasst;
b) eine variable Domäne der schweren Kette, die SEQ ID NO: 34-38 umfasst und eine variable Domäne der leichten Kette, die SEQ ID NO: 30-33 umfasst; oder
c) eine variable Domäne der schweren Kette, die SEQ ID NO: 43-47 umfasst und eine variable Domäne der leichten Kette, die SEQ ID NO: 39-42 umfasst.

6. Antikörper nach einem der Ansprüche 1-2, wobei der Antikörper ein chimärer oder einzelkettiger Antikörper ist.

7. Antikörper nach Anspruch 1, wobei der Antikörper ein humanisierter Antikörper ist.

8. Polypeptid, das an SEQ ID NO: 9 bindet und den Antigenbindungsteil, das Fab-Fragment oder F(ab')2-Fragment des Antikörpers nach einem der Ansprüche 1-7 umfasst.

9. Hybridoma, die den Antikörper nach einem der Ansprüche 1 -7 herstellt.

10. Pharmazeutische Zusammensetzung, die Folgendes umfasst:

a) den Antikörper oder das Antigen-bindende Fragment nach einem der Ansprüche 1-7; oder
b) das Polypeptid nach Anspruch 8.

11. Antikörper oder Antigen-bindendes Fragment nach einem der Ansprüche 1-7 zur Verwendung zum Behandeln einer B-Zell-bezogenen Störung.

12. Antikörper oder Antigen-bindendes Fragment zur Verwendung wie in Anspruch 11, wobei die B-Zell-bezogene Störung ein Plasmozytom, ein Hodgkins Lymphom, follikuläre Lymphome, kleine nicht-gespaltene Zelllymphome, ein endemisches Burkitt-Lymphom, ein sporadisches Burkitt-Lymphom, ein Randzonenlymphom, ein extranodales Schleimhaut-assozüertes lymphatisches Gewebelymphom, ein nodales monozytoides B-Zelllymphom, ein Milzlymphom, ein Mantelzelllymphom, ein großzelliges Lymphom, ein diffuses Gemischtzelllymphom, ein immunoblastisches Lymphom, ein primäres mediastinales B-Zelllymphom, ein angiozentrisches pulmonares B-Zelllymphom, ein kleines lymphozytisches Lymphom, B-Zellwucherungen von unsicherem Malignitätspotential, lymphomatoide Granulomatose, eine Post-Transplantations lymphoproliferative Erkrankung, eine immunregulatorische Störung, rheumatoide Arthritis, Myasthenia gravis, idiopathische thrombozytopenische Purpura, Anti-Phospholipid Syndrom, Chagas Krankheit, Morbus Basedow, Wegener Granulomatose, Polyarteritis nodosa, Sjögren Syndrom, Pemphigus vulgaris, Sklerodermie, Multiple Sklerose, Anti-Phospholipid Syndrom, ANCA-assoziierte Vaskulitis, Goodpasture Syndrom, Kawasaki Krankheit, autoimmune hämolytische Anämie und schnell fortschreitende Glomerulonephritis,

Schwerkettenkrankheit, primäre oder Immunozyten-assoziierte Amyloidose, oder monoklonale Gammopathie unklarer Signifikanz ist/sind.

13. Antikörper oder Antigen-bindendes Fragment zur Verwendung nach Anspruch 12, wobei die B-Zell-bezogene Störung die Folgende ist

a) eine B-Zell-Malignität, wie etwa eine Plasmazell-Malignität;
b) eine Autoimmunerkrankung;
c) idiopathische thrombozytopenische Purpura;
d) Myasthenia gravis; oder
e) autoimmune hämolytische Anämie.

14. Antikörper oder das Antigen-bindende Fragment zur Verwendung nach Anspruch 13, wobei die Plasmazell-Malignität ein multiples Myelom ist.

15. Antikörper oder das Antigen-bindende Fragment zur Verwendung nach Anspruch 13, wobei die Autoimmunerkrankung systemischer Lupus erythematosus oder rheumatoide Arthritis ist.

16. Antikörper oder das Antigen-bindende Fragment zur Verwendung nach Anspruch 11 oder 12, wobei der Antikörper oder das Antigen-bindende Fragment in Verbindung mit RITUXAN™ verabreicht wird.

Revendications

1. Anticorps isolé ou fragment de liaison à l'antigène de celui-ci qui se lie au polypeptide de SEQ ID NO 9, dans lequel l'anticorps ou le fragment de liaison à l'antigène comprend :

a) un domaine variable à chaîne lourde comprenant une région CDR1 qui comprend les acides aminés 31 à 35 de la SEQ ID NO 3, une région CDR2 qui comprend les acides aminés 50 à 66 de la SEQ ID NO 3, et une région CDR3 qui comprend les acides aminés 99 à 106 de la SEQ ID NO 3 ; et un domaine variable à chaîne légère comprenant une région CDR1 qui comprend les acides aminés 24 à 38 de l'une quelconque des SEQ ID NO 4, 11 et 12, une région CDR2 qui comprend les acides aminés 54 à 60 de l'une quelconque des SEQ ID NO 4, 11 et 12, et une région CDR3 qui comprend les acides aminés 93 à 101 de l'une quelconque des SEQ ID NO 4, 11 et 12 ;
b) un domaine variable à chaîne lourde comprenant une région CDR1 qui comprend les acides aminés 31 à 35 de la SEQ ID NO 5, une région CDR2 qui comprend les acides aminés 50 à 66 de la SEQ ID NO 5, et une région CDR3 qui comprend les acides aminés 99 à 106 de la SEQ ID NO 5 ; et un domaine variable à chaîne légère comprenant une région CDR1 qui comprend les acides aminés 24 à 38 de la SEQ ID NO 6, une région CDR2 qui comprend les acides aminés 54 à 60 de la SEQ ID NO 6, et une région CDR3 qui comprend les acides aminés 93 à 101 de la SEQ ID NO 6 ; ou
c) un domaine variable à chaîne lourde comprenant une région CDR1 qui comprend les acides aminés 31 à 35 de la SEQ ID NO 7, une région CDR2 qui comprend les acides aminés 50 à 66 de la SEQ ID NO 7, et une région CDR3 qui comprend les acides aminés 99 à 106 de la SEQ ID NO 7 ; et un domaine variable à chaîne légère comprenant une région CDR1 qui comprend les acides aminés 24 à 38 de la SEQ ID NO 8, une région CDR2 qui comprend les acides aminés 54 à 60 de la SEQ ID NO 8, et une région CDR3 qui comprend les acides aminés 93 à 101 de la SEQ ID NO 8.

2. Anticorps ou fragment de liaison à l'antigène selon la revendication 1, dans lequel l'anticorps ou le fragment de liaison à l'antigène comprend :

a) un domaine variable à chaîne lourde comprenant la SEQ ID NO 3 et un domaine variable à chaîne légère comprenant la SEQ ID NO 12 ;
b) un domaine variable à chaîne lourde comprenant la SEQ ID NO 3 et un domaine variable à chaîne légère comprenant la SEQ ID NO 4 ;
c) un domaine variable à chaîne lourde comprenant la SEQ ID NO 3 et un domaine variable à chaîne légère comprenant la SEQ ID NO 11 ;
d) un domaine variable à chaîne lourde comprenant la SEQ ID NO 5 et un domaine variable à chaîne légère comprenant la SEQ ID NO 6 ; ou

e) un domaine variable à chaîne lourde comprenant la SEQ ID NO 7 et un domaine variable à chaîne légère comprenant la SEQ ID NO 8.

3. Anticorps ou fragment de liaison à l'antigène selon la revendication 1, dans lequel l'anticorps ou le fragment de liaison à l'antigène comprend :

a) une chaîne lourde comprenant la SEQ ID NO 15 et une chaîne légère comprenant la SEQ ID NO 16 ou la SEQ ID NO 17 ;
b) une chaîne lourde comprenant la SEQ ID NO 18 et une chaîne légère comprenant la SEQ ID NO 19 ; ou
c) une chaîne lourde comprenant la SEQ ID NO 20 et une chaîne légère comprenant la SEQ ID NO 21.

4. Anticorps ou fragment de liaison à l'antigène selon la revendication 1, dans lequel l'anticorps ou le fragment de liaison à l'antigène comprend :

a) un domaine variable à chaîne lourde comprenant une séquence qui est au moins 95 % identique à une séquence choisie parmi les SEQ ID NO 25 à 29 et un domaine variable à chaîne légère comprenant une séquence qui est au moins 95 % identique à une séquence choisie parmi les SEQ ID NO 22 à 24 ;
b) un domaine variable à chaîne lourde comprenant une séquence qui est au moins 95 % identique à une séquence choisie parmi les SEQ ID NO 34 à 38 et un domaine variable à chaîne légère comprenant une séquence qui est au moins 95 % identique à une séquence choisie parmi les SEQ ID NO 30 à 33 ; ou
c) un domaine variable à chaîne lourde comprenant une séquence qui est au moins 95 % identique à une séquence choisie parmi les SEQ ID NO 43 à 47 et un domaine variable à chaîne légère comprenant une séquence qui est au moins 95 % identique à une séquence choisie parmi les SEQ ID NO 39 à 42.

5. Anticorps ou fragment de liaison à l'antigène selon la revendication 4, dans lequel l'anticorps ou le fragment de liaison à l'antigène comprend :

a) un domaine variable à chaîne lourde comprenant l'une quelconque des SEQ ID NO 25 à 25 et un domaine variable à chaîne légère comprenant l'une quelconque des SEQ ID NO 22 à 24 ;
b) un domaine variable à chaîne lourde comprenant l'une quelconque des SEQ ID NO 34 à 38 et un domaine variable à chaîne légère comprenant l'une quelconque des SEQ ID NO 30 à 33 ; ou
c) un domaine variable à chaîne lourde comprenant l'une quelconque des SEQ ID NO 43 à 47 et un domaine variable à chaîne légère comprenant l'une quelconque des SEQ ID NO 39 à 42.

6. Anticorps selon l'une quelconque des revendications 1 à 2, dans lequel l'anticorps est un anticorps chimérique ou à liaison unique.

7. Anticorps selon la revendication 1, dans lequel l'anticorps est un anticorps humanisé.

8. Polypeptide qui se lie à la SEQ ID NO 9 et comprend la partie de liaison à l'antigène, fragment Fab, ou fragment F(ab')2 de l'anticorps selon l'une quelconque des revendications 1 à 7.

9. Hybridome qui produit l'anticorps selon l'une quelconque des revendications 1 à 7.

10. Composition pharmaceutique comprenant :

a) l'anticorps ou le fragment de liaison à l'antigène selon l'une quelconque des revendications 1 à 7 ; ou
b) le polypeptide selon la revendication 8.

11. Anticorps ou fragment de liaison à l'antigène selon l'une quelconque des revendications 1 à 7 pour une utilisation dans le traitement d'un trouble lié aux cellules B.

12. Anticorps ou fragment de liaison à l'antigène pour une utilisation selon la revendication 11, dans lequel le trouble lié aux cellules B est le plasmocytome, le lymphome de Hodgkin, les lymphomes folliculaires, les lymphomes à petites cellules non clivées, le lymphome de Burkitt endémique, le lymphome de Burkitt sporadique, le lymphome de la zone marginale, le lymphome du tissu lymphoïde extranodal associé aux muqueuses, le lymphome monocytoïde nodal à cellules B, le lymphome splénique, le lymphome à cellules du manteau, le lymphome à grandes cellules, le lymphome diffus à cellules mixtes, le lymphome immunoblastique, le lymphome médiastinal primitif à

cellules B, le lymphome angiocentrique pulmonaire à cellules B, le lymphome à petits lymphocytes, la proliférations des cellules B de potentiel malin incertain, la granulomatose lymphomatoïde, un trouble lymphoprolifératif post-transplantation, un trouble de l'immunorégulation, la polyarthrite rhumatoïde, la myasthénie grave, le purpura thrombocytopénique idiopathique, le syndrome antiphospholipidique, la maladie de Chagas, la maladie de Grave, la granulomatose de Wegener, la poly-artérite noueuse, le syndrome de Sjogren, le pemphigus vulgaire, la sclérodermie, la sclérose en plaques, le syndrome antiphospholipidique, la vascularite associée aux ANCA, la maladie de Goodpasture, la maladie de Kawasaki, l'anémie hémolytique auto-immune, et la glomérulonéphrite à progression rapide, la maladie des chaînes lourdes, l'amylose primitive ou associée aux immunocytes ou la gammapathie monoclonale de signification indéterminée.

13. Anticorps ou fragment de liaison à l'antigène pour une utilisation selon la revendication 12, dans lequel le trouble lié aux cellules B est

a) une tumeur maligne des cellules B, telles qu'une tumeur maligne des cellules plasmatiques ;
b) une maladie auto-immune ;
c) le purpura thrombocytopénique idiopathique ;
d) la myasthénie grâce ; ou
e) l'anémie hémolytique auto-immune.

14. Anticorps ou fragment de liaison à l'antigène pour une utilisation selon la revendication 13, dans lequel la tumeur maligne des cellules plasmatiques est le myélome multiple.

15. Anticorps ou fragment de liaison à l'antigène pour une utilisation selon la revendication 13, dans lequel la maladie auto-immune est le lupus érythémateux disséminé ou la polyarthrite rhumatoïde.

16. Anticorps ou fragment de liaison à l'antigène pour une utilisation selon la revendication 11 ou 12, dans lequel l'anticorps ou le fragment de liaison à l'antigène est administré conjointement avec RITUXAN™.

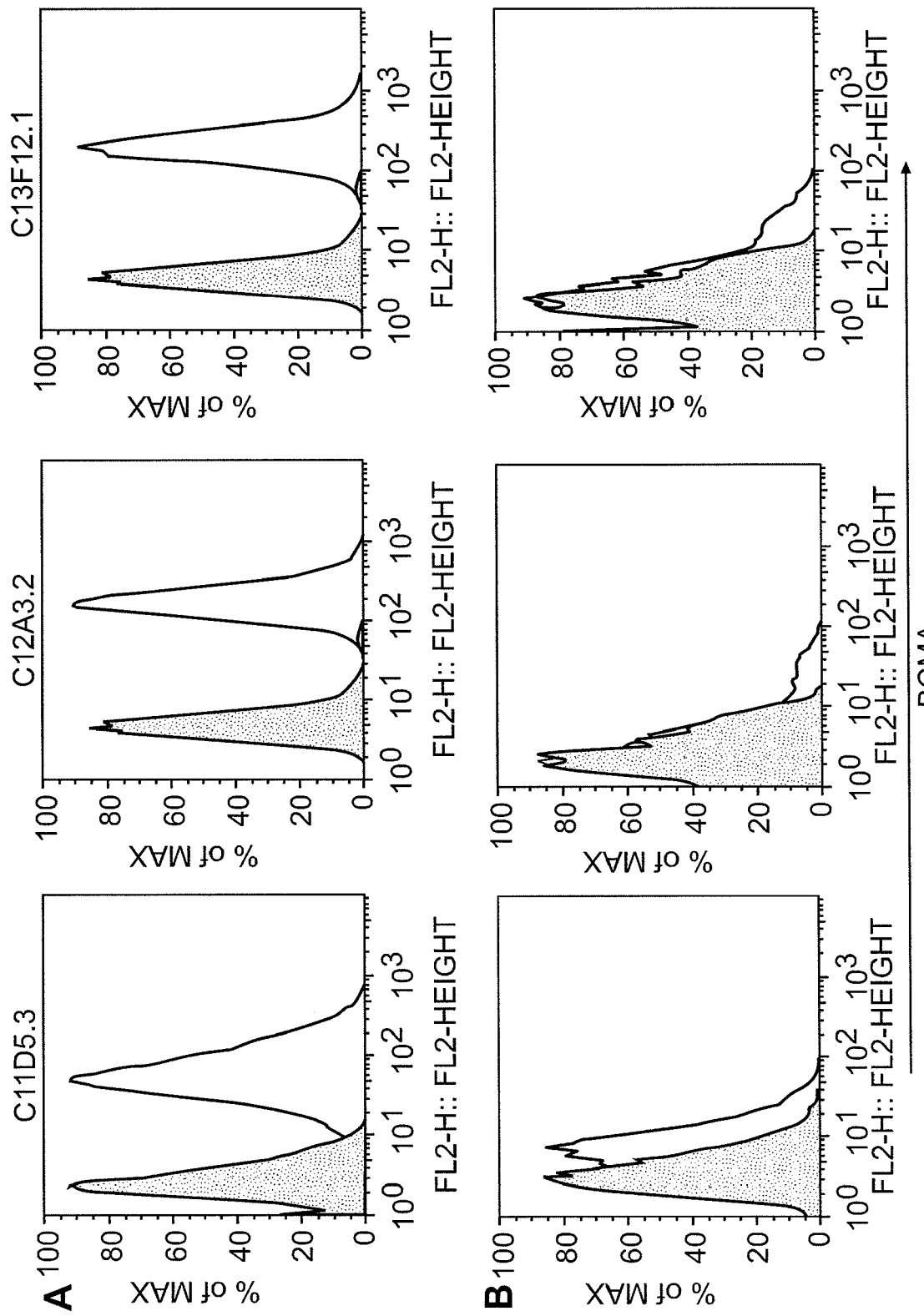


FIG. 1A

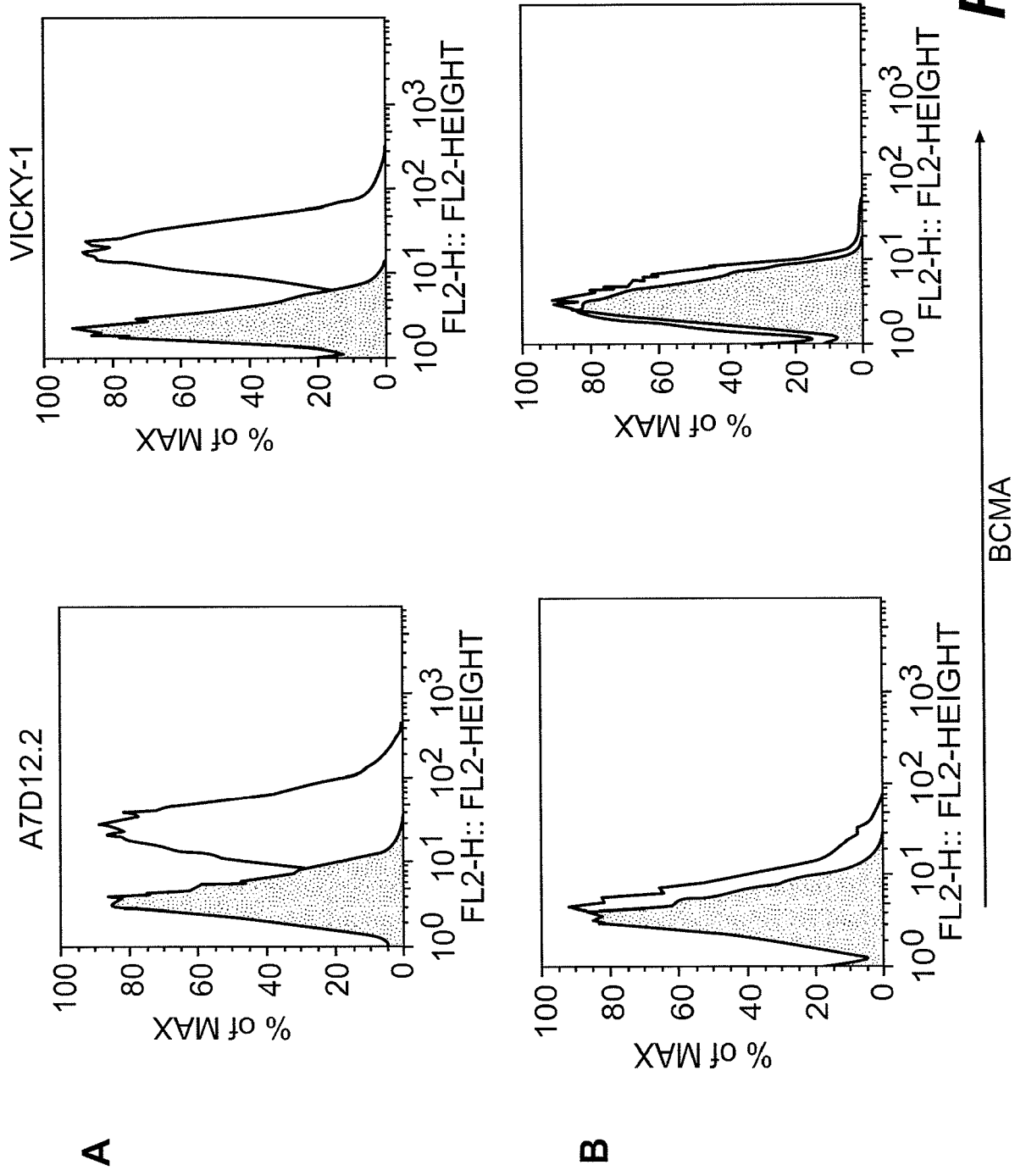


FIG. 1B

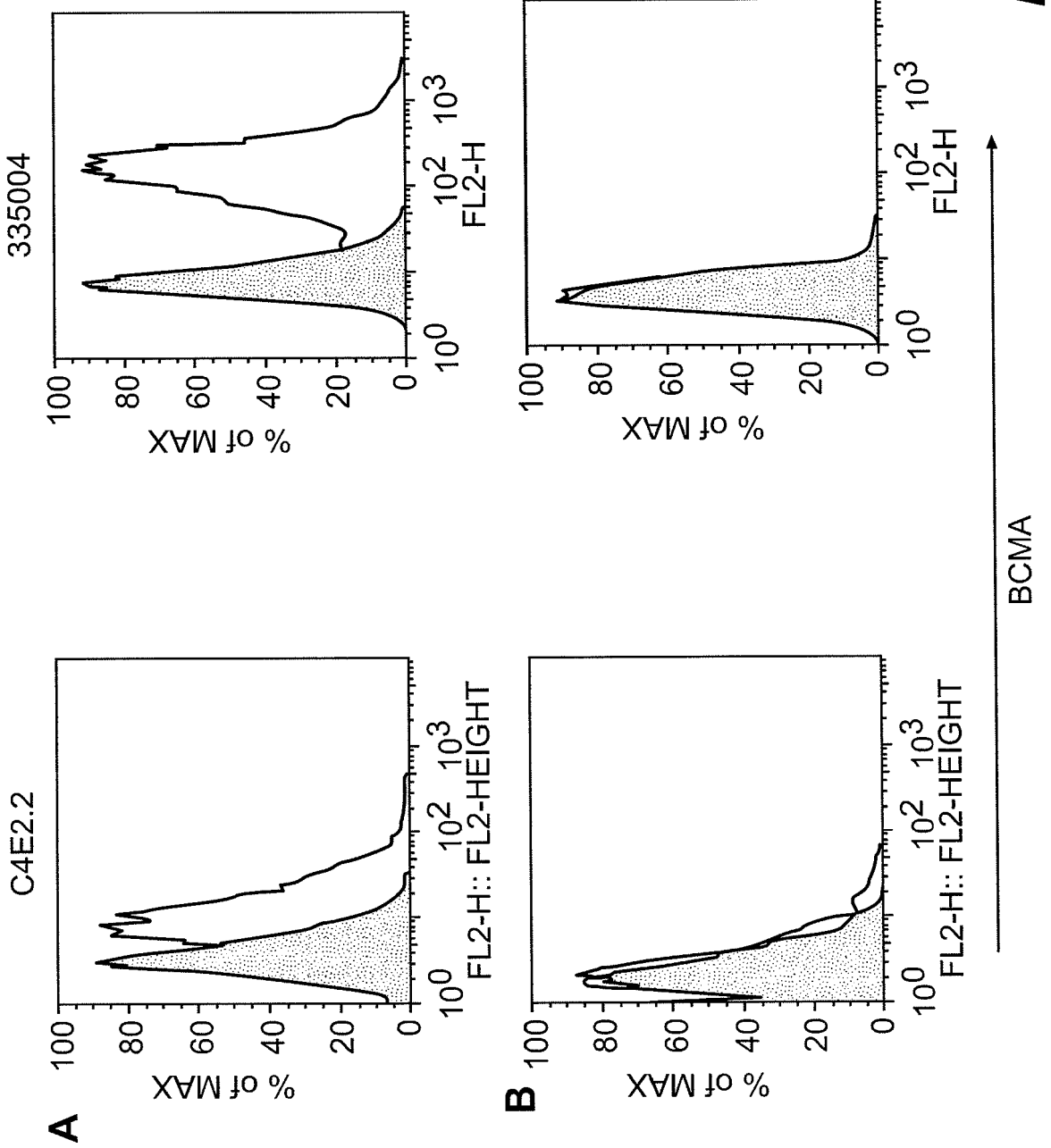


FIG. 1C

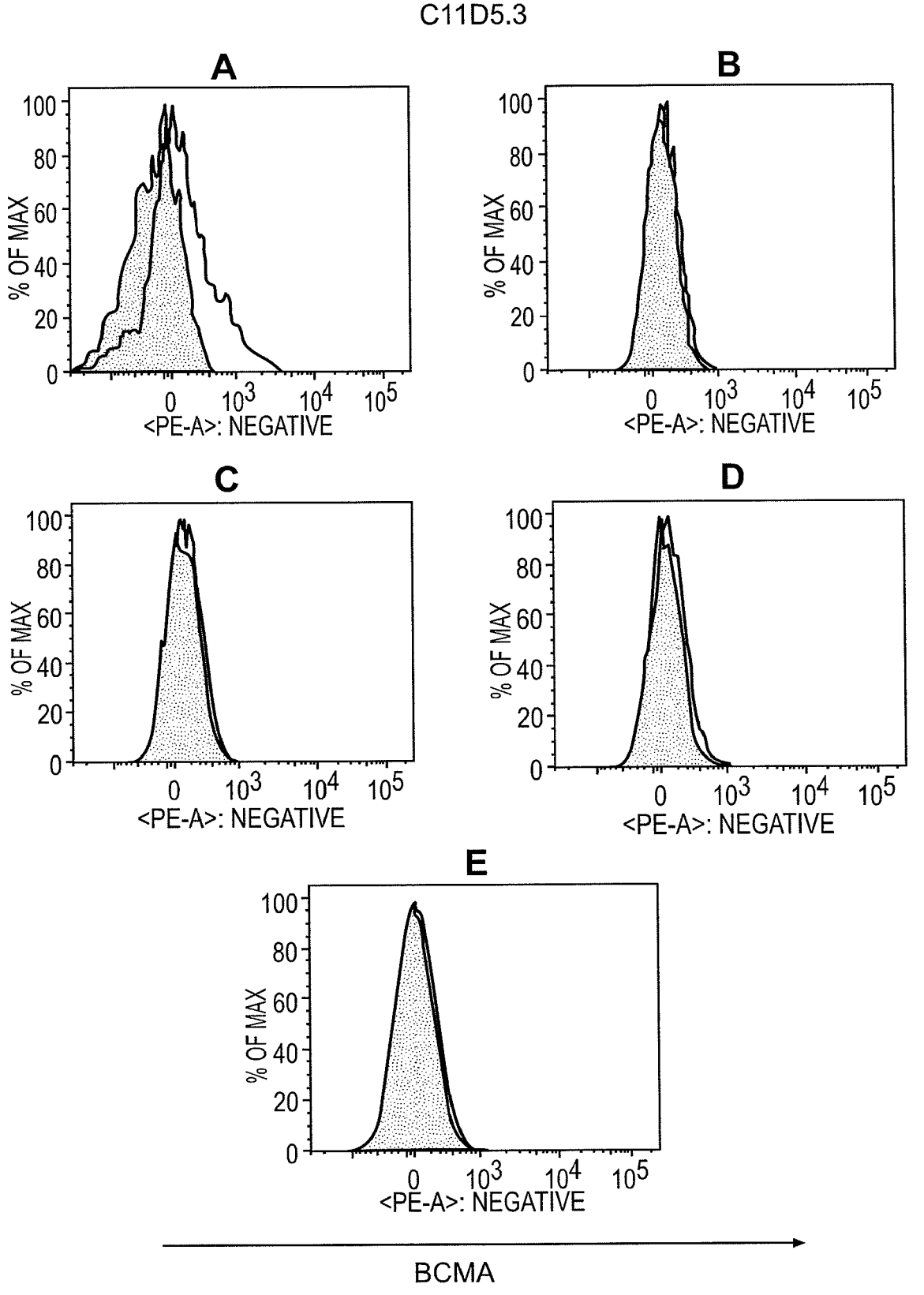


FIG. 2A

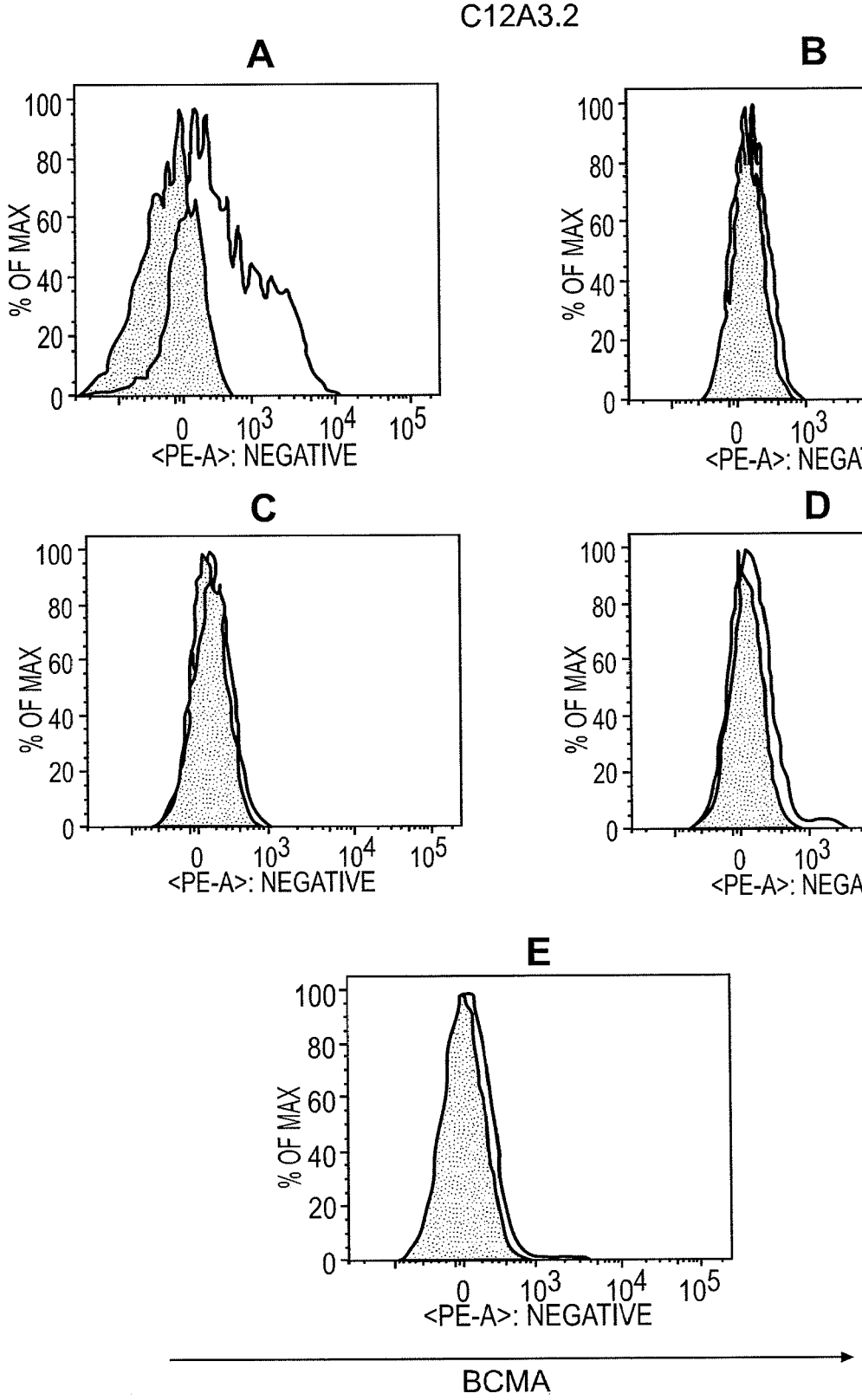


FIG. 2B

C13F12.1

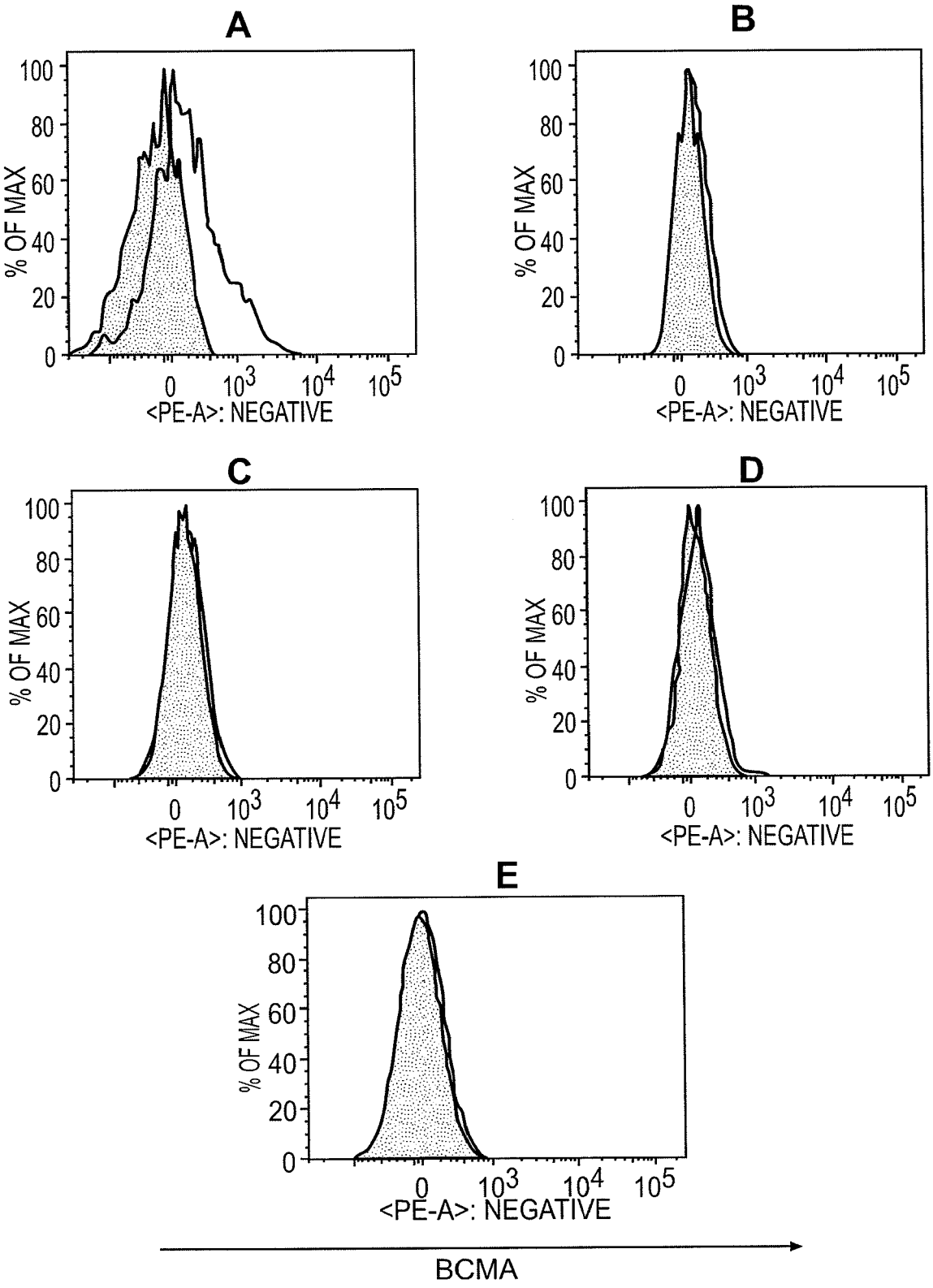
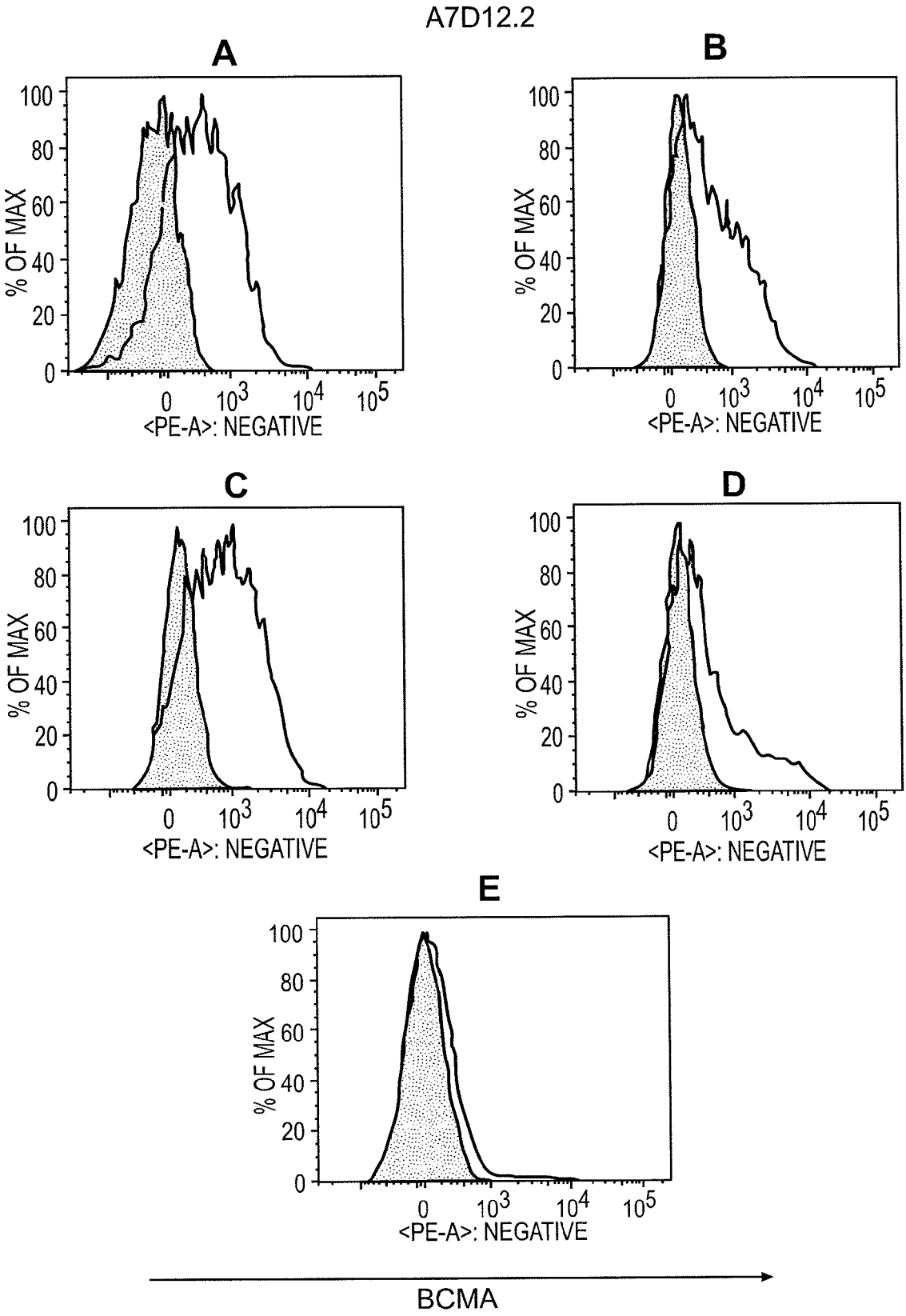


FIG. 2C


A7D12.2
A
B
C
D
E
% OF MAX
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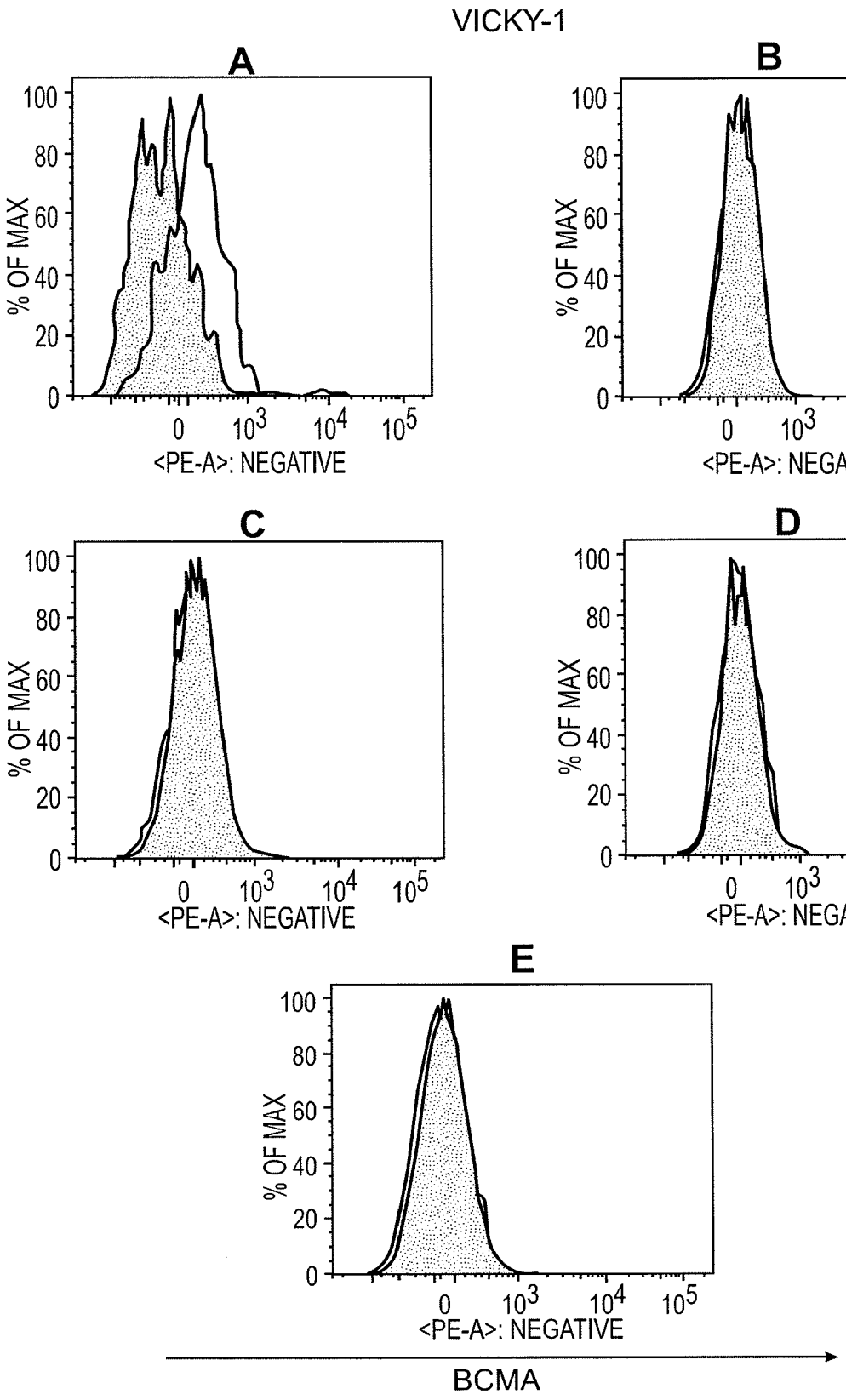
80
60
40
20
0
0
10^3
10^4
10^5
<PE-A>: NEGATIVE
BCMA

FIG. 2D


VICKY-1
A
B
C
D
E
% OF MAX
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80
60
40
20
0
0
10^3
10^4
10^5
<PE-A>: NEGATIVE
BCMA

FIG. 2E

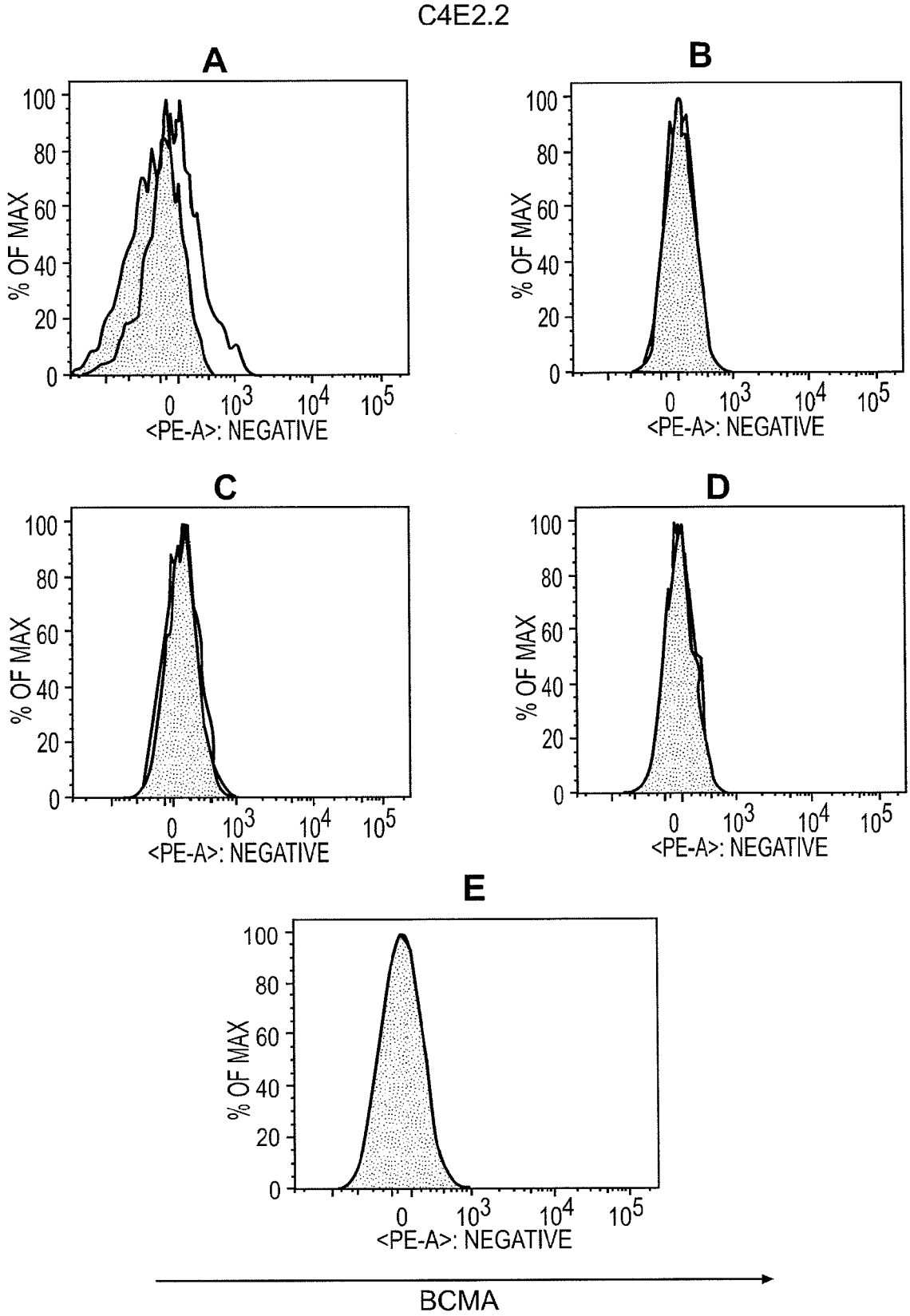

FIG. 2F

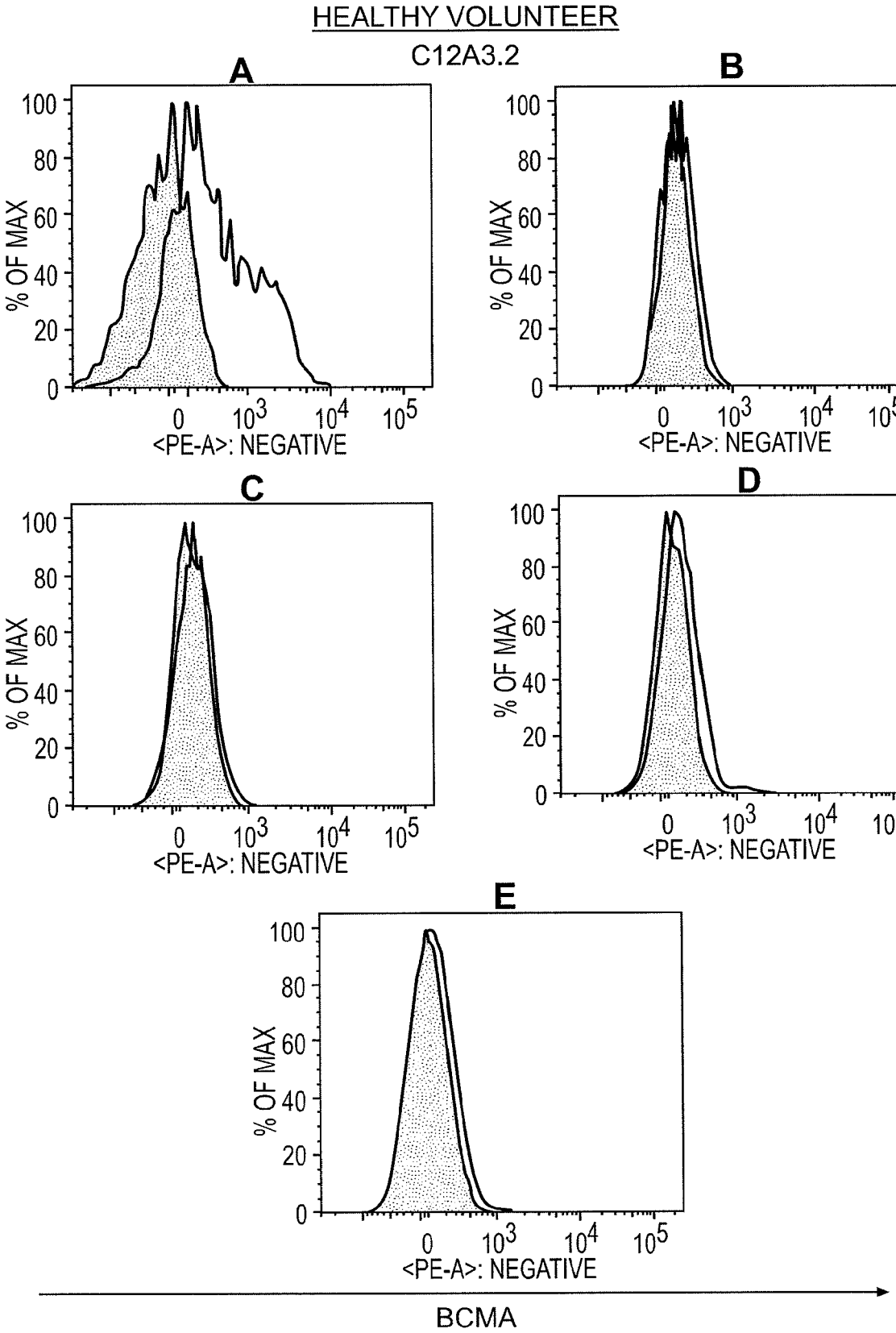

FIG. 3A

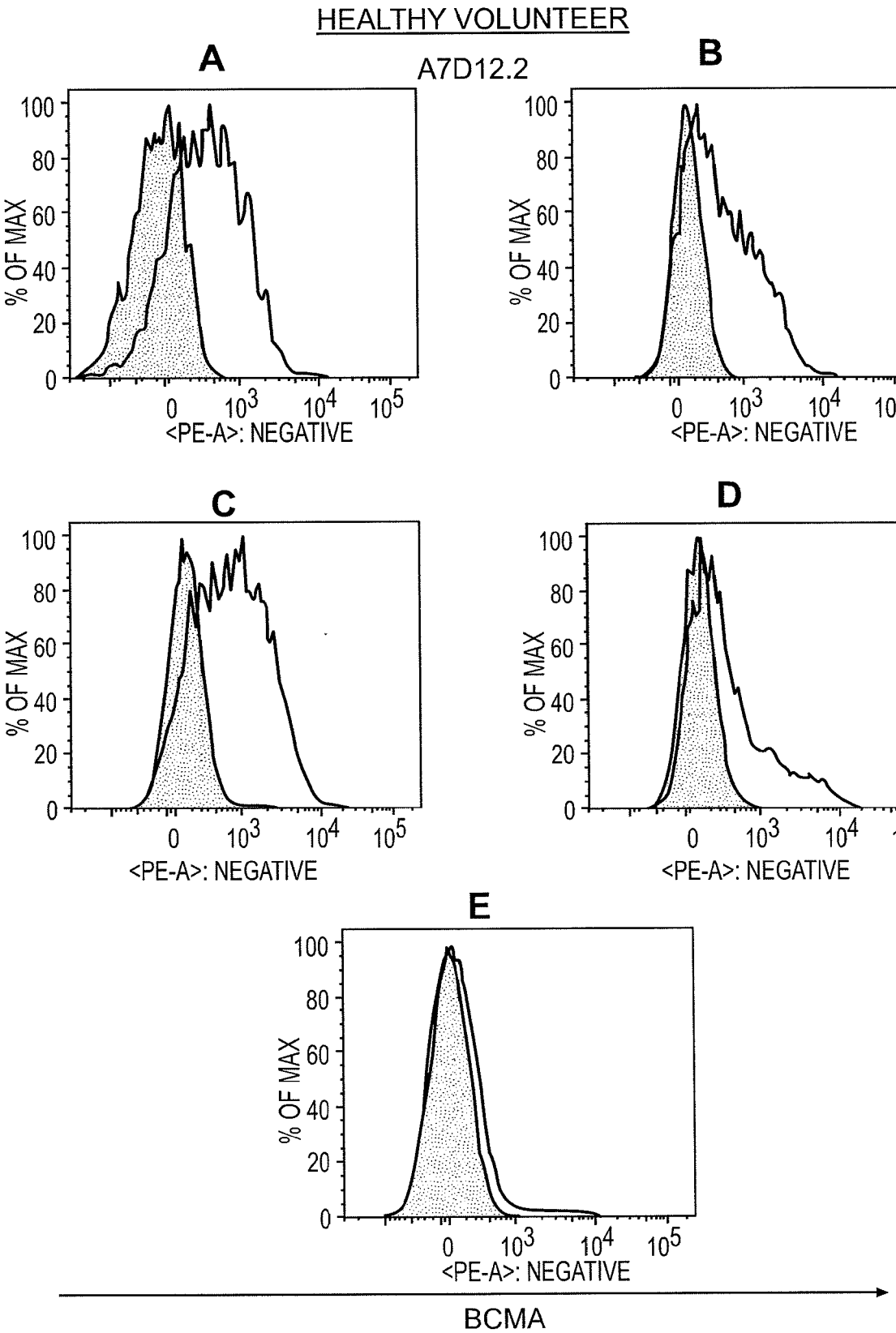

FIG. 3B

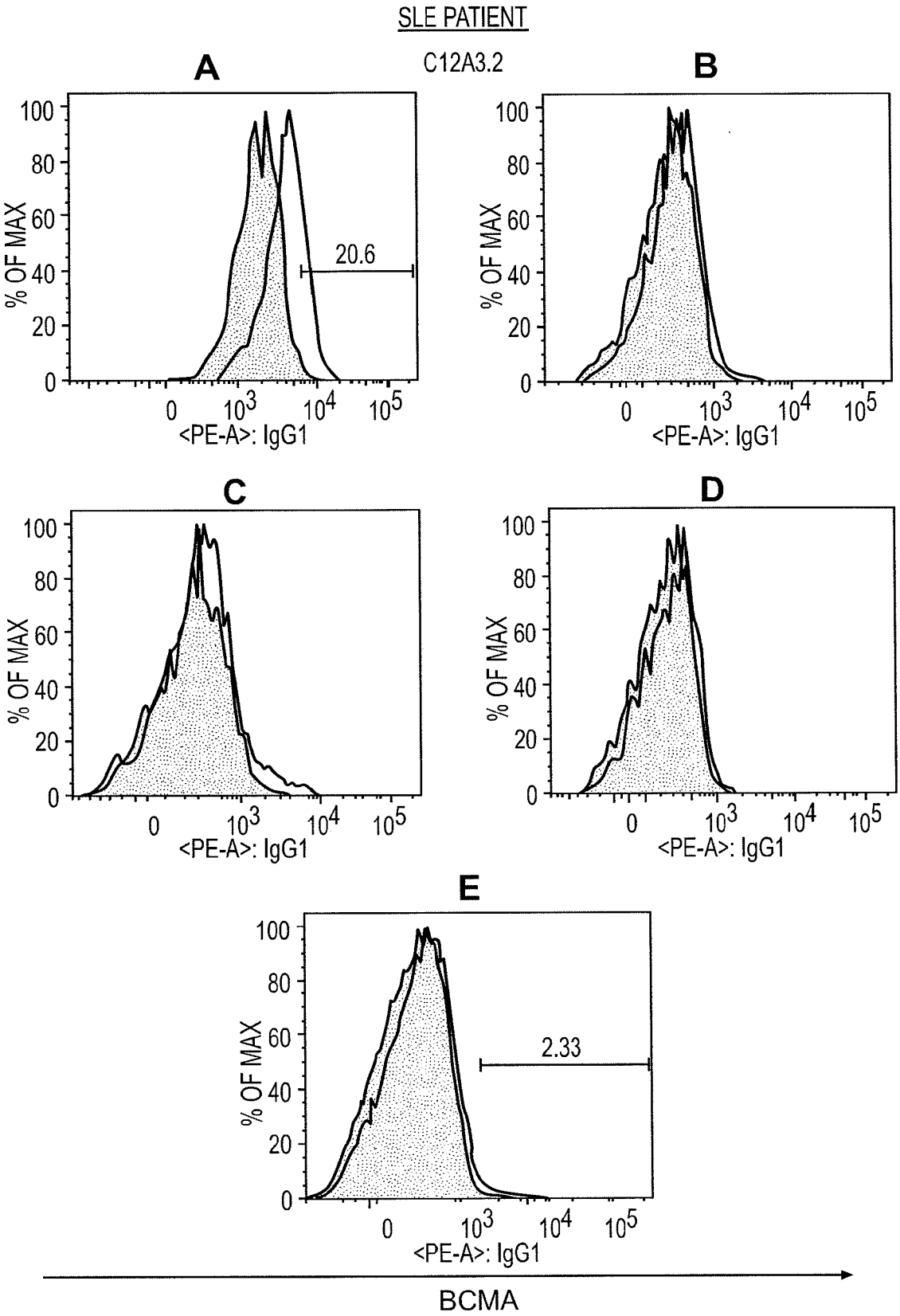

FIG. 3C

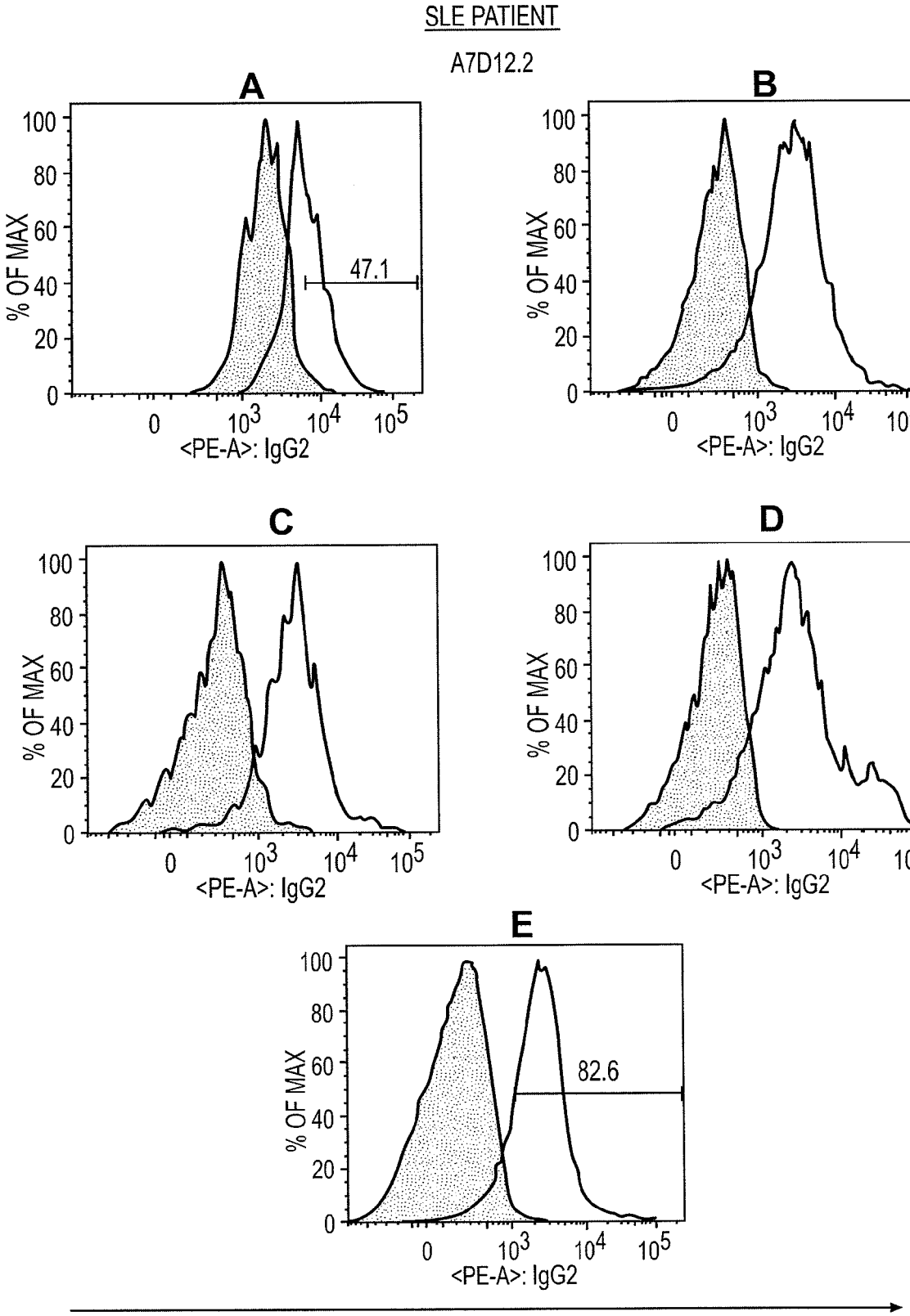

FIG. 3D

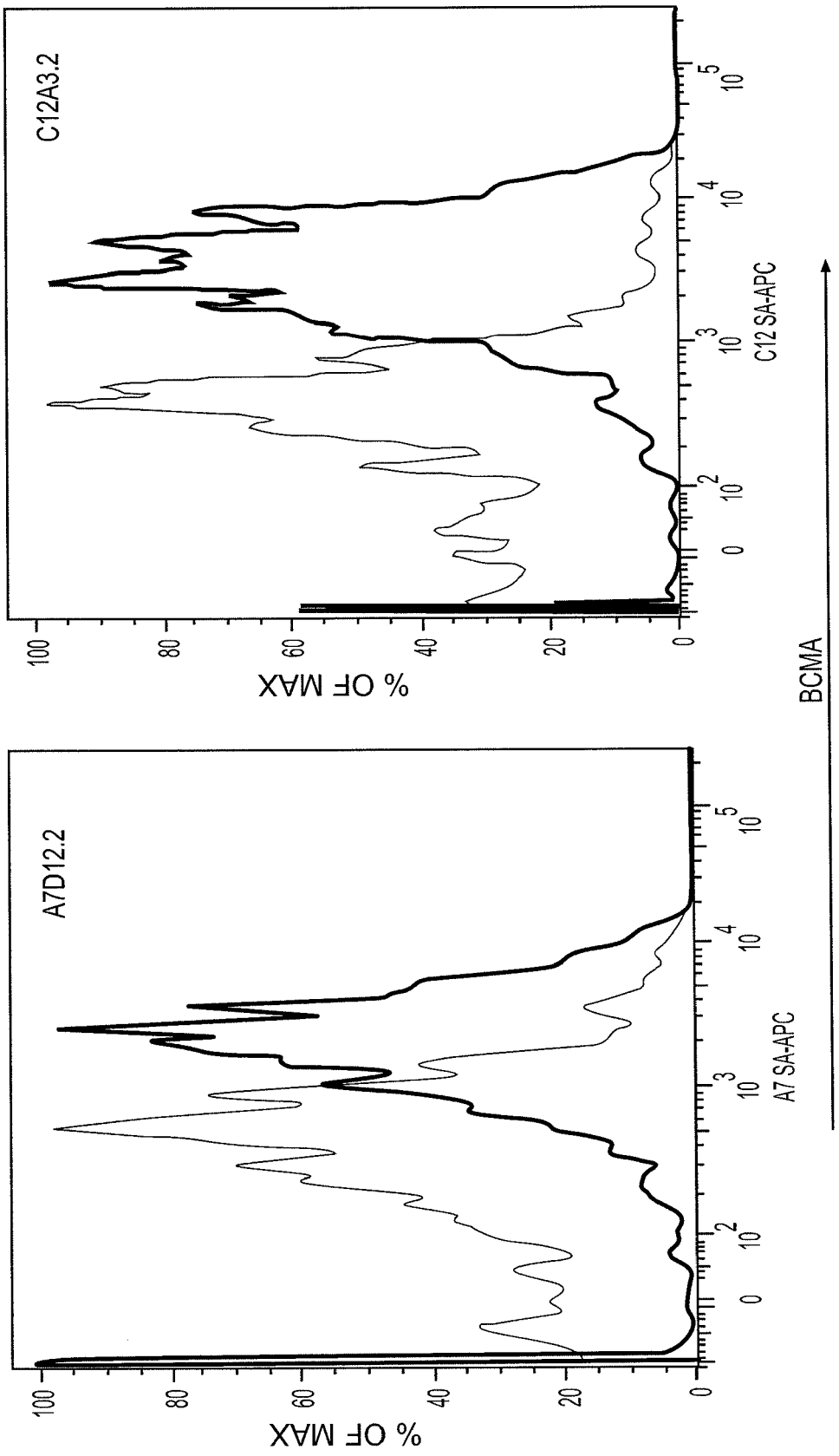

FIG. 4

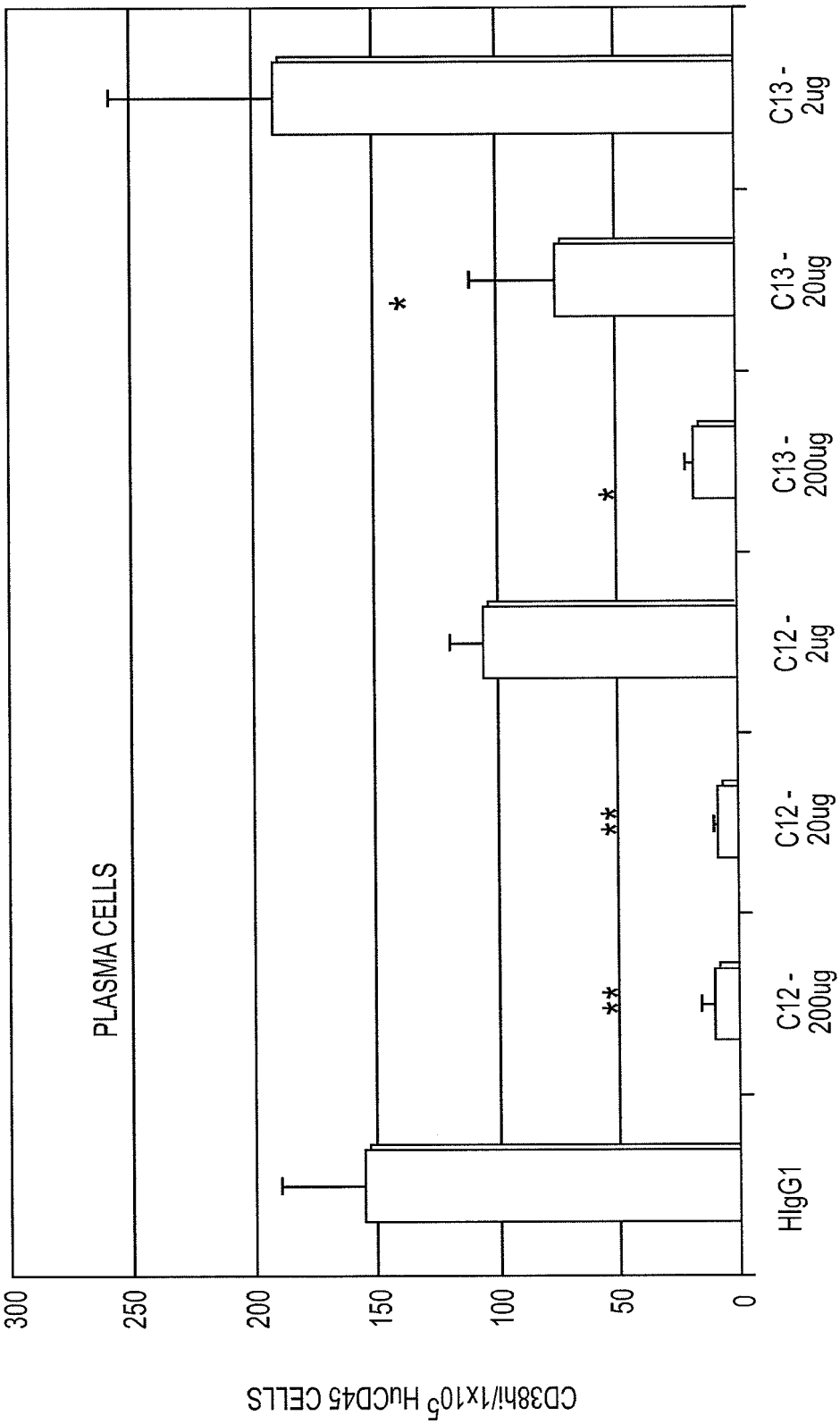
CD38hi/1x10^5 HuCD45 CELLS
300
250
200
150
100
50
0
PLASMA CELLS
HIgG1
C12 - 200ug
C12 - 20ug
C12 - 2ug
C13 - 200ug
C13 - 20ug
C13 - 2ug
**
**
*
*

FIG. 5

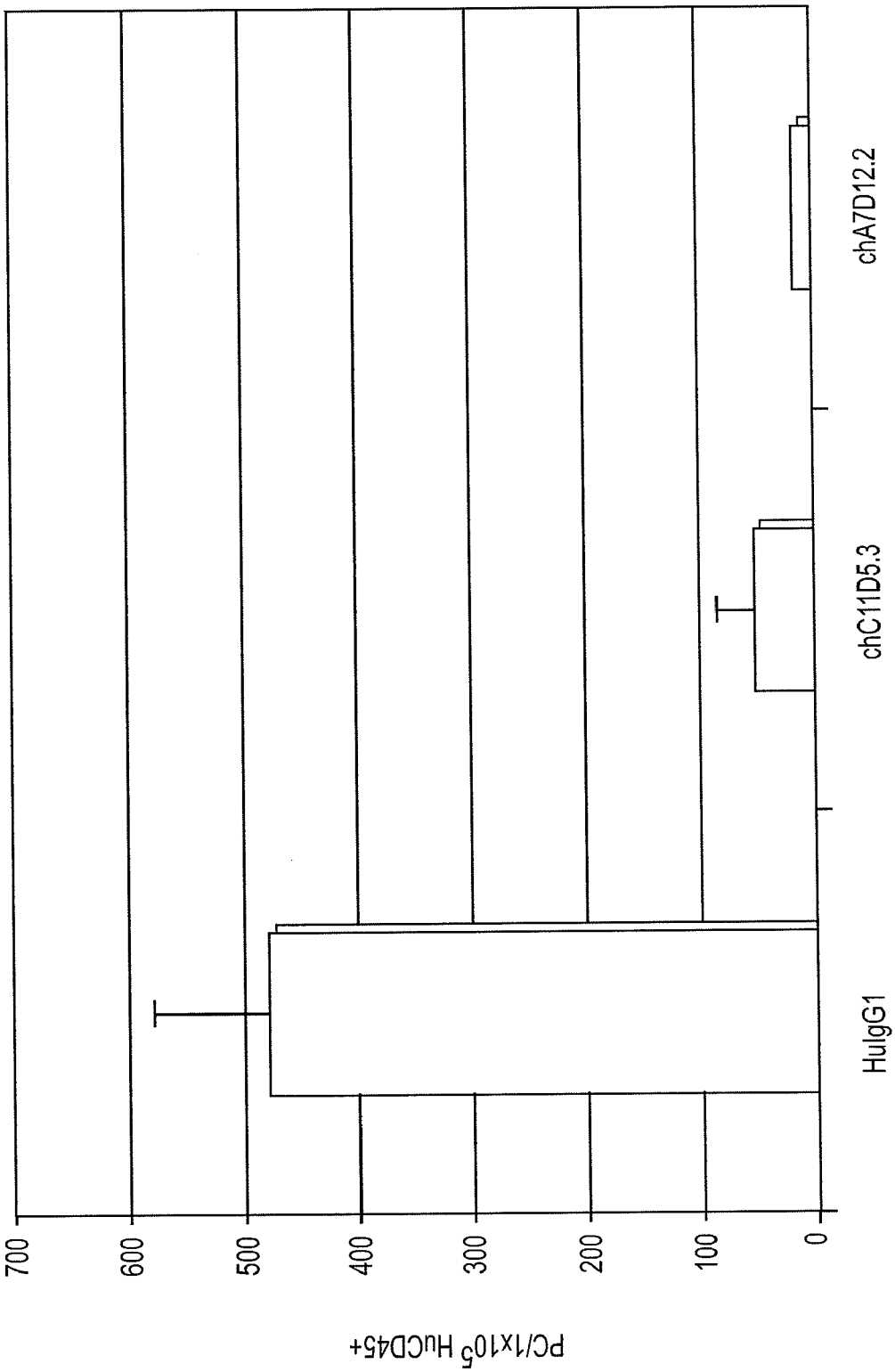
700
600
500
400
300
200
100
0
PC/1x10^5 HuCD45+
HulgG1
chC11D5.3
chA7D12.2

FIG. 6

REFERENCES CITED IN THE DESCRIPTION

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