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(54) **LEVELS OF BCMA PROTEIN EXPRESSION ON B CELLS AND USE IN METHODS OF TREATING SYSTEMIC LUPUS ERYTHEMATOSUS**

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C07K 14/705 (2006.01)
C07K 16/24 (2006.01)
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G01N 33/564 (2006.01)

(52) **U.S. Cl.**

CPC **C07K 16/24** (2013.01); **C07K 14/70578** (2013.01); **G01N 33/5091** (2013.01); **G01N 33/564** (2013.01); **G01N 2333/70575** (2013.01); **G01N 2800/042** (2013.01); **G01N 2800/065** (2013.01); **G01N 2800/101** (2013.01); **G01N 2800/102** (2013.01); **G01N 2800/104** (2013.01); **G01N 2800/24** (2013.01); **G01N 2800/285** (2013.01); **G01N 2800/347** (2013.01)

(58) **Field of Classification Search**

CPC **C07K 14/70578**; **G01N 33/5091**; **G01N 33/564**; **G01N 2333/70575**; **G01N 2800/104**

See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a method of measuring the levels of BCMA in a biological sample, specifically upon the B cell surface. The diagnostic assays are useful in predicting an individual’s likelihood of developing or currently suffering from an autoimmune disease, such as SLE, and for methods for treating an individual clinically diagnosed with an autoimmune disease. This diagnostic test serves to predict a patient’s likelihood to respond to a specific drug treatment, in particular treatment with BLyS antagonists, either singly or in combination with other immune suppressive drugs.

6 Claims, 20 Drawing Sheets

Specification includes a Sequence Listing.

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FIGURE 1A

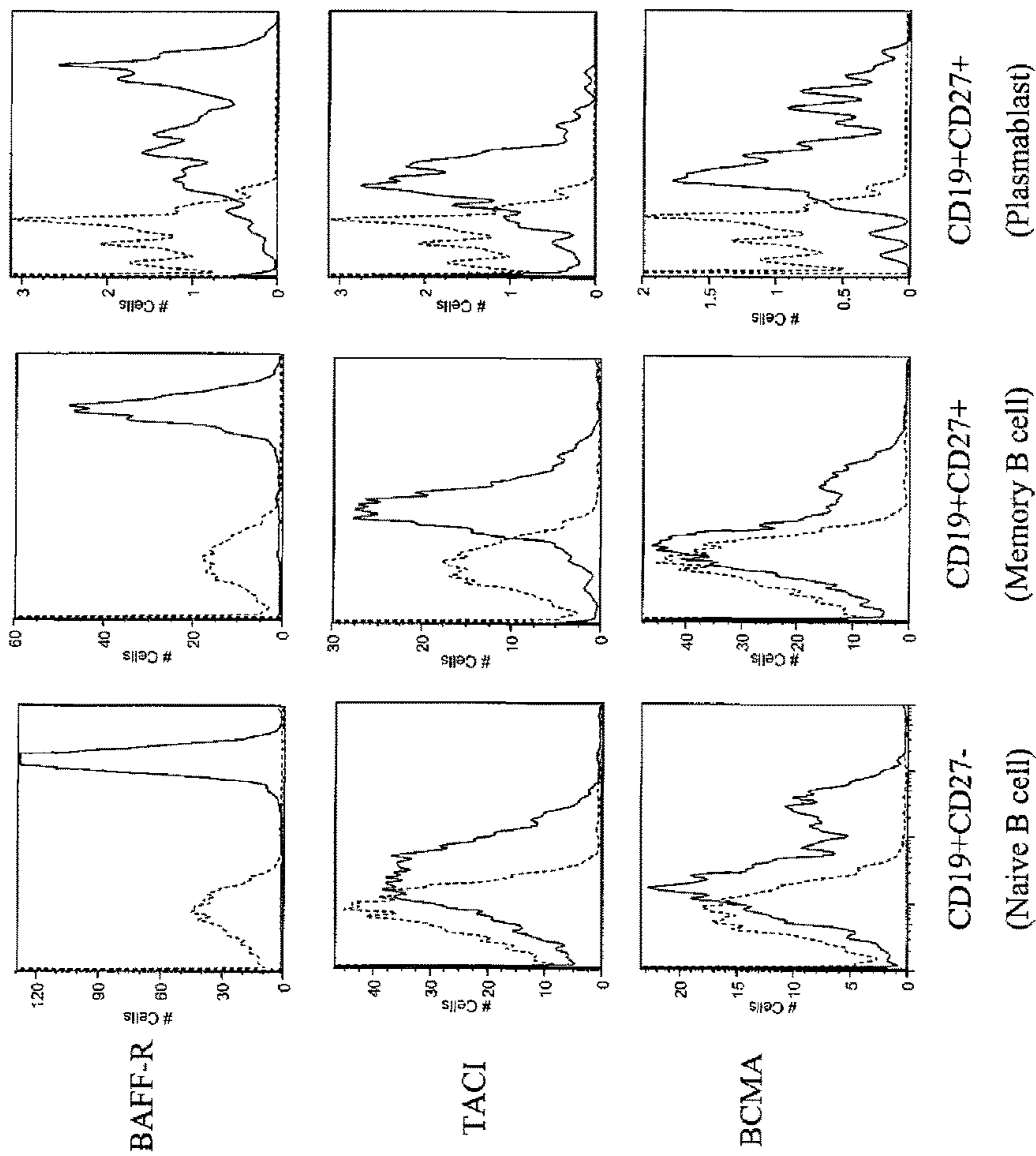


FIGURE 1B

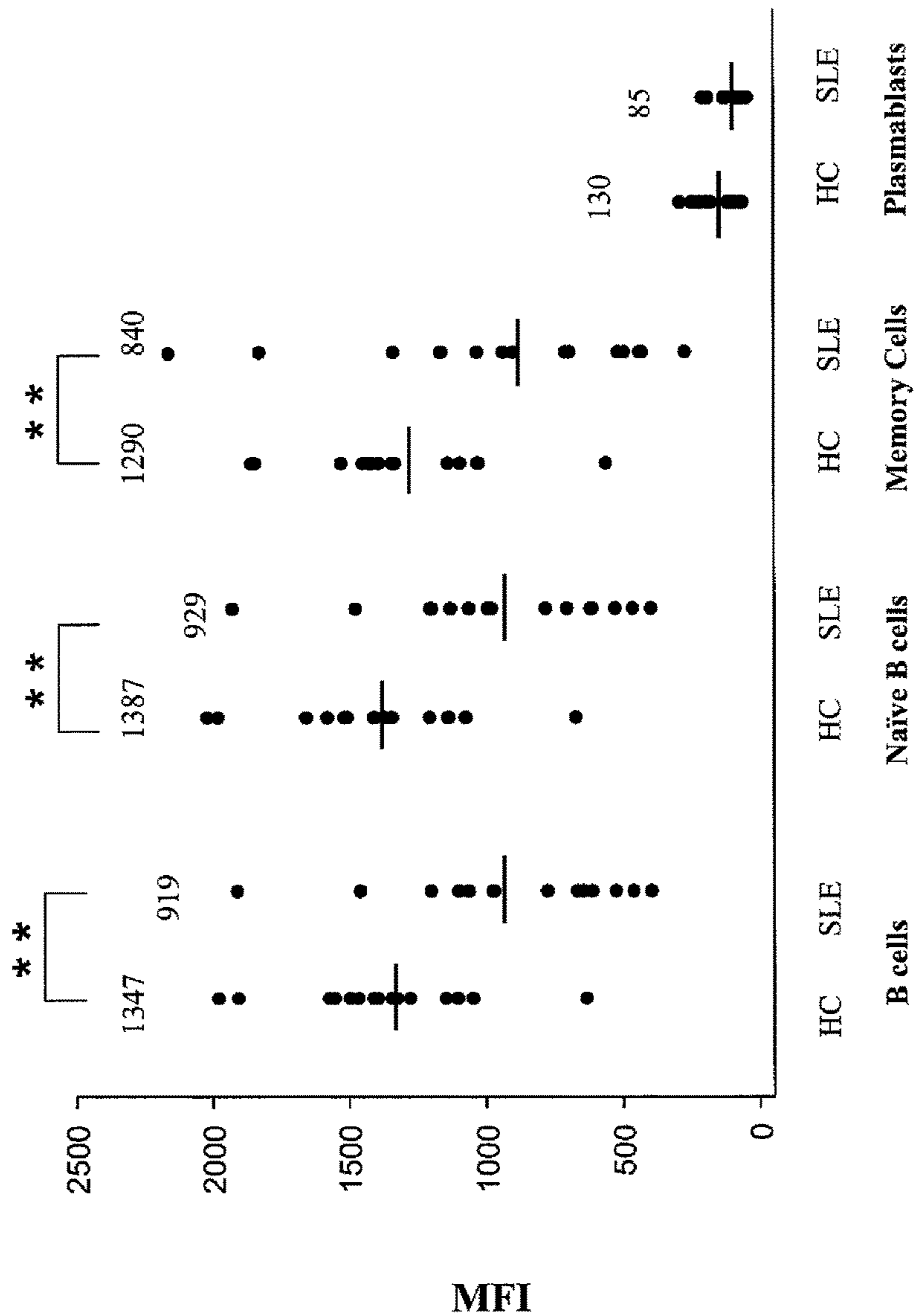


FIGURE 1C

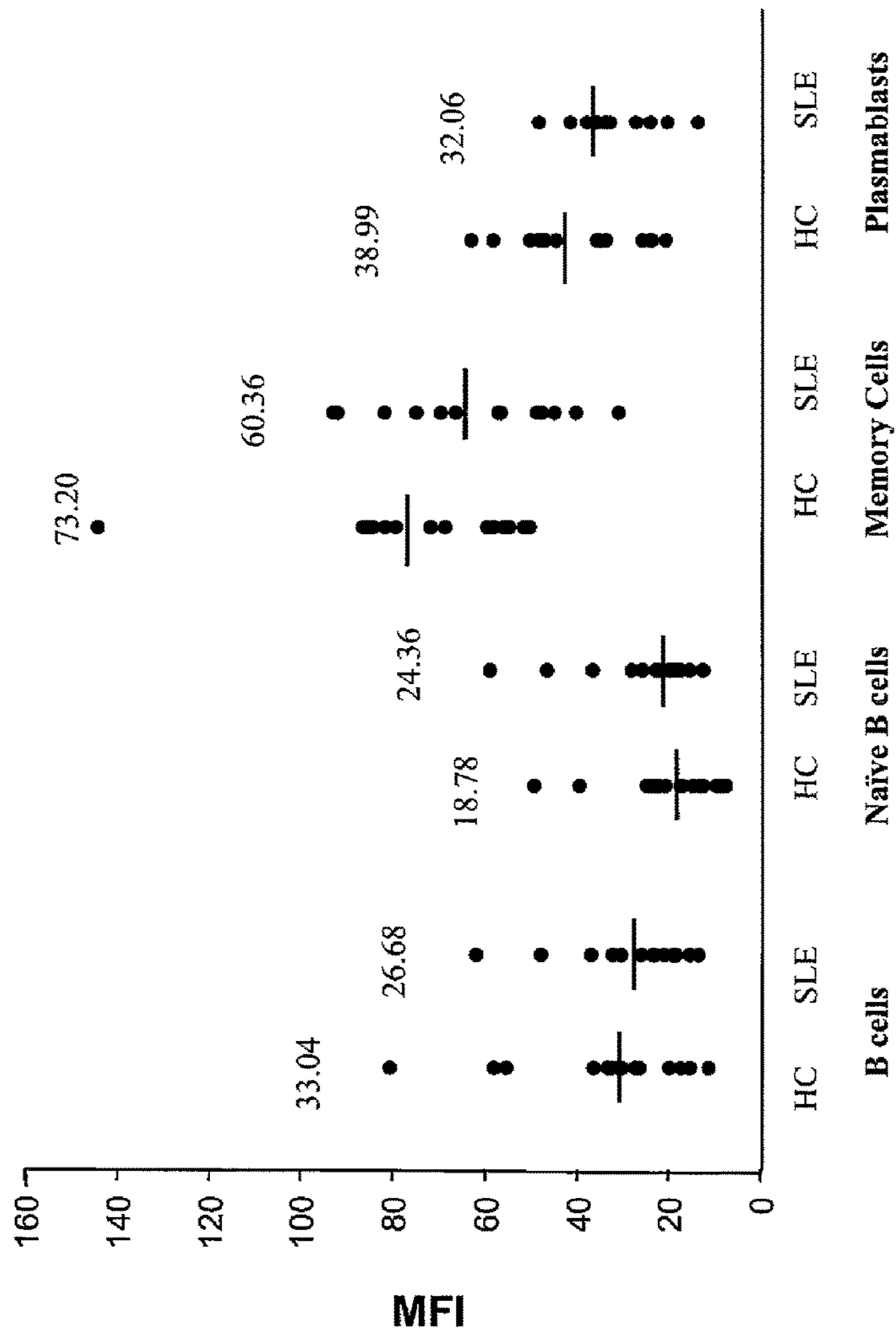


FIGURE 1D

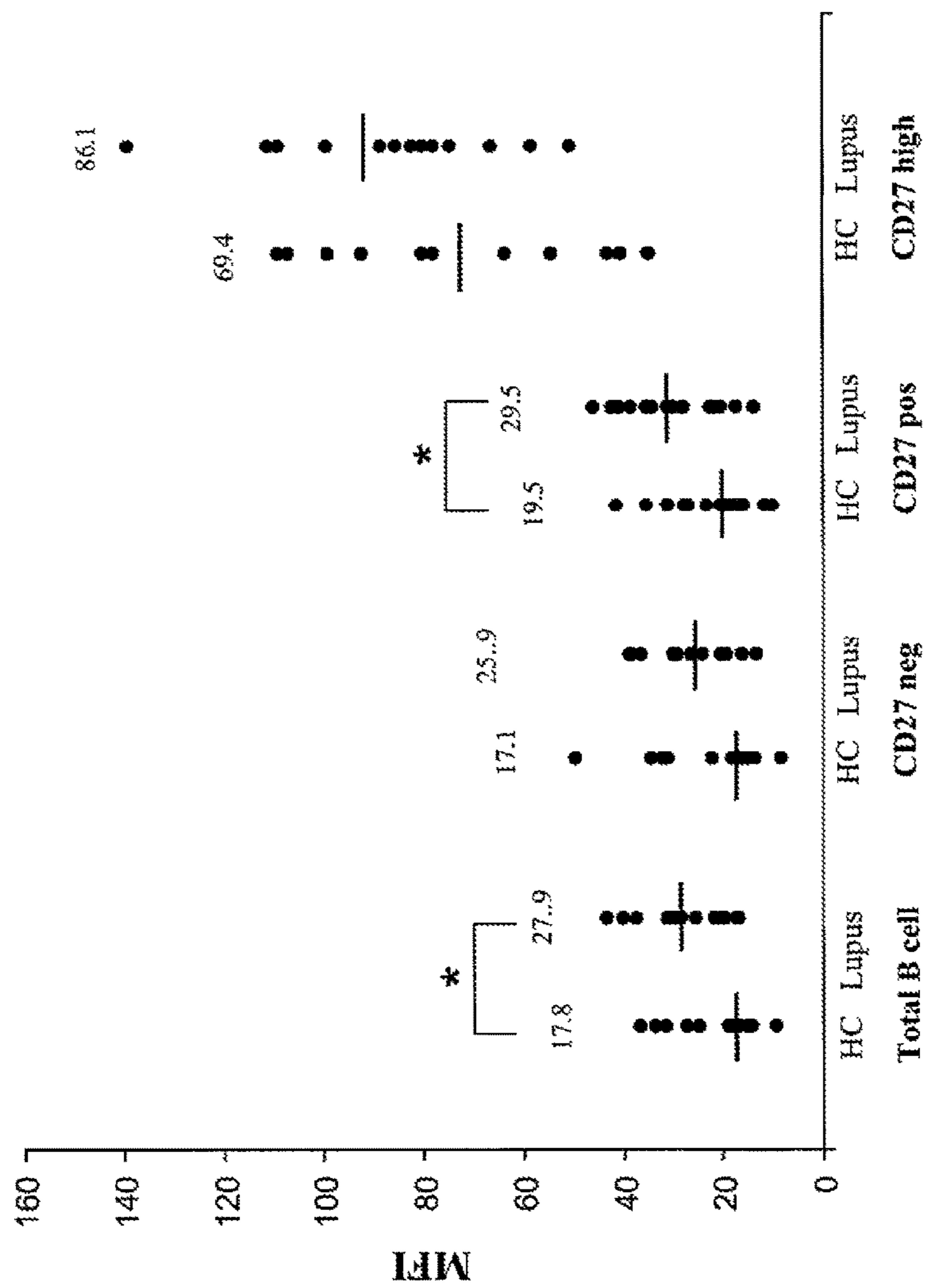


FIGURE 2

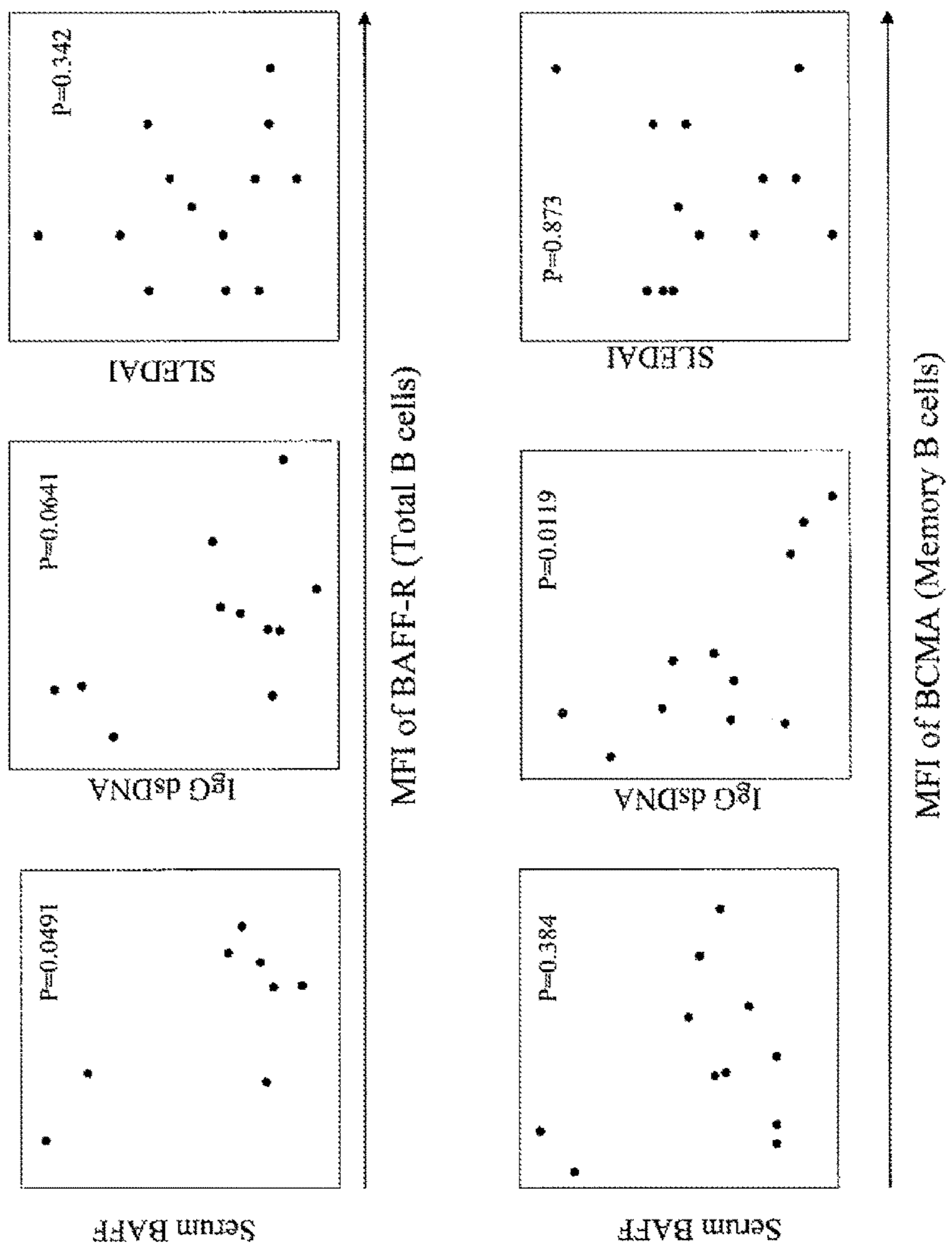


FIGURE 3A

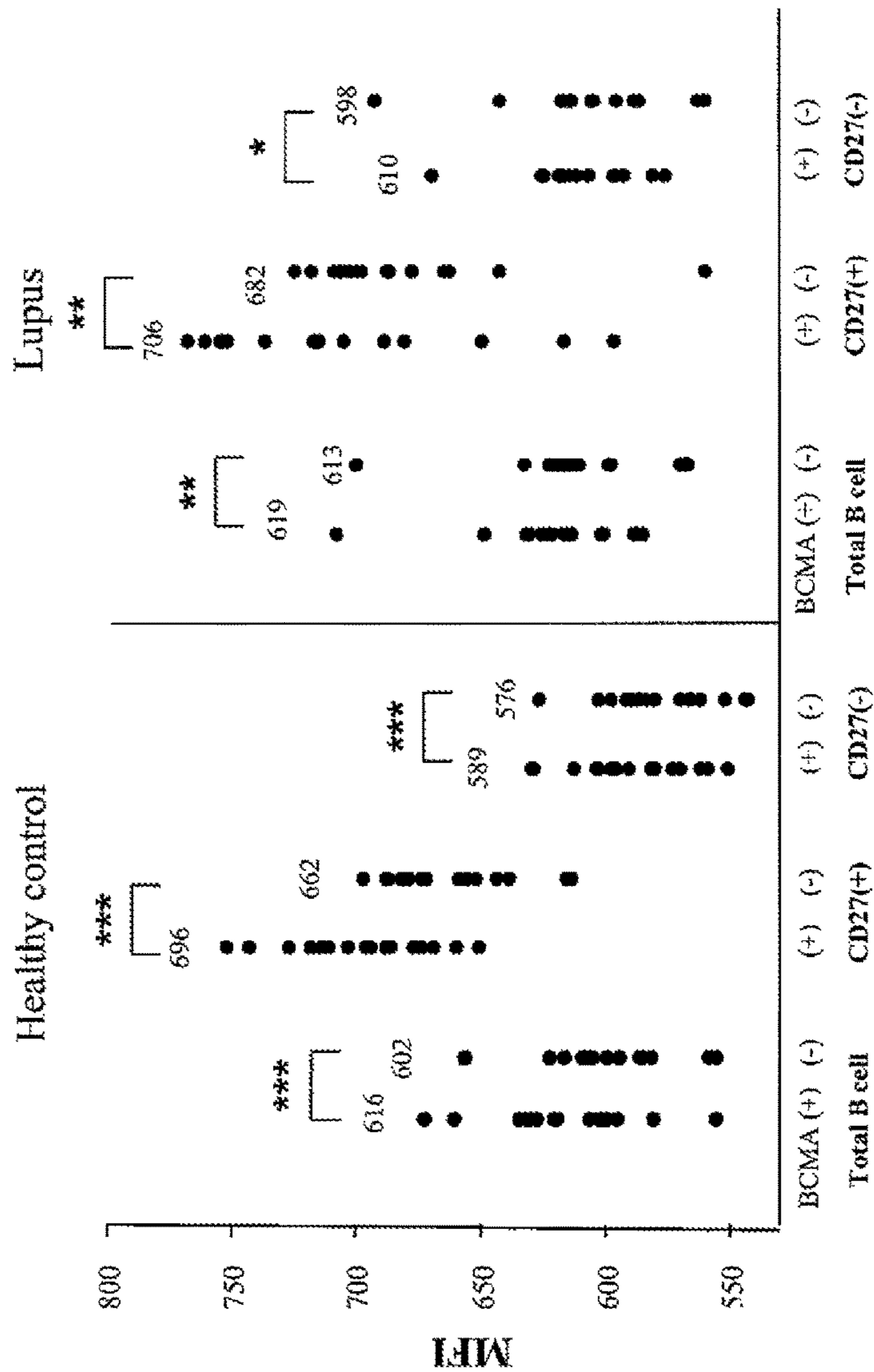


FIGURE 3B

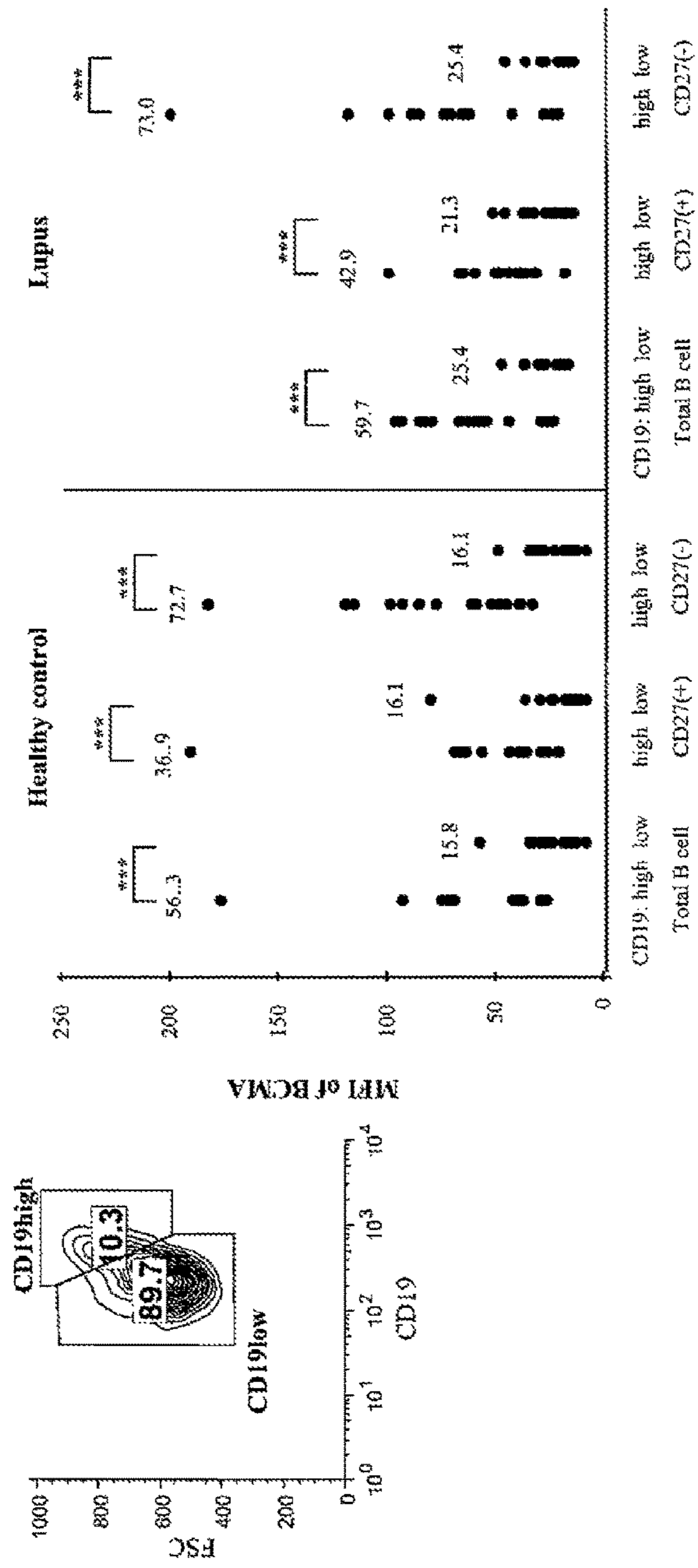


FIGURE 4A

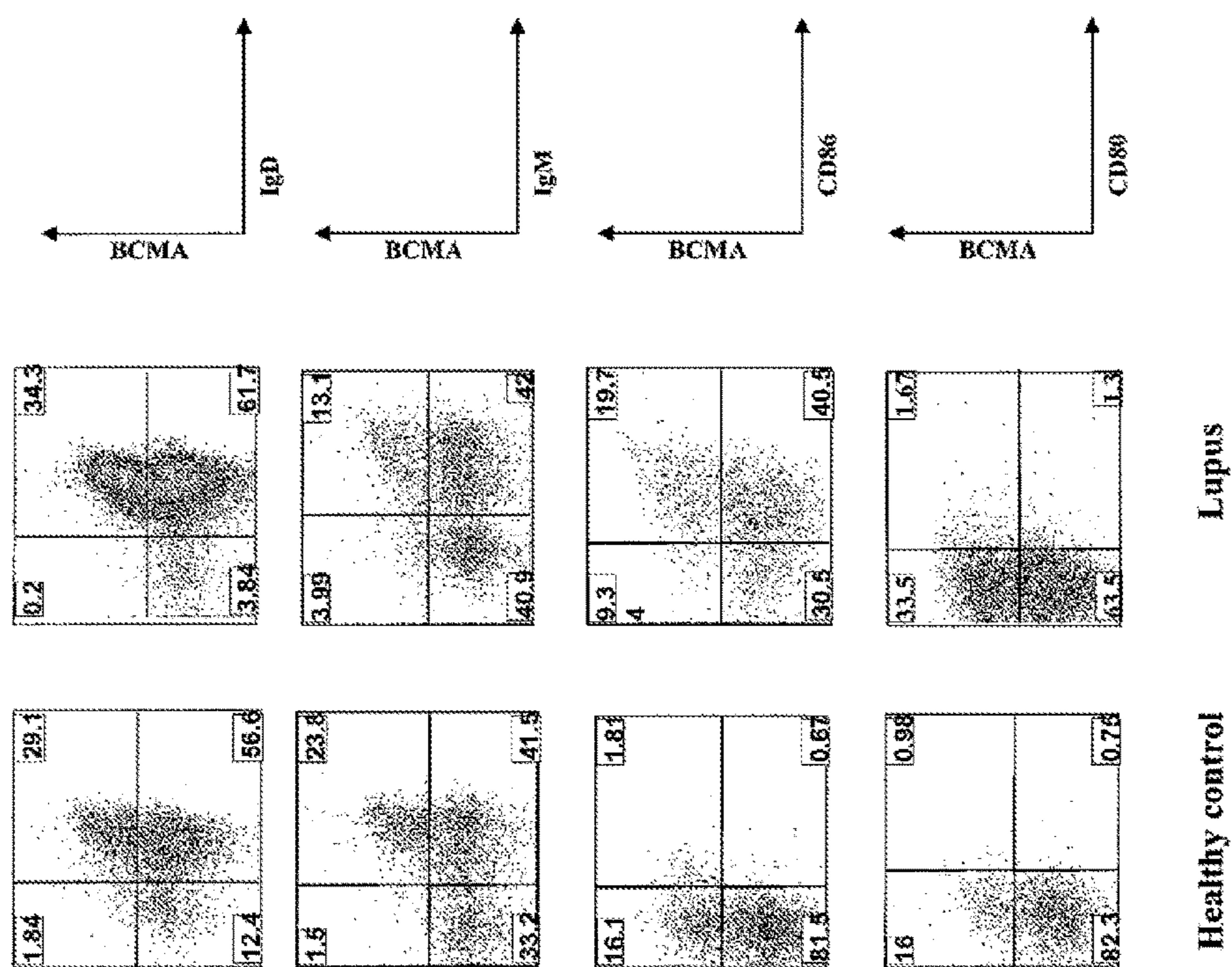


FIGURE 4B

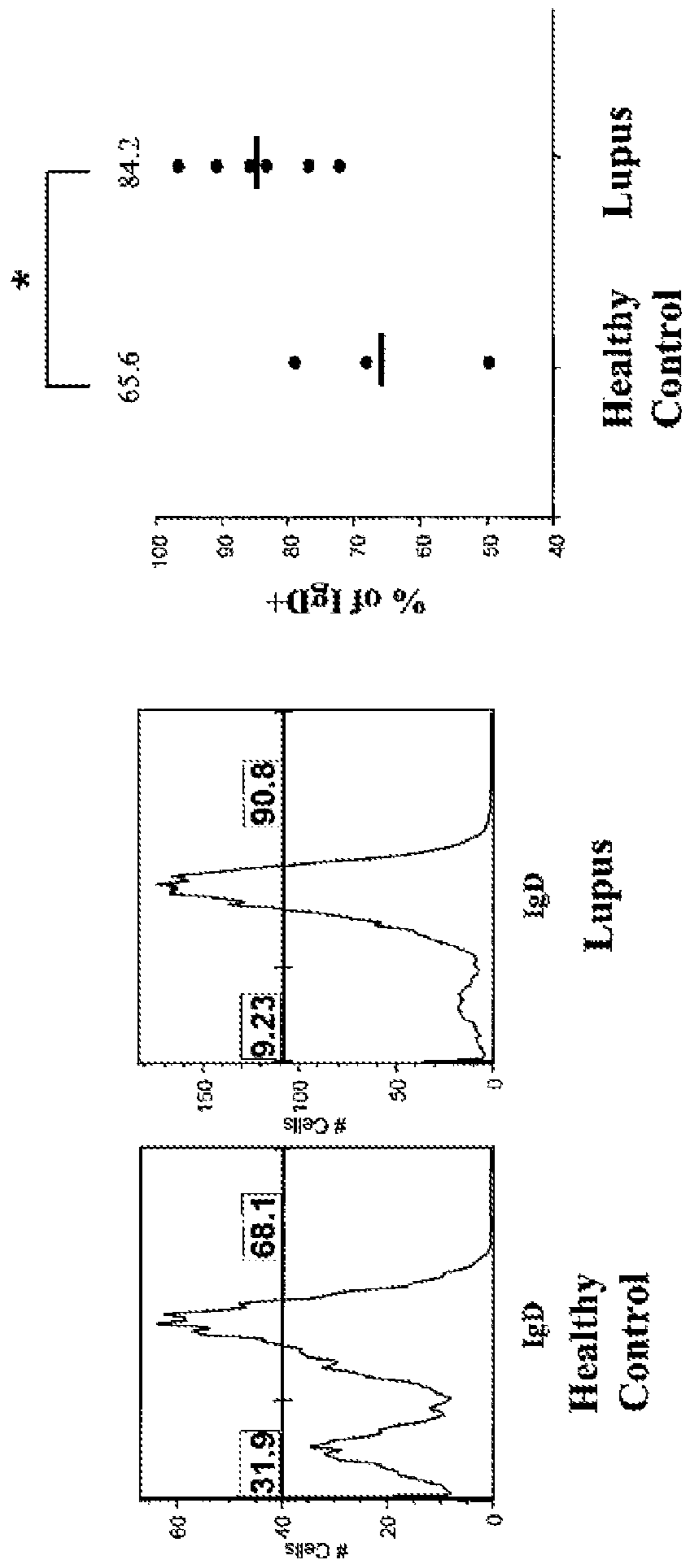


FIGURE 5A

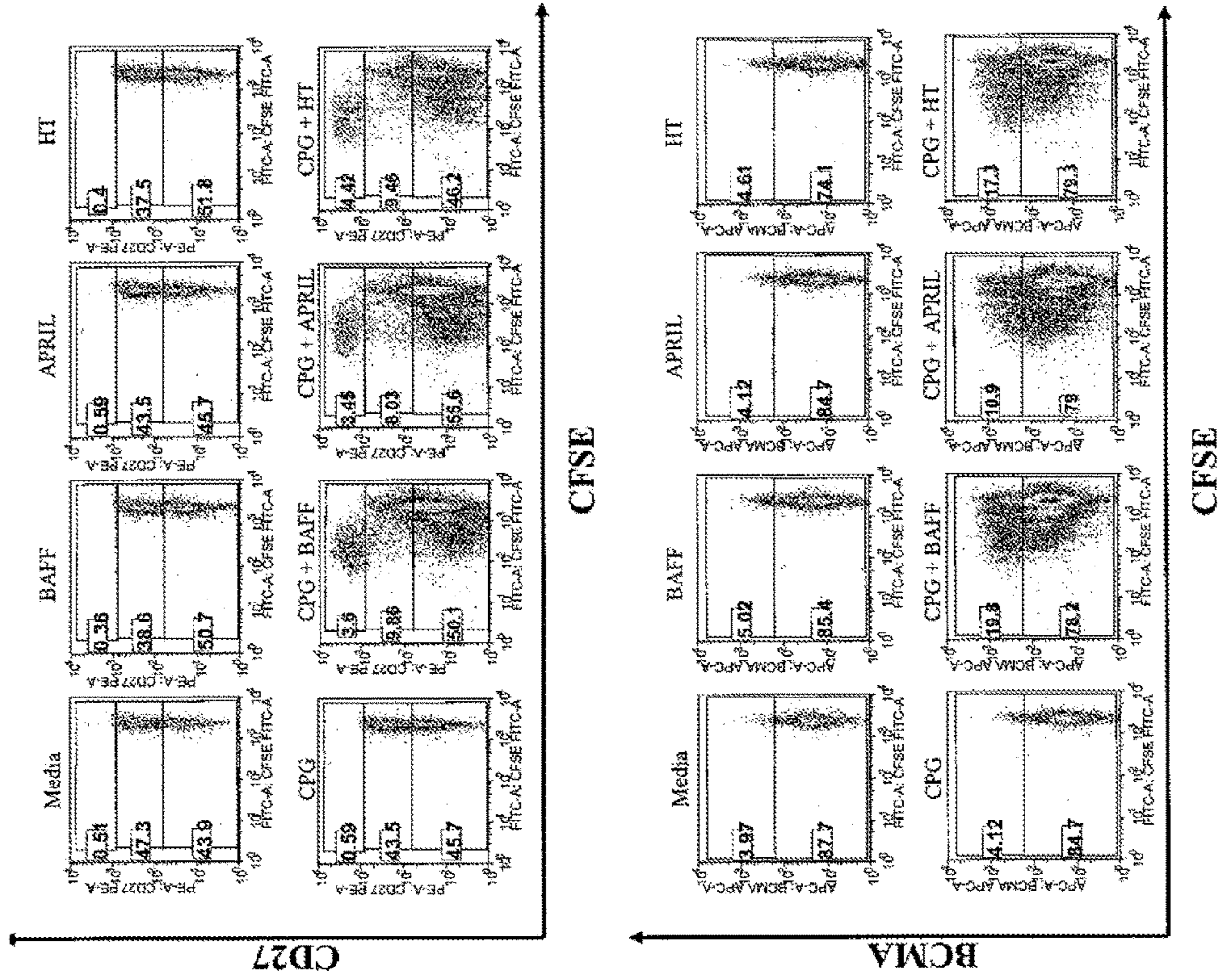


FIGURE 5B

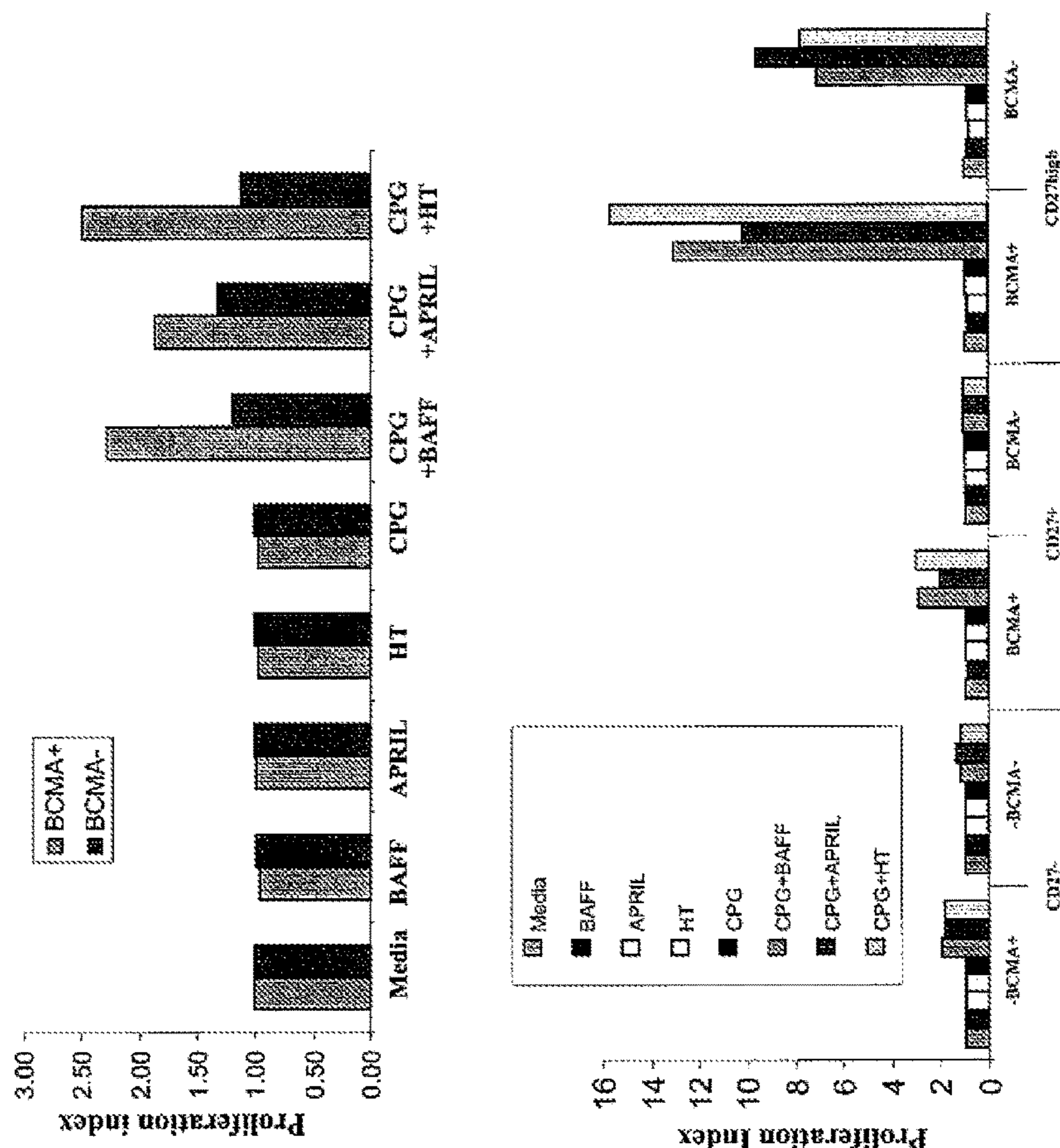


FIGURE 5C

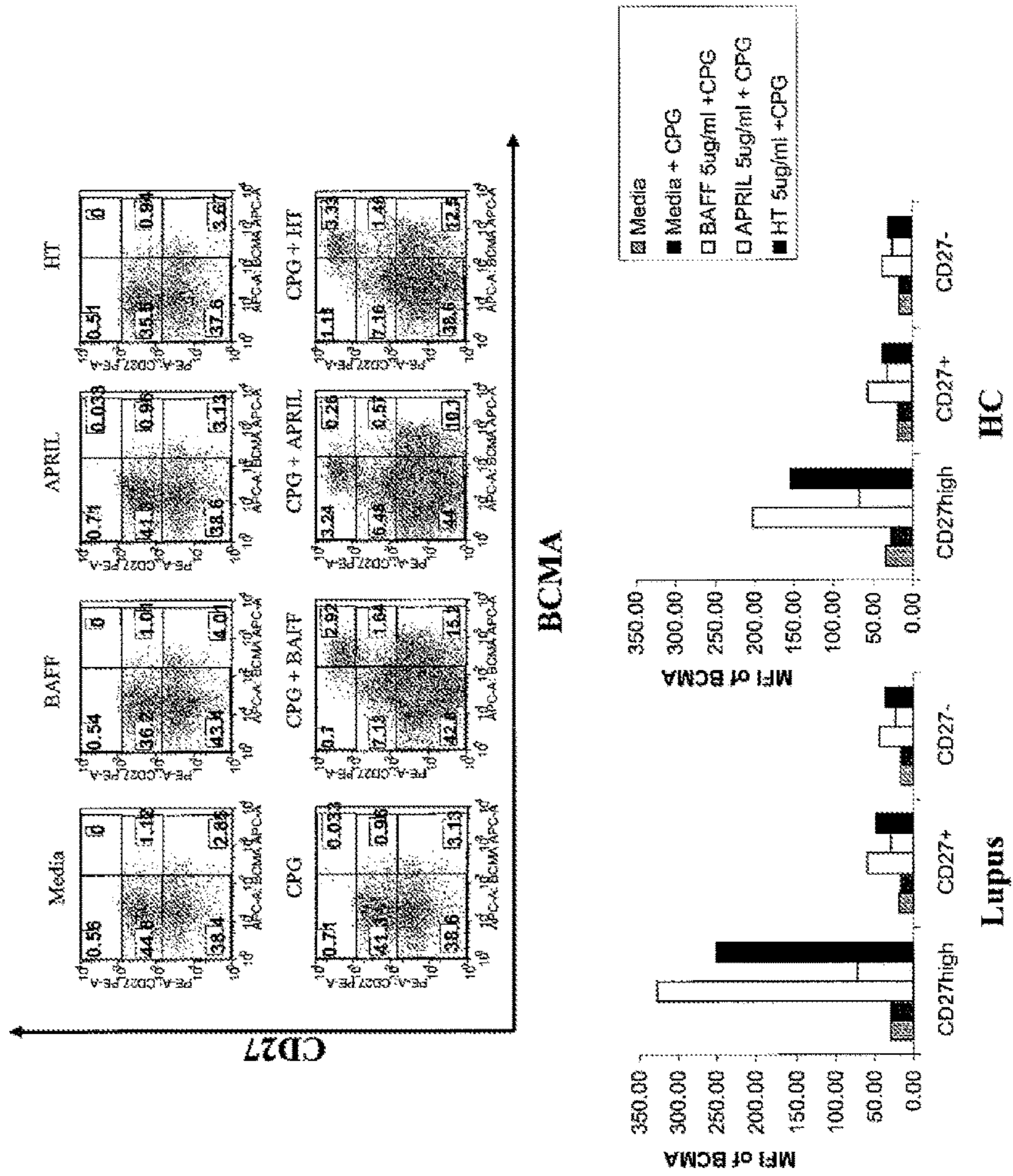


FIGURE 5D

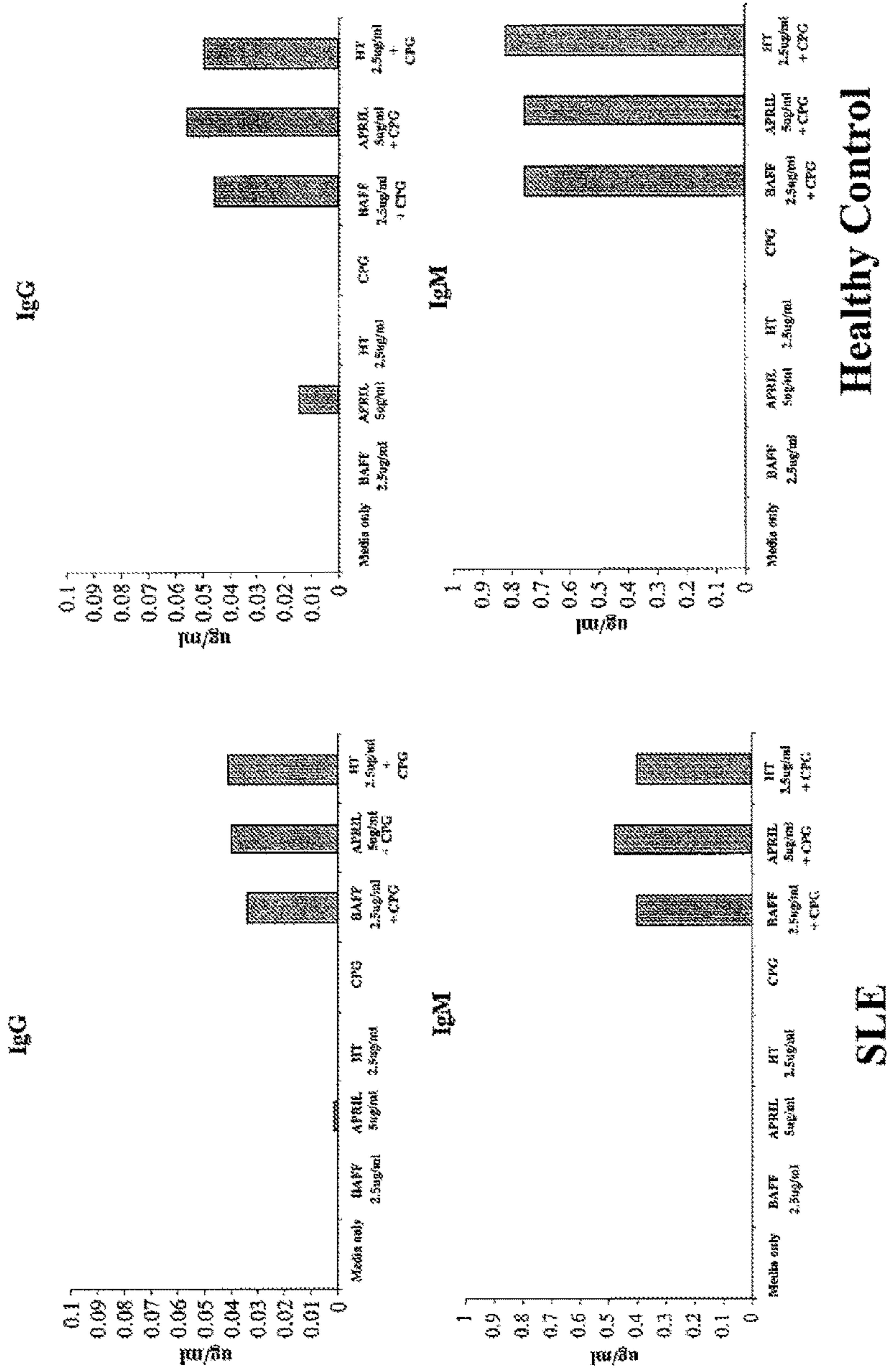


FIGURE 6A

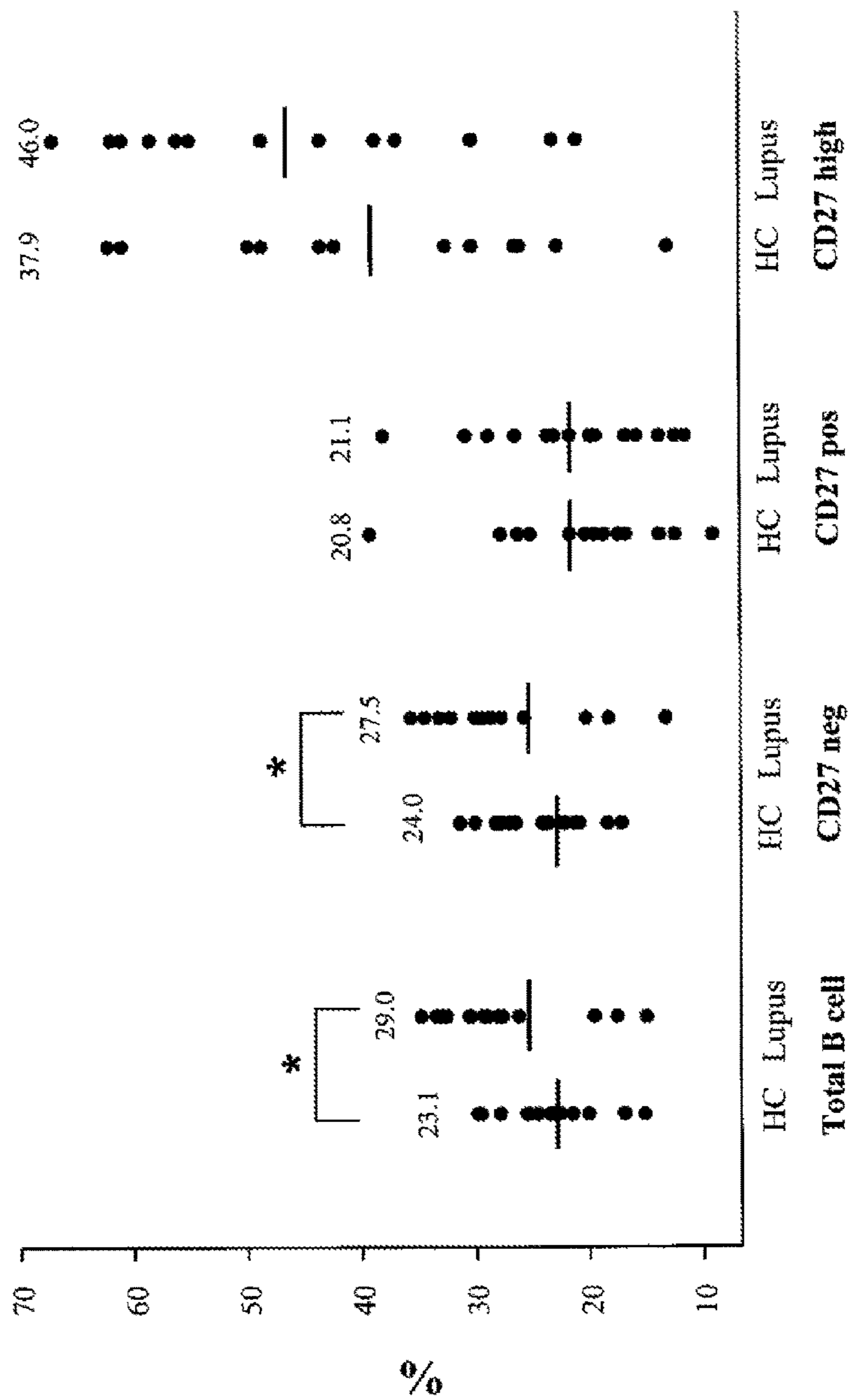


FIGURE 6B

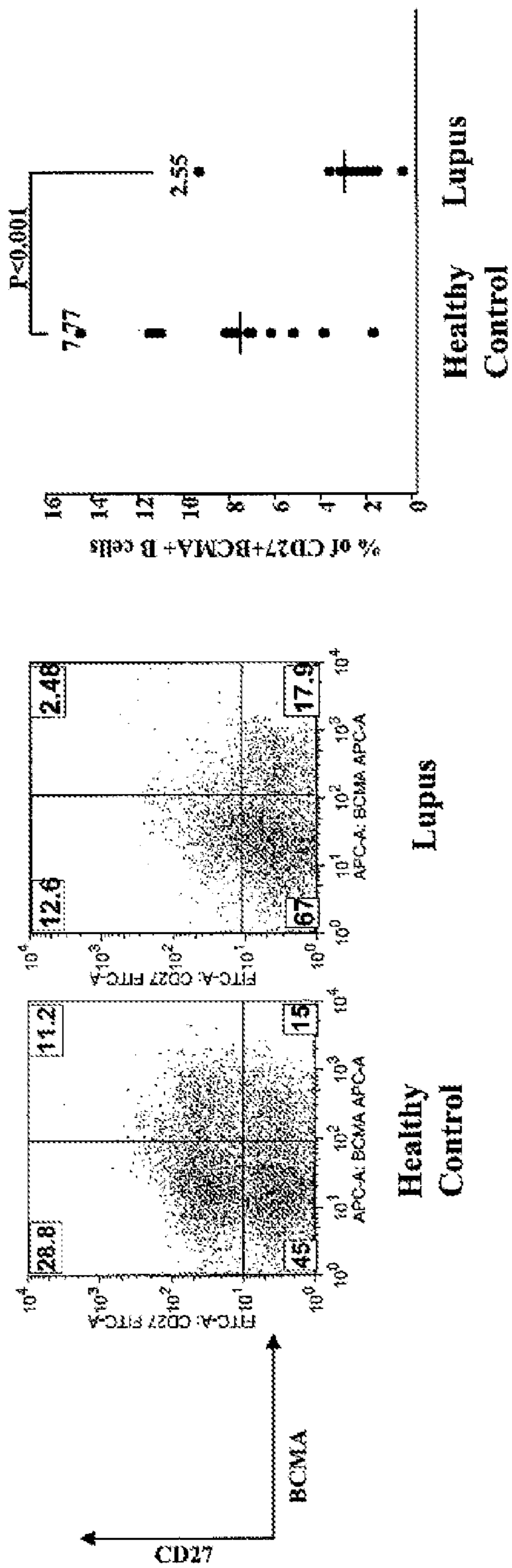


FIGURE 7

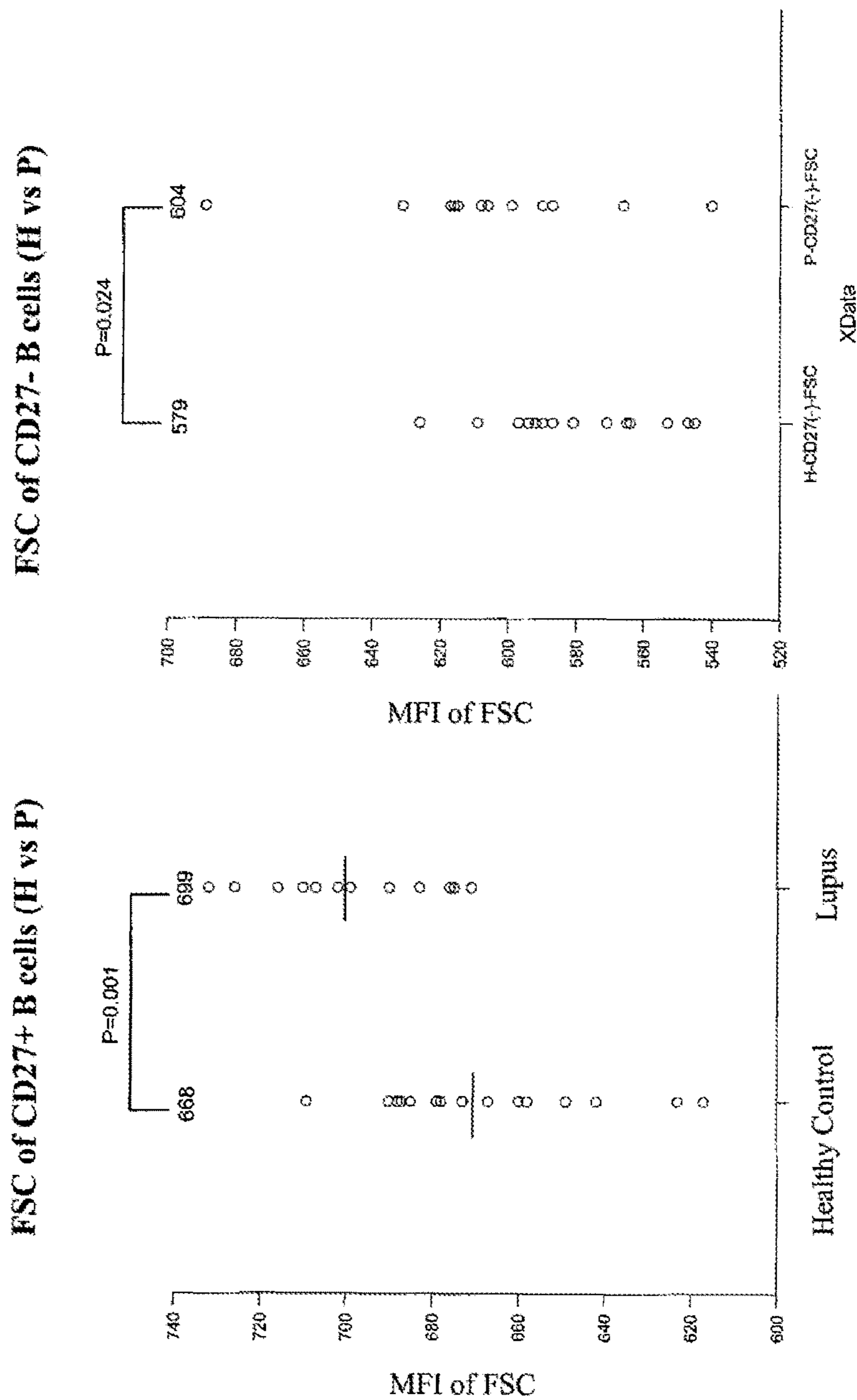


FIGURE 8A

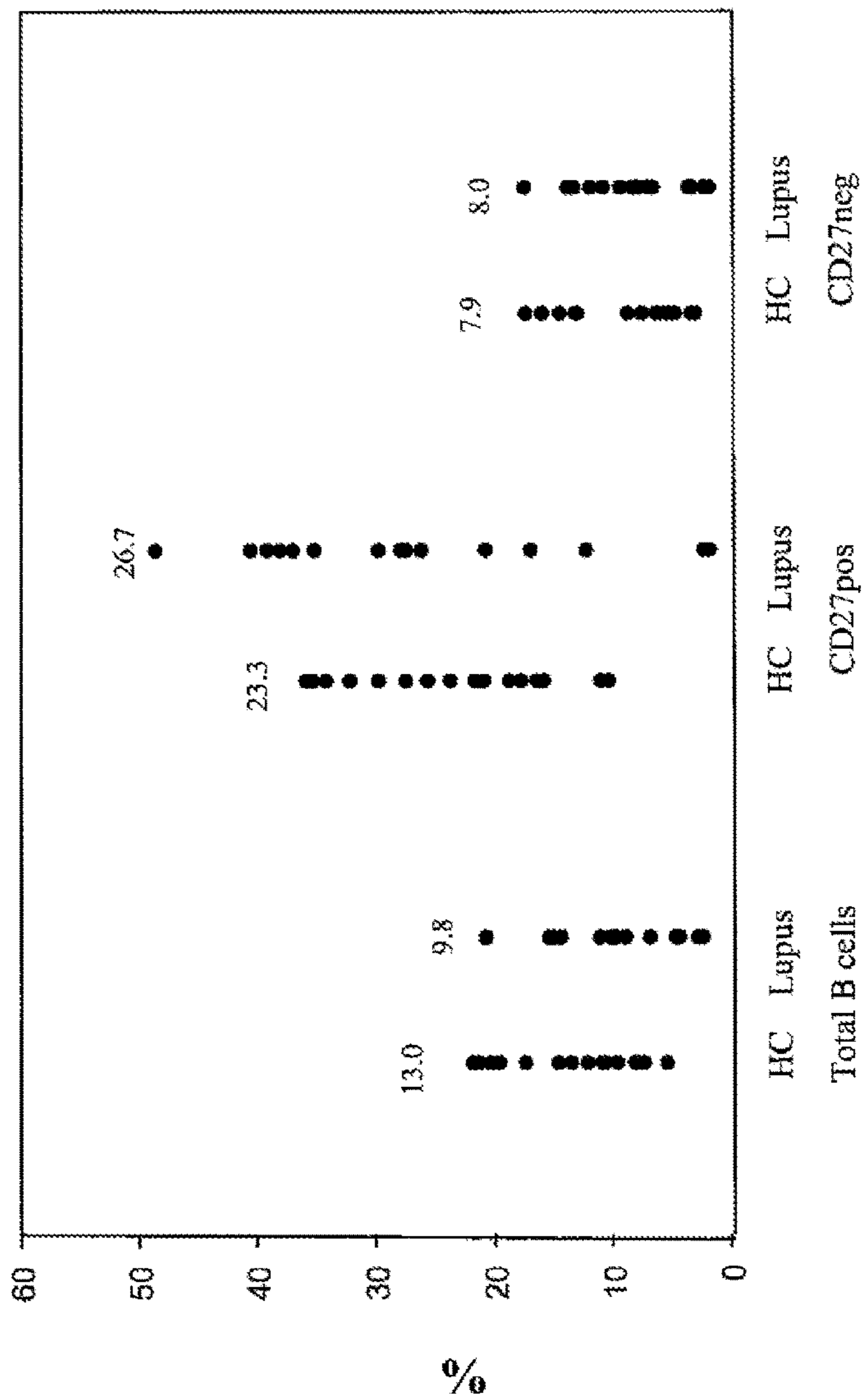


FIGURE 8B

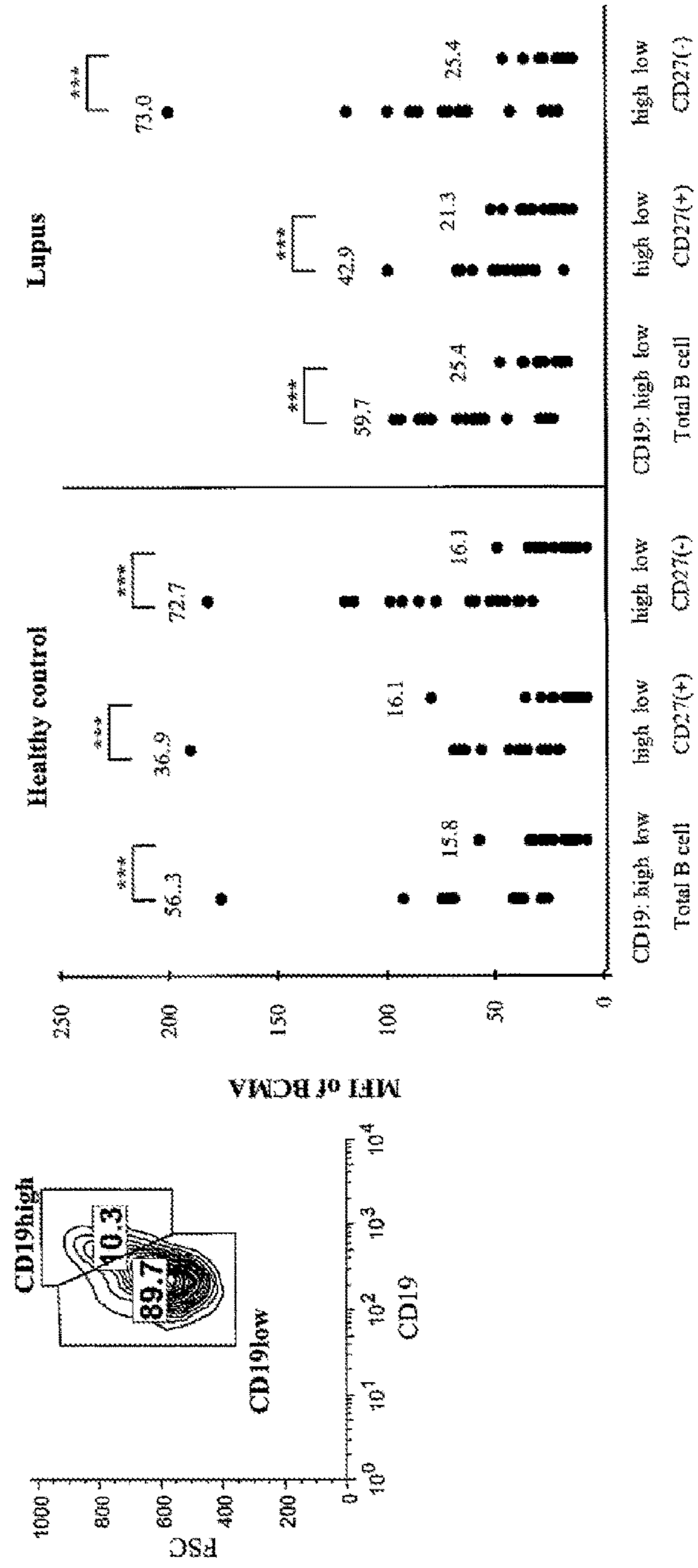


FIGURE 9

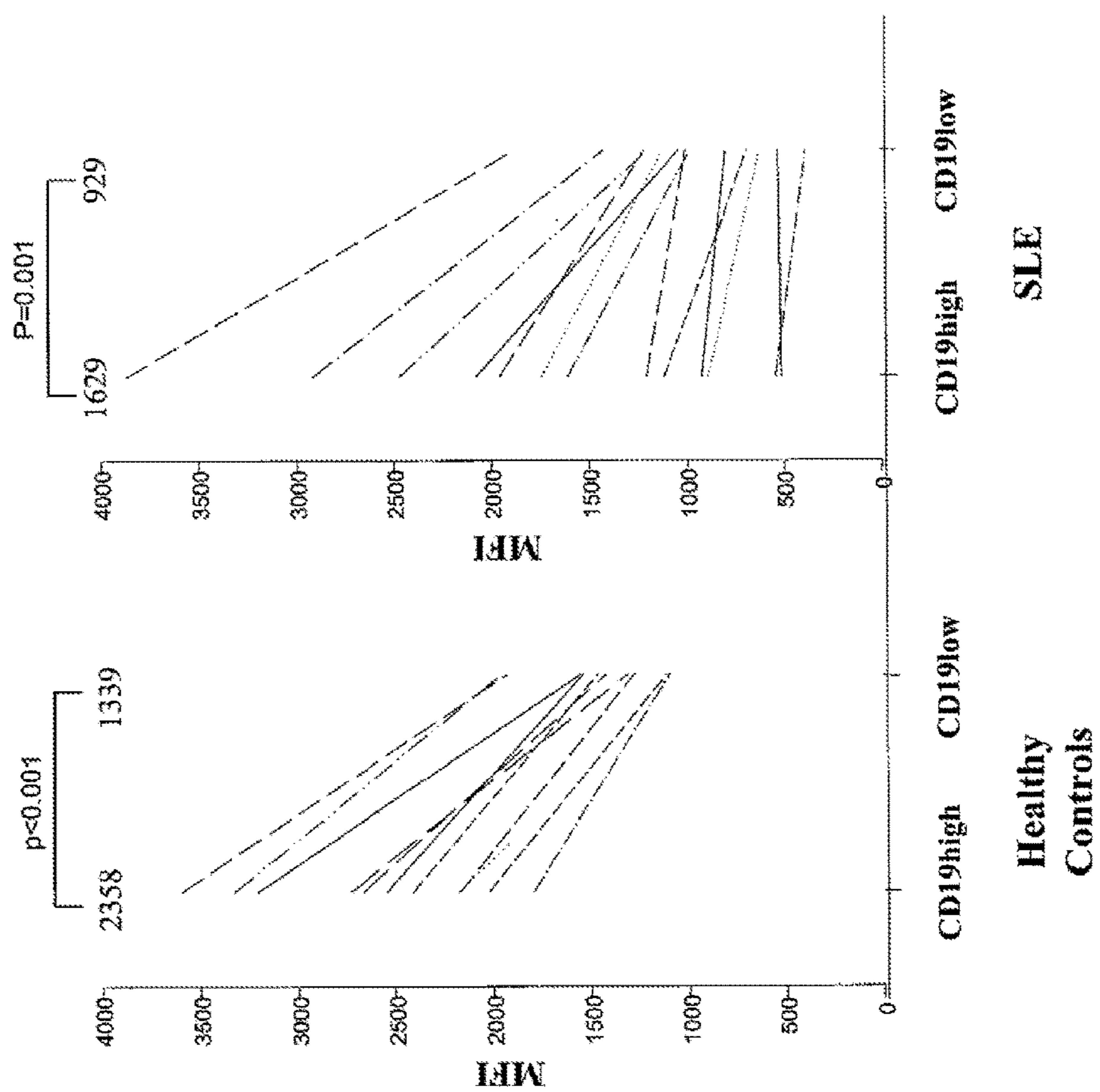
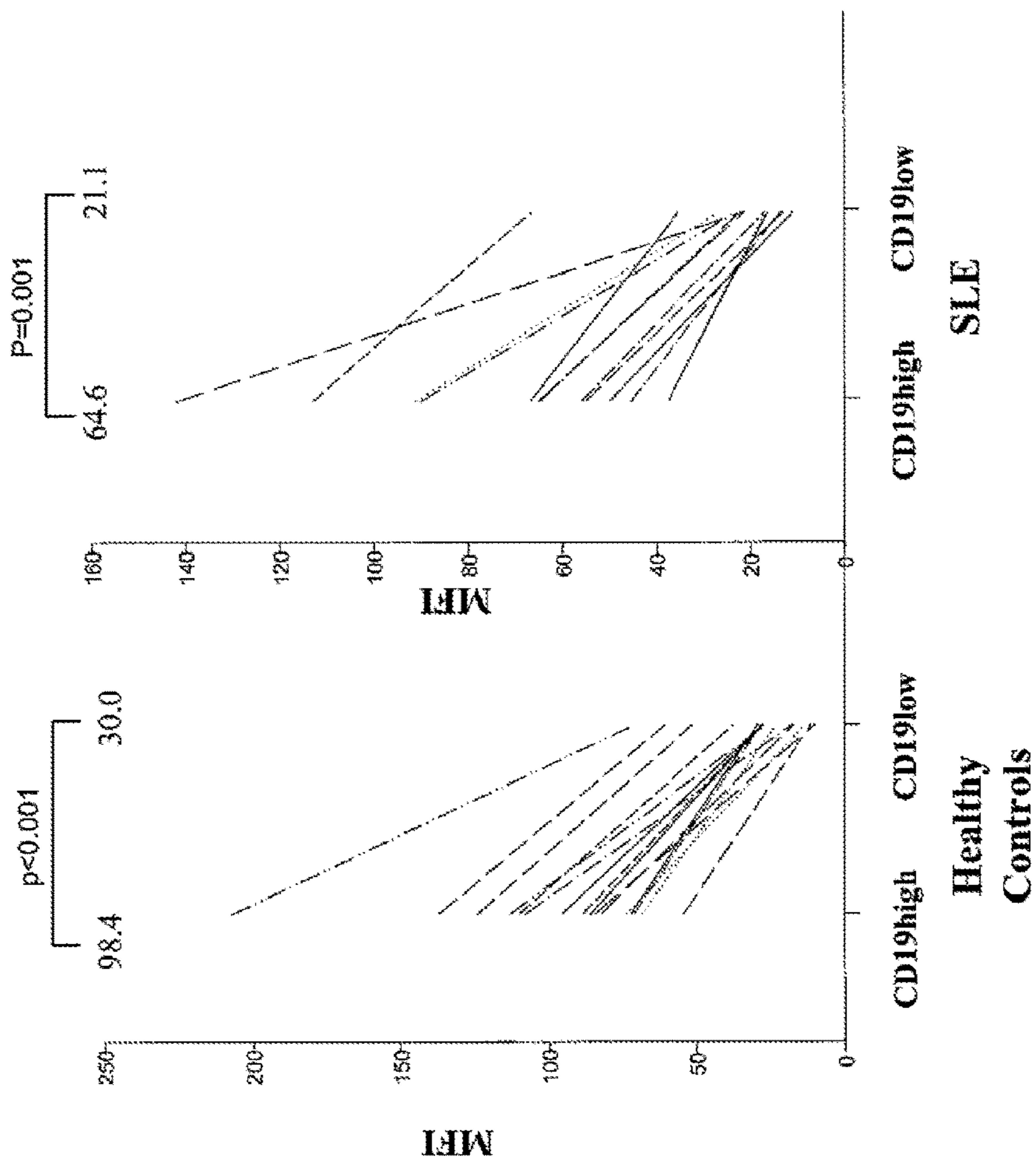


FIGURE 10



**LEVELS OF BCMA PROTEIN EXPRESSION
ON B CELLS AND USE IN METHODS OF
TREATING SYSTEMIC LUPUS
ERYTHEMATOSUS**

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

[CROSS-REFERENCE TO RELATED APPLICATIONS] *CROSS REFERENCE TO RELATED APPLICATIONS*

This application is a *reissue application of U.S. Pat. No. 9,725,506, granted Aug. 8, 2017, which issued from U.S. application Ser. No. 14/192,911 filed Feb. 28, 2014, which is a divisional of U.S. application Ser. No. 12/429,502, filed Apr. 24, 2009, which claims the benefit of U.S. Provisional Application No. 61/047,869 filed Apr. 25, 2008, each of which are herein incorporated by reference in their entirety.*

REFERENCE TO A SEQUENCE LISTING
SUBMITTED AS A TEXT FILE VIA EFS-WEB

The official copy of the sequence listing is submitted concurrently with the specification as a text file via EFS-Web, in compliance with the American Standard Code for Information Interchange (ASCII), with a file name of 442957seqlist.txt, a creation date of Feb. 27, 2014, and a size of 66.7 KB. The sequence listing filed via EFS-Web is part of the specification and is hereby incorporated in its entirety by reference herein.

BACKGROUND OF THE INVENTION

Cellular interactions which occur during an immune response are regulated by members of several families of cell surface receptors, including the tumor necrosis factor receptor (TNFR) family. The TNFR family consists of a number of integral membrane glycoprotein receptors many of which, in conjunction with their respective ligands, regulate interactions between different hematopoietic cell lineages (Smith et al., *The TNF Receptor Superfamily of Cellular and Viral Proteins: Activation, Costimulation and Death*, 76:959-62, 1994; Cosman, *Stem Cells* 12:440-55, 1994).

One such receptor is BCMA, a nonglycosylated integral membrane type I protein that is preferentially expressed in mature B lymphocytes (Gras et al., *Int. Immunol.* 17:1093-106, 1995). BCMA is located on the cell surface, as well as in a perinuclear Golgi-like structure. Overexpression of BCMA in 293 cells activates NF-kappa B, Elk-1, the c-Jun N-terminal kinase, and the p38 mitogen-activated protein kinase, thus producing signals for cell survival and proliferation (Hatzoglou et al., *J. Immunol.*, 165: 1322-30, 2000). Another such receptor is TACI, transmembrane activator and CAML-interactor (von Bülow and Bram, *Science* 228: 138-41, 1997 and WIPO Publication WO 98/39361). TACI is a membrane bound receptor having an extracellular domain containing two cysteine-rich pseudo-repeats, a transmembrane domain and a cytoplasmic domain that interacts with CAML (calcium-modulator and cyclophilin ligand), an integral membrane protein located at intracellular

vesicles which is a co-inducer of NF-AT activation when overexpressed in Jurkat cells. A third receptor from the TNFR family expressed on the surface of B cells is BAFF-R (Thompson et al., *Science*, 293: 2108-11, 2001. Signaling of this receptor, also known as BAFF/BLyS receptor 3 (BR3), promotes processing of the transcription factor NF-kappaB2/p100 to p52. This cascade is physiologically relevant for survival of B cells, and therefore, the progression of B cells to maturation (Claudio et al., *Nat. Immunol.*, 3: 898-9, 2002; Kayagaki et al., *Immunity*, 17: 515-24, 2002).

A number of BLyS and/or APRIL antagonists have been developed in order to block the binding of these ligands to the receptor members of the family, in order to block results of this binding which include but should not be limited to B cell costimulation, plasmablast and plasma cell survival, Ig class switching, enhanced B-cell antigen presenting cell function, survival of malignant B cells, development of B-1 cell function, B cell development beyond the T-1 stage, and complete germinal centre formation. Some of these molecules can also bind to and block the effect of APRIL on B cells and other components of the immune system (Dillon et al. (2006) *Nat. Rev. Drug Dis.* 5, 235-246). Molecules that have been developed to affect B cell function by interfering with BLyS and/or APRIL binding include BLyS antibodies such as Lymphostat-B (Belimumab) (Baker et al, (2003) *Arthritis Rheum*, 48, 3253-3265 and WO 02/02641); receptor-extracellular domain/Fc domain fusions proteins such as TACI-Ig, including one particular embodiment, atacicept (U.S. Patent Application No. 20060034852), BAFF-R-Fc (WO 05/0000351), and BCMA-Ig or other fusion proteins utilizing receptor extracellular domains. A further class of BLyS and/or APRIL antagonists include other molecules relying on BLyS binding ability to block binding to its receptors such as AMG 623, receptor antibodies, and other molecules disclosed in WO 03/035846 and WO 02/16312.

There remains a need in the art for further identification of cell surface expression patterns of these TNFR family members that are statistically associated with autoimmune disease, such as systemic lupus erythromatosus (SLE). Such information is important for identifying individuals who have a propensity toward developing such autoimmune diseases, are in an active disease state, and for identifying those that will respond favorably to BLyS and/or APRIL antagonist treatment of these diseases. The present invention addresses this need by providing a cell surface expression pattern associated with autoimmune diseases and providing diagnostic tests determining the presence of this expression pattern, namely increased BCMA expression on B cells for those suffering from autoimmune disease as compared to healthy controls.

SUMMARY OF THE INVENTION

The present invention provides a method of screening for levels of TNFR family members on the B cell surface. As it has been shown that elevated levels of BCMA are significantly associated with autoimmune disease, such as SLE, this measurement is useful as a diagnostic assay. Such diagnostic assays are useful in predicting an individual's likelihood of having a condition associated with autoimmune activity, such as SLE. The invention further provides methods for determining appropriate treatment for an individual with an autoimmune disease, such as SLE.

Detection of high levels of BCMA on B cells of patients exhibiting autoimmune activity, such as those diagnosed with SLE, allows selection of a treatment plan that is most likely to be effective in treating the condition. These treat-

ment plans generally involve the use of BLYS antagonists, either singly or in combination with another pharmaceutical such as an immune suppressive drug (like MMF or Cellcept®) or a CD 20 antagonist (like Rituxan®).

Thus, the invention further provides methods for treating an individual clinically diagnosed with an autoimmune condition, generally comprising detecting high levels of BCMA on cells, as compared to levels seen on B cells of healthy controls, and selecting a treatment plan that is most effective for individuals clinically diagnosed with an autoimmune disease. Detection of high levels of BCMA on B cells also allows one to predict a patient's likelihood to respond to a specific drug treatment, particularly BLYS and/or APRIL antagonists. Thus, the invention further provides methods of predicting a patient's likelihood to respond to BLYS and/or APRIL antagonists (either singly or in combination with other drugs) during treatment for an autoimmune condition, such as SLE.

Very specifically, the present invention describes a method of detecting increased BCMA protein expression on the surface of B cells of an individual comprising measuring a first level of BCMA protein expression in a biological sample and comparing that level to a second level of BCMA protein expression present on the surface of B cells of a healthy individual and determining the first level is increased as compared to the second level, wherein said increased BCMA protein expression is associated with an autoimmune disease. The autoimmune disease in the present invention can be selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome and glomerulonephritis. In particular, the autoimmune disease is SLE.

The present invention also describes a method of treating an individual clinically diagnosed with an autoimmune disease, comprising analyzing a biological sample from an individual clinically diagnosed with autoimmune disease for the presence or absence of elevated BCMA protein expression levels on their B cells, wherein the presence of elevated BCMA protein expression levels is associated with the clinical diagnosis of autoimmune disease; and selecting a treatment plan that is most effective for individuals clinically diagnosed as having a condition associated with an increased BCMA protein expression level. The treatment plan can involve administration of a BLYS antagonist. And said BLYS antagonist can also be an APRIL antagonist. For this method the autoimmune disease can be selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome and glomerulonephritis. In particular, the autoimmune disease is SLE.

Furthermore, the present invention describes methods for predicting a patient's likelihood to respond to a drug treatment for an autoimmune disease, comprising determining the level of BCMA protein expression on the patient's B cells, wherein the presence of elevated BCMA protein

expression levels is predictive of the patient's likelihood to respond to a drug treatment for the condition. The autoimmune disease can be selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome and glomerulonephritis. In particular, the autoimmune disease is SLE. Additionally, the present invention method can include a drug treatment involves administration of a BLYS antagonist and said BLYS antagonist can also be an APRIL antagonist.

The present invention also encompasses an in vitro method of detecting increased BCMA protein expression on the surface of B cells of an individual, comprising measuring the level of BCMA protein expression on the surface of B cells in a test biological sample from the individual; comparing that level to the level of BCMA protein expression on the surface of B cells in a sample from a healthy control; and determining whether the level of BCMA protein expression on the surface of B cells in the test biological sample is increased as compared to the level in the control sample; wherein said increased BCMA protein expression is associated with an autoimmune disease. The autoimmune disease in this method can be selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome and glomerulonephritis. In particular, the autoimmune disease is SLE.

In a further embodiment, the present invention includes an in vitro method of selecting a treatment plan that is most effective for treating an individual clinically diagnosed with an autoimmune disease, comprising analyzing in vitro a biological sample from an individual clinically diagnosed with autoimmune disease for the presence or absence of elevated BCMA levels on their B cells, wherein the presence of elevated BCMA levels is associated with the clinical diagnosis of autoimmune disease. For this method, the treatment plan can involve the use of a BLYS antagonist and the BLYS antagonist can also be an APRIL antagonist. The autoimmune disease can be selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome and glomerulonephritis.

In particular, the autoimmune disease is SLE.

In a still further embodiment, the present invention includes an in vitro method for predicting a patient's likelihood to respond to a drug treatment for an autoimmune disease, comprising determining the level of BCMA expression on the surface of B cells in a sample from the patient; wherein the presence of elevated B cell levels is predictive of the patient's likelihood to respond to a drug treatment for the condition. The autoimmune disease can be selected from

the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome and glomerulonephritis. In particular, the autoimmune disease is SLE. The drug treatment of the present invention can comprise a BLYS antagonist and said BLYS antagonist can also be an APRIL antagonist.

Finally, the present invention contemplates a BLYS antagonist for use in the treatment of an autoimmune disease in a patient, wherein said patient has elevated levels of BCMA expression on B cells. The antagonist can be a BLYS antibody, such as Lymphostat-B. The antagonist can also be a receptor-extracellular domain/Fc domain fusion protein selected from the group consisting of TACI-Ig, BCMA-Ig, and BAFF-R-Ig. In particular, the receptor-extracellular domain/Fc domain fusion protein can be TACI-Ig, such as atacicept.

These and other aspects of the invention will become apparent to those persons skilled the art upon reading the details of the invention as more fully described below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A shows the levels of BAFF-R, TACI, and BCMA present on the cells surface of naïve B cells, memory B cells, and plasmablasts.

FIG. 1B graphs the median fluorescence intensity (MFI) of BAFF-R in total B cells, naïve B cells, memory cells, and plasmablasts comparing healthy controls (HC) and lupus patients (SLE).

FIG. 1C graphs the median fluorescence intensity (MFI) of TACI in total B cells, naïve B cells, memory cells, and plasmablasts comparing healthy controls (HC) and lupus patients (SLE).

FIG. 1D graphs the median fluorescence intensity (MFI) of BCMA in total B cells, naïve B cells, memory cells, and plasmablasts comparing healthy controls (HC) and lupus patients (SLE).

FIG. 2 upper level graphs the inverse relationship between BAFF-R expression on total B cells and serum BAFF (BCMA) but the lack of a statistically significant correlation between BAFF-R expression and serum IgG anti-dsDNA and SLEDAI score (disease activity). FIG. 2 lower level graphs the inverse relationship between serum IgG anti-dsDNA and the lack of correlation between serum BAFF (BCMA) and SLEDAI score (disease activity).

FIG. 3A graphs the forward angle light scatter (FSC) measured as MFI of the BCMA+ and BCMA- B cells in healthy controls and lupus patients. FSC is an indication of activation in B cells. FIG. 3B shows the results of comparing CD19 high and CD 19 low B cells for the MFI of BCMA detection in both healthy controls and lupus patients.

FIG. 4A shows results that indicate that BCMA+ cells are IgD+ and IgM+ and therefore have not undergone class switching. It also graphs the higher levels of CD86 seen in BCMA+ cells of lupus patients and the relatively low levels of CD80 seen in both healthy controls and lupus patients. FIG. 4B graphs the higher percentage of IgD+ B cells seen in lupus patients as compared to healthy controls.

FIG. 5A discloses the results of labeling the peripheral blood mononuclear cells (PBMC) of healthy controls and lupus patients with 5-carboxyfluorescein diacetate succin-

imidyl ester (CSFE) and incubating with CpG with and without ligands. The upper level shows plasmablast induction (CD27 high) and the lower level shows BCMA induction. FIG. 5B graphs the experiment disclosed in 5A but focusing on the proliferation results. FIG. 5C upper level graphs the results from the experiment of 5A charting the increase of CD27 high cells with the increase of BCMA. The lower level reports the MFI of BCMA in this experiment in lupus and healthy controls with the various inductions. FIG. 5D discloses the production of IgG and IgM in the sorted B cells of the experiment disclosed in 5A.

FIG. 6A graphs the percentage of BCMA positive cells comparing Healthy Controls (HC) and Lupus patients in naïve B cells (CD27 neg), memory cells (CD27 pos), and plasmablasts (CD27 high). FIG. 6B graphs production of CD27 high (plasmablasts) vs the production of BCMA on the cell surface for Healthy controls and Lupus patients.

FIG. 7 reports the MFI of the FSC of CD27 pos and CD27 neg cells healthy controls vs. patients.

FIG. 8A discloses the percentage of CD19 high B cells found in Healthy Controls (HC) and Lupus patients in naïve B cells (CD27 neg), memory cells (CD27 pos), and plasmablasts (CD27 high). FIG. 8B charts the MFI of BCMA in CD19 high and CD19 low B cells for healthy controls and lupus patients.

FIG. 9 graphically shows the levels of BAFF-R on the surface (by MFI) on the surface of CD19 high and CD19 low B cells for healthy controls and lupus patients.

FIG. 10 graphically shows the levels of TACI on the surface (by MFI) on the surface of CD19 high and CD19 low B cells for healthy controls and lupus patients.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides a method for screening TNFR family members on the surface of B cells and the use of this information for predicting the presence of autoimmune disease and predicting the likelihood that a patient would respond to BLYS antagonist treatment. The invention is based on the finding that the levels of BCMA protein expression on the surface of B cells is elevated and BLYS antagonists selectively neutralize the production of IgG by said cells. This observation allows development of diagnostic assays to detect the presence of increased BCMA on the B cells surface where these higher levels are associated with autoimmune disease, such as SLE, and also may predict the likelihood that an individual will successfully respond to treatment methods that neutralize such B cells, i.e., BLYS and/or APRIL antagonists.

Before the present invention is described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

It must be noted that as used herein and in the appended claims, the singular forms “a”, “and”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a polymorphism includes a plurality of such polymorphisms, reference to “a nucleic acid molecule” includes a plurality of such nucleic acid molecules, and reference to “the method” includes reference to one or more methods, method steps, and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

Definitions

As used herein, the term “BCMA” is intended to generically refer to both the wild-type and variant forms of the gene sequence, unless specifically denoted otherwise. As it is commonly used in the art, the term “gene” is intended to refer to the genomic region encompassing 5' untranslated region(s) (UTR), exons, introns, and 3' UTR. Individual segments may be specifically referred to, e.g. promoter, coding region, etc. Combinations of such segments that provide for a complete BCMA protein may be referred to generically as a protein coding sequence. The nucleotide sequence of BCMA are publicly available (GenBank Accession number as BC058291). There are four major haplotypes of the BCMA gene in the human genome, in the present disclosure the term “BCMA” is meant to encompass all four (Kawasaki et al., *Genes Immun.* 2:276-9, 2001).

The term “polymorphism”, as used herein, refers to a difference in the nucleotide or amino acid sequence of a given region as compared to a nucleotide or amino acid sequence in a homologous-region of another individual, in particular, a difference in the nucleotide of amino acid sequence of a given region which differs between individuals of the same species. A polymorphism is generally defined in relation to a reference sequence. Polymorphisms include single nucleotide differences, differences in sequence of more than one nucleotide, and single or multiple nucleotide insertions, inversions and deletions; as well as single amino acid differences, differences in sequence of more than one amino acid, and single or multiple amino acid insertions, inversions, and deletions.

The terms “polynucleotide” and “nucleic acid molecule” are used interchangeably herein to refer to polymeric forms of nucleotides of any length. The polynucleotides may contain deoxyribonucleotides, ribonucleotides, and/or their analogs. Nucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The term “polynucleotide” includes single-, double-stranded and triple helical molecules. “Oligonucleotide” generally refers to polynucleotides of between about 5 and about 100 nucleotides of single- or double-stranded DNA. However, for the purposes of this disclosure, there is no upper limit to the length of an oligonucleotide. Oligonucleotides are also known as oligomers or oligos and may be isolated from genes, or chemically synthesized by methods known in the art.

The following are non-limiting embodiments of polynucleotides: a gene or gene fragment, exons, introns, mRNA, tRNA, rRNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any

sequence, nucleic acid probes, and primers. A nucleic acid molecule may also comprise modified nucleic acid molecules, such as methylated nucleic acid molecules and nucleic acid molecule analogs. Analogs of purines and pyrimidines are known in the art. Nucleic acids may be naturally occurring, e.g. DNA or RNA, or may be synthetic analogs, as known in the art. Such analogs may be preferred for use as probes because of superior stability under assay conditions. Modifications in the native structure, including alterations in the backbone, sugars or heterocyclic bases, have been shown to increase intracellular stability and binding affinity. Among useful changes in the backbone chemistry are phosphorothioates; phosphorodithioates, where both of the non-bridging oxygens are substituted with sulfur; phosphoroamidites; alkyl phosphotriesters and boranophosphates. Achiral phosphate derivatives include 3'-O'-5'-S-phosphorothioate, 3'-S-5'-O-phosphorothioate, 3'-CH₂-5'-O-phosphonate and 3'-NH-5'-O-phosphoroamidate. Peptide nucleic acids replace the entire ribose phosphodiester backbone with a peptide linkage.

Sugar modifications are also used to enhance stability and affinity. The α -anomer of deoxyribose may be used, where the base is inverted with respect to the natural β -anomer. The 2'-OH of the ribose sugar may be altered to form 2'-O-methyl or 2'-O-allyl sugars, which provides resistance to degradation without comprising affinity.

Modification of the heterocyclic bases must maintain proper base pairing. Some useful substitutions include deoxyuridine for deoxythymidine; 5-methyl-2'-deoxycytidine and 5-bromo-2'-deoxycytidine for deoxycytidine. 5-propynyl-2'-deoxyuridine and 5-propynyl-2'-deoxycytidine have been shown to increase affinity and biological activity when substituted for deoxythymidine and deoxycytidine, respectively.

The terms “polypeptide” and “protein”, used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified peptide backbones. The term includes fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence, fusions with heterologous and homologous leader sequences, with or without N-terminal methionine residues; immunologically tagged proteins; and the like.

In the broadest sense, as used herein, the terms “autoimmune disease,” refer to a disease wherein a patient’s immune system is producing an unwanted immune response to one or more of their own proteins. Representative examples of autoimmune diseases include rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis (LN), Wegener’s disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud’s syndrome, Sjorgen’s syndrome and glomerulonephritis.

A “substantially isolated” or “isolated” polynucleotide is one that is substantially free of the sequences with which it is associated in nature. By substantially free is meant at least 50%, preferably at least 70%, more preferably at least 80%, and even more preferably at least 90% free of the materials with which it is associated in nature. As used herein, an “isolated” polynucleotide also refers to recombinant polynucleotides, which, by virtue of origin or manipulation: (1) are not associated with all or a portion of a polynucleotide with which it is associated in nature, (2) are linked to a

polynucleotide other than that to which it is linked in nature, or (3) does not occur in nature.

Hybridization reactions can be performed under conditions of different "stringency". Conditions that increase stringency of a hybridization reaction of widely known and published in the art. See, for example, Sambrook et al. (1989). Examples of relevant conditions include (in order of increasing stringency): incubation temperatures of 25° C., 37° C., 50° C. and 68° C.; buffer concentrations of 10×SSC, 6×SSC, 1×SSC, 0.1×SSC (where SSC is 0.15 M NaCl and 15 mM citrate buffer) and their equivalents using other buffer systems; formamide concentrations of 0%, 25%, 50%, and 75%; incubation times from 5 minutes to 24 hours; 1, 2, or more washing steps; wash incubation times of 1, 2, or 15 minutes; and wash solutions of 6×SSC, 1×SSC, 0.1×SSC, or deionized water. Examples of stringent conditions are hybridization and washing at 50° C. or higher and in 0.1×SSC (9 mM NaCl/0.9 mM sodium citrate).

" T_m " is the temperature in degrees Celsius at which 50% of a polynucleotide duplex made of complementary strands hydrogen bonded in anti-parallel direction by Watson-Crick base pairing dissociates into single strands under conditions of the experiment. T_m may be predicted according to a standard formula, such as: where $[X^+]$ is the cation concentration (usually sodium ion, Na^+) in mol/L; (% G/C) is the number of G and C residues as a percentage of total residues in the duplex; (% F) is the percent formamide in solution (wt/vol); and L is the number of nucleotides in each strand of the duplex.

Stringent conditions for both DNA/DNA and DNA/RNA hybridization are as described by Sambrook et al. *Molecular Cloning, A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, herein incorporated by reference. For example, see page 7.52 of Sambrook et al.

The term "host cell" includes an individual cell or cell culture which can be or has been a recipient of any recombinant vector(s) or isolated polynucleotide of the invention. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation and/or change. A host cell includes cells transfected or infected in vivo or in vitro with a recombinant vector or a polynucleotide of the invention. A host cell which comprises a recombinant vector of the invention is a "recombinant host cell".

The term "binds specifically," in the context of antibody binding, refers to high avidity and/or high affinity binding of an antibody to a specific polypeptide i.e., epitope of a polymorphic BCMA polypeptide. Antibody binding to an epitope on a specific polymorphic BCMA polypeptide (also referred to herein as "a polymorphic BCMA epitope") is preferably stronger than binding of the same antibody to any other epitope, particularly those which may be present in molecules in association with, or in the same sample, as the specific polypeptide of interest, e.g., binds more strongly to a specific BCMA polymorphic epitope than to a different BCMA epitope so that by adjusting binding conditions the antibody binds almost exclusively to the specific BCMA polymorphic epitope and not to any other BCMA epitope, and not to any other BCMA polypeptide which does not comprise the polymorphic epitope. Antibodies which bind specifically to a polypeptide of interest may be capable of binding other polypeptides at a weak, yet detectable, level (e.g., 10% or less of the binding shown to the polypeptide of interest). Such weak binding, or background binding, is

readily discernible from the specific antibody binding to the compound or polypeptide of interest, e.g. by use of appropriate controls. In general, antibodies of the invention which bind to a specific BCMA polypeptide with a binding affinity of 10^7 mole/l or more, preferably 10^8 mole/l or more are said to bind specifically to the specific BCMA polypeptide. In general, an antibody with a binding affinity of 10^6 mole/liters or less is not useful in that it will not bind an antigen at a detectable level using conventional methodology currently used.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i. e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that can be present in minor amounts.

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

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81: 6851-6855 (1984)). Methods of making chimeric antibodies are known in the art.

"Humanized" forms of non-human (e. g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F (ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin.

For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are found neither in the recipient antibody

nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence although the FR regions may include one or more amino acid substitutions that improve binding affinity. The number of these amino acid substitutions in the FR are typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., *Nature*, 321: 522-525 (1986); Reichmann et al., *Nature*, 332: 323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2: 593-596 (1992). The humanized antibody includes a PRIMATIZED antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by, e. g., immunizing macaque monkeys with the antigen of interest. Methods of making humanized antibodies are known in the art.

Human antibodies can also be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381 (1991); Marks et al., *J. Mol. Biol.*, 222: 581 (1991). The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies. Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al., *J. Immunol.*, 147(1): 86-95 (1991).

"Functional fragments" of the binding antibodies of the invention are those fragments that retain binding to BlyS, TACI, BAFF-R, or BCMA with substantially the same affinity as the intact full chain molecule from which they are derived and may be able to deplete B cells as measured by in vitro or in vivo assays such as those described herein.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: Clq binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e. g. B cell receptor); and B cell activation.

"Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e. g. Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing-target cell and subsequently kill the-target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Ann. Rev. Immunol* 9: 457-92 (1991). To assess ADCC activity of a molecule of interest, an in vitro ADCC assay, such as that described in U.S. Pat. Nos. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed

in vivo, e. g., in a animal model such as that disclosed in Clynes et al. *PNAS (USA)* 95: 652-656 (1998).

"Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e. g. as described in Gazzano-Santoro et al., *J. Immunol. Methods* 202: 163 (1996), may be performed.

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The terms "detectably labeled antibody" refers to an antibody (or antibody fragment which retains binding specificity for a BCMA polypeptide or epitope), having an attached detectable label. The detectable label is normally attached by-chemical conjugation, but where the label is a polypeptide, it could alternatively be attached by genetic engineering techniques. Methods for production of detectably labeled proteins are well known in the art. Detectable labels may be selected from a variety of such labels known in the art, including, but not limited to, radioisotopes, fluorophores, paramagnetic labels, enzymes (e.g., horseradish peroxidase), or other moieties or compounds which either emit a detectable signal (e.g., radioactivity, fluorescence, color) or emit a detectable signal after exposure of the label to its substrate. Various detectable label/substrate pairs (e.g., horseradish peroxidase/diaminobenzidine, avidin/streptavidin, luciferase/luciferin), methods for labeling antibodies, and methods for using labeled antibodies are well known in the art (see, for example, Harlow and Lane, eds. (*Antibodies: A Laboratory Manual* (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.)).

A "biological sample" encompasses a variety of sample types obtained from an individual and can be used in a diagnostic or monitoring assay. The definition encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived there from and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as polynucleotides. The term "biological sample" encompasses a clinical sample, and also includes cells in culture, cell supernatants, cell lysates, serum, plasma, biological fluid, and tissue samples.

As used herein, the terms "treatment", "treating", and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms

of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse affect attributable to the disease. "Treatment", as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

"Immunosuppressive drugs" are any molecules that interfere with the immune system and blunt its response to foreign or self antigens. Cyclophosphamide (CYC) and mycophenolate mofetil (MMF) are two such kinds of molecules. This term is intended to encompass any drug or molecule useful as a therapeutic agent in downregulating the immune system.

A "fusion protein" and a "fusion polypeptide" refer to a polypeptide having two portions covalently linked together, where each of the portions is a polypeptide having a different property. The property may be a biological property, such as activity in vitro or in vivo. The property may also be a simple chemical or physical property, such as binding to a target molecule, catalysis of a reaction, etc. The two portions may be linked directly by a single peptide bond or through a peptide linker containing one or more amino acid residues. Generally, the two portions and the linker will be in reading frame with each other.

A "conjugate" refers to any hybrid molecule, including fusion proteins and as well as molecules that contain both amino acid or protein portions and non-protein portions. Conjugates may be synthesized by a variety of techniques known in the art including, for example, recombinant DNA techniques, solid phase synthesis, solution phase synthesis, organic chemical synthetic techniques or a combination of these techniques. The choice of synthesis will depend upon the particular molecule to be generated. For example, a hybrid molecule not entirely "protein" in nature may be synthesized by a combination of recombinant techniques and solution phase techniques.

As used herein, the term "Fc-fusion protein" designates antibody-like molecules which combine the binding specificity of a heterologous protein with the effector functions of immunoglobulin constant domains. Structurally, the Fc-fusion proteins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i. e., is "heterologous"), and an immunoglobulin constant domain sequence. The Fc-fusion protein molecule typically includes a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the Fc-fusion protein can be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM. For example, useful Fc-fusion proteins according to this invention are polypeptides that comprise the BLYS binding portions of a BLYS receptor without the transmembrane or cytoplasmic sequences of the BLYS receptor. In one embodiment, the extracellular domain of BAFF-R, TACI or BCMA is fused to a constant domain of an immunoglobulin sequence.

The terms "individual," "subject," and "patient," used interchangeably herein, refer to a mammal, including, but not limited to, murines, simians, humans, mammalian farm animals, mammalian sport animals, and mammalian pets.

The term "mammal" refers to any animal classified as a mammal, including humans, domestic and farm animals,

and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal herein is human.

Detection of BCMA Polypeptides

The present invention provides for detection of BCMA polypeptides. The term "BCMA polypeptide" encompasses an amino acid sequence encoded by an open reading frame (ORF) of a known BCMA polynucleotide, including the full-length native polypeptide and fragments thereof, particularly biologically active fragments and/or fragments corresponding to functional domains, e.g. a region or domain having biological activity, etc.; antigenic fragments thereof, and including fusions of the subject polypeptides to other proteins or parts thereof. The amino acid sequences of BCMA polypeptides have been disclosed. (See e.g. Laabi et al., *Nucleic Acids Research* 22: 1147-1154, 1994; Laabi et al., *EMBO J.*, 11: 3897-3904 (1992); Gras et al., *Int. Immunology*, 7: 1093-1106 (1995); and Madry et al., *Int. Immunology*, 10: 1693-1702 (1998). The BCMA polypeptides of the invention can be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant and/or synthetic methods. A polymorphism in a BCMA polypeptide is generally defined relative to a reference sequence.

As used herein, "polymorphic BCMA polypeptide" refers to an amino acid sequence of a recombinant or non-recombinant polypeptide having an amino acid sequence of i) a native polymorphic BCMA polypeptide, ii) a fragment of a polymorphic BCMA polypeptide, iii) polypeptide analogs of a polymorphic BCMA polypeptide, iv) variants of a polymorphic BCMA polypeptide; v) an immunologically active fragment of a polymorphic BCMA polypeptide; and vi) fusion proteins comprising a polymorphic BCMA polypeptide. Polymorphic BCMA polypeptides of the invention can be obtained from a biological sample, or from any source whether natural, synthetic, semi-synthetic or recombinant.

The term "polymorphic BCMA polypeptide" or "BCMA polypeptide" encompasses a polypeptide comprising from at least about 5 amino acids, at least about 10 amino acids, at least about 15 amino acids, at least about 25 amino acids, at least about 50 amino acids, at least about 75 amino acids, at least about 100 amino acids, at least about 200 amino acids, at least about 300 amino acids, at least about 400 amino acids, or up to the entire polypeptide of a polymorphic BCMA polypeptide. In some embodiments, a polymorphic BCMA polypeptide exhibits biological activity, e.g., the polypeptide causes proliferation of B-cells and production of immunoglobulin in an in vitro assay. Other assays for BCMA biological activity are known in the art and can be used to determine whether a polymorphic BCMA polypeptide exhibits biological activity and, if desired, to quantitate BCMA biological activity. BCMA biological assays are described in various publications, e.g., Moore et al., supra.

BCMA polypeptides can be obtained by any known method, or a combination of such methods, including isolation from natural sources; production by chemical synthesis; and production by standard recombinant techniques. BCMA polypeptides can be isolated from a biological source, using affinity chromatography, e.g., using antibodies specific for a BCMA polypeptide are immobilized on a solid support. The polypeptides may be expressed in prokaryotes or eukaryotes in accordance with conventional ways, depending upon the purpose for expression. For large scale production of the protein, a unicellular organism, such as *E. coli*, *B. subtilis*, *S. cerevisiae*, insect cells in combination with baculovirus vectors, or cells of a higher organism such as vertebrates, particularly mammals, e.g. COS 7 cells, CHO cells, HEK293 cells, and the like, may be used as the

expression host cells. In some situations, it is desirable to express the gene in eukaryotic cells, where the protein will benefit from native folding and post-translational modifications. The polypeptide can then be isolated from cell culture supernatant or from cell lysates using affinity chromatography methods or anion exchange/size exclusion chromatography methods, as described above.

With the availability of the protein or fragments thereof in large amounts, by employing an expression host, the protein may be isolated and purified in accordance with conventional ways. A lysate may be prepared of the expression host and the lysate purified using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. The isolated proteins can be used to produce antibodies, which are in turn, used to detect the presence of that protein using standard assay systems, e.g., ELISA or FACS analysis.

Preparation of BCMA Polypeptides

In addition to the plurality of uses described in greater detail in following sections, the BCMA nucleic acid compositions are used in the preparation of all or a portion of the BCMA polypeptides, as described above. The polynucleotides (including cDNA or the full-length gene) are used to express a partial or complete gene product. Constructs comprising the subject polynucleotides can be generated synthetically. Alternatively, single-step assembly of a gene and entire plasmid from large numbers of oligodeoxyribonucleotides is described by, e.g., Stemmer et al., *Gene* (Amsterdam) (1995) 164(1):49-53. In this method, assembly PCR (the synthesis of long DNA sequences from large numbers of oligodeoxyribonucleotides (oligos)) is described. The method is derived from DNA shuffling (Stemmer, *Nature* (1994) 370:389-391), and does not rely on DNA ligase, but instead relies on DNA polymerase to build increasingly longer DNA fragments during the assembly process. Appropriate polynucleotide constructs are purified using standard recombinant DNA techniques as described in, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., (1989) Cold Spring Harbor Press, Cold Spring Harbor, N.Y., and under current regulations described in United States Dept. of HHS, National Institute of Health (NIH) Guidelines for Recombinant DNA Research.

Polynucleotide molecules comprising a polynucleotide sequence provided herein are propagated by placing the molecule in a vector. Viral and non-viral vectors are used, including plasmids. The choice of plasmid will depend on the type of cell in which propagation is desired and the purpose of propagation. Certain vectors are useful for amplifying and making large amounts of the desired DNA sequence. Other vectors are suitable for expression in cells in culture. Still other vectors are suitable for transfer and expression in cells in a whole animal or person. The choice of appropriate vector is well within the skill of the art. Many such vectors are available commercially. The partial or full-length polynucleotide is inserted into a vector typically by means of DNA ligase attachment to a cleaved restriction enzyme site in the vector. Alternatively, the desired nucleotide sequence can be inserted by homologous recombination in vivo. Typically this is accomplished by attaching regions of homology to the vector on the flanks of the desired nucleotide sequence. Regions of homology are added by ligation of oligonucleotides, or by polymerase chain reaction using primers comprising both the region of homology and a portion of the desired nucleotide sequence, for example.

For expression, an expression cassette or system may be employed. The gene product encoded by a polynucleotide of

the invention is expressed in any convenient expression system, including, for example, bacterial, yeast, insect, amphibian and mammalian systems. Suitable vectors and host cells are described in U.S. Pat. No. 5,654,173. In the expression vector, a BCMA polypeptide-encoding polynucleotide is linked to a regulatory sequence as appropriate to obtain the desired expression properties. These can include promoters (attached either at the 5' end of the sense strand or at the 3' end of the antisense strand), enhancers, terminators, operators, repressors, and inducers. The promoters can be regulated or constitutive. In some situations it may be desirable to use conditionally active promoters, such as tissue-specific or developmental stage-specific promoters. These are linked to the desired nucleotide sequence using the techniques described above for linkage to vectors. Any techniques known in the art can be used. In other words, the expression vector will provide a transcriptional and translational initiation region, which may be inducible or constitutive, where the coding region is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region. These control regions may be native to the BCMA gene, or may be derived from exogenous sources.

Expression vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences encoding heterologous proteins. A selectable marker operative in the expression host may be present. Expression vectors may be used for the production of fusion proteins, where the exogenous fusion peptide provides additional functionality, i.e. increased protein synthesis, stability, reactivity with defined antisera, an enzyme marker, e.g. β -galactosidase, etc.

Expression cassettes may be prepared comprising a transcription initiation region, the gene or fragment thereof, and a transcriptional termination region. Of particular interest is the use of sequences that allow for the expression of functional epitopes or domains, usually at least about 8 amino acids in length, more usually at least about 15 amino acids in length, to about 25 amino acids, and up to the complete open reading frame of the gene. After introduction of the DNA, the cells containing the construct may be selected by means of a selectable marker, the cells expanded and then used for expression.

BCMA polypeptides may be expressed in prokaryotes or eukaryotes in accordance with conventional ways, depending upon the purpose for expression. For large scale production of the protein, a unicellular organism, such as *E. coli*, *B. subtilis*, *S. cerevisiae*, insect cells in combination with baculovirus vectors, or cells of a higher organism such as vertebrates, particularly mammals, e.g. COS 7 cells, HEK 293, CHO, *Xenopus* Oocytes, etc., may be used as the expression host cells. In some situations, it is desirable to express a polymorphic BCMA nucleic acid molecule in eukaryotic cells, where the polymorphic BCMA protein will benefit from native folding and post-translational modifications. Small peptides can also be synthesized in the laboratory. Polypeptides that are subsets of the complete BCMA sequence may be used to identify and investigate parts of the protein important for function.

Specific expression systems of interest include bacterial, yeast, insect cell and mammalian cell derived expression systems. Representative systems from each of these categories is are provided below:

Bacteria. Expression systems in bacteria include those described in Chang et al., *Nature* (1978) 275:615; Goeddel et al., *Nature* (1979) 281:544; Goeddel et al., *Nucleic Acids Res.* (1980) 8:4057; EP 0 036,776; U.S. Pat. No. 4,551,433;

DeBoer et al., Proc. Natl. Acad. Sci. (USA) (1983) 80:21-25; and Siebenlist et al., Cell (1980) 20:269.

Yeast. Expression systems in yeast include those described in Hinnen et al., Proc. Natl. Acad. Sci. (USA) (1978) 75:1929; Ito et al., J. Bacteriol. (1983) 153:163; Kurtz et al., Mol. Cell. Biol. (1986) 6:142; Kunze et al., J. Basic Microbiol. (1985)25:141; Gleeson et al., J. Gen. Microbiol. (1986) 132:3459; Roggenkamp et al., Mol. Gen. Genet. (1986) 202:302; Das et al., J. Bacteriol. (1984) 158:1165; De Louvencourt et al., J. Bacteriol. (1983) 154:737; Van den Berg et al., Bio/Technology (1990)8:135; Kunze et al., J. Basic Microbiol. (1985)25:141; Cregg et al., Mol. Cell. Biol. (1985) 5:3376; U.S. Pat. Nos. 4,837,148 and 4,929,555; Beach and Nurse, Nature (1981) 300:706; Davidow et al., Curr. Genet. (1985) 10:380; Gaillardin et al., Curr. Genet. (1985) 10:49; Ballance et al., Biochem. Biophys. Res. Commun. (1983) 112:284-289; Tilburn et al., Gene (1983) 26:205-221; Yelton et al., Proc. Natl. Acad. Sci. (USA) (1984) 81:1470-1474; Kelly and Hynes, EMBO J. (1985) 4:475479; EP 0 244,234; and WO 91/00357.

Insect Cells. Expression of heterologous genes in insects is accomplished as described in U.S. Pat. No. 4,745,051; Friesen et al., "The Regulation of Baculovirus Gene Expression", in: The Molecular Biology Of Baculoviruses (1986) (W. Doerfler, ed.); EP 0 127,839; EP 0 155,476; and Vlak et al., J. Gen. Virol. (1988) 69:765-776; Miller et al., Ann. Rev. Microbiol. (1988) 42:177; Carbonell et al., Gene (1988) 73:409; Maeda et al., Nature (1985) 315:592-594; Lebacqz-Verheyden et al., Mol. Cell. Biol. (1988) 8:3129; Smith et al., Proc. Natl. Acad. Sci. (USA) (1985) 82:8844; Miyajima et al., Gene (1987) 58:273; and Martin et al., DNA (1988) 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow et al., Bio/Technology (1988) 6:47-55; Miller et al., Generic Engineering (1986) 8:277-279, and Maeda et al., Nature (1985) 315:592-594.

Mammalian Cells. Mammalian expression is accomplished as described in Dijkema et al., EMBO J. (1985) 4:761; Gorman et al., Proc. Natl. Acad. Sci. (USA) (1982) 79:6777; Boshart et al., Cell (1985) 41:521 and U.S. Pat. No. 4,399,216. Other features of mammalian expression are facilitated as described in Ham and Wallace, Meth. Enz. (1979) 58:44; Barnes and Sato, Anal. Biochem. (1980) 102:255, U.S. Pat. Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, WO 90/103430, WO 87/00195, and U.S. Pat. No. RE 30,985.

When any of the above host cells, or other appropriate host cells or organisms, are used to replicate and/or express the polynucleotides or nucleic acids of the invention, the resulting replicated nucleic acid, RNA, expressed protein or polypeptide, is within the scope of the invention as a product of the host cell or organism. The product is recovered by any appropriate means known in the art.

Once the gene corresponding to a selected polynucleotide is identified, its expression can be regulated-in the cell to which the gene is native. For example, an endogenous gene of a cell can be regulated by an exogenous regulatory sequence inserted into the genome of the cell at location sufficient to at least enhance expressed of the gene in the cell. The regulatory sequence may be designed to integrate into the genome via homologous recombination, as disclosed in U.S. Pat. Nos. 5,641,670 and 5,733,761, the disclosures of which are herein incorporated by reference, or may be designed to integrate into the genome via non-homologous recombination, as described in WO 99/15650, the disclosure of which is herein incorporated by reference. As such, also encompassed in the subject invention is the

production of BCMA proteins without manipulation of the encoding nucleic acid itself, but instead through integration of a regulatory sequence into the genome of cell that already includes a gene encoding the desired protein, as described in the above incorporated patent documents.

Preparation of Antibodies Specific for BCMA Polypeptides

The invention further can encompass the use of antibodies, particularly isolated antibodies, that are specific for BCMA polypeptides. The antibodies of the invention are useful in a variety of diagnostic assays or treatments, as described in further detail below. For example, an antibody can be used to detect and/or measure the levels of a BCMA polypeptide in a biological sample.

Isolated BCMA polypeptides of the invention are useful for the production of antibodies, where short fragments provide for antibodies specific for the particular polypeptide, and larger fragments or the entire protein allow for the production of antibodies over the surface of the polypeptide. Accordingly, the methods of the present invention can utilize isolated antibodies which specifically bind a BCMA polypeptide, or antigenic fragment thereof. Antibodies may be raised to the wild-type or variant forms. Antibodies may be raised to isolated peptides corresponding to these domains, or to the native protein. Antibodies may be raised to polypeptides and/or peptide fragments of BCMA from any mammalian species. As one non-limiting example, an enzyme-linked immunosorbent assay (ELISA) can be used to determine the specificity of a given monoclonal antibody for a BCMA polypeptide.

The BCMA polypeptides are useful for the production of antibodies, where short fragments provide for antibodies specific for the particular polypeptide, and larger fragments or the entire protein allow for the production of antibodies over the surface of the polypeptide. As used herein, the term "antibodies" includes antibodies of any isotype, fragments of antibodies which retain specific binding to antigen, including, but not limited to, Fab, Fv, scFv, and Fd fragments, fusion proteins comprising such antibody fragments, detectably labeled antibodies, and chimeric antibodies. "Antibody specificity", in the context of antibody-antigen interactions, is a term well understood in the art, and indicates that a given antibody binds to a given antigen, wherein the binding can be inhibited by that antigen or an epitope thereof which is recognized by the antibody, and does not substantially bind to unrelated antigens. Methods of determining specific antibody binding are well known to those skilled in the art, and can be used to determine the specificity of antibodies for a BCMA polypeptide. In specific embodiments, the BCMA antibody binds to the extracellular domain of BCMA. See, for example, Carter et al. (2007) Mol Can Ther 6:3009-18. In still further embodiments, the BCMA antibody binds to the extracellular domain of BCMA and further blocks BCMA activity. Methods for determining if a BCMA antibody blocks BCMA activity are known.

Antibodies are prepared in accordance with conventional ways, where the expressed is polypeptide or protein is used as an immunogen, by itself or conjugated to known immunogenic carriers, e.g. KLH, pre-S HBsAg, other viral or eukaryotic proteins, or the like. Various adjuvants may be employed, with a series of injections, as appropriate. For monoclonal antibodies, after one or more booster injections, the spleen is isolated, the lymphocytes immortalized by cell fusion, and then screened for high affinity antibody binding. The immortalized cells, i.e. hybridomas, producing the desired antibodies may then be expanded. For further description, see Monoclonal Antibodies: A Laboratory

Manual, Harlow and Lane eds., Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y., 1988. If desired, the mRNA encoding the heavy and light chains may be isolated and mutagenized by cloning in *E. coli*, and the heavy and light chains mixed to further enhance the affinity of the antibody. Alternatives to *in vivo* immunization as a method of raising antibodies include binding to phage display libraries, usually in conjunction with *in vitro* affinity maturation.

Antibodies may be attached, directly or indirectly (e.g., via a linker molecule) to a solid support for use in a diagnostic assay to determine and/or measure the presence of BCMA polypeptide in a biological sample. Attachment is generally covalent, although it need not be. Solid supports include, but are not limited to, beads (e.g., polystyrene beads, magnetic beads, and the like); plastic surfaces (e.g., polystyrene or polycarbonate multi-well plates typically used in an ELISA or radioimmunoassay (RIA), and the like); sheets, e.g., nylon, nitrocellulose, and the like; and chips, e.g., SiO₂ chips such as those used in microarrays. Accordingly, the invention further provides assay devices comprising antibodies attached to a solid support.

A single antibody or a battery of different antibodies can then be used to create an assay device. Such an assay device can be prepared using conventional technology known to those skilled in the art. The antibody can be purified and isolated using known techniques and bound to a support surface using known procedures. The resulting surface having antibody bound thereon can be used to assay a test sample, e.g., a biological sample, *in vitro* to determine if the sample contains one or more types of BCMA polypeptides. For example, antibodies which bind only to a specific BCMA epitope can be attached to the surface of a material. Alternatively, a plurality of specific antibodies, which may be arranged in an array, wherein antibodies specific for two or more different BCMA epitopes are attached to the solid support, can be used. A test sample is brought into contact with the antibodies bound to the surface of material. Specific binding can be detected using any known method. If specific binding is not detected, it can be deduced that the sample does not contain the specific BCMA epitope. As one non-limiting example of how specific binding can be detected, once the test sample has been contacted with the antibodies bound to the solid support, a second, detectably-labeled antibody can be added, which recognizes a BCMA epitope distinct from the epitope recognized by the solid support-bound antibody.

A variety of other reagents may be included in the assays to detect BCMA polypeptides described herein. These include reagents such as salts, neutral proteins, e.g. albumin, detergents, etc., that are used to facilitate optimal protein-protein binding, and/or reduce non-specific or background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, anti-microbial agents, etc. may be used. The components are added in any order that provides for the requisite binding. Incubations are performed at any suitable temperature, typically between 4° C. and 40° C. Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high-throughput screening. Typically between 0.1 and 1 hour will be sufficient.

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of the B cell surface marker. Other such antibodies may bind a first B cell marker and further bind a second B cell surface marker. Alternatively, an anti-B cell marker binding arm may be combined with an arm which binds to a triggering

molecule on a leukocyte such as a T-cell receptor molecule (e. g. CD2 or CD3), or Fc receptors for IgG (FcyR), such as FcyRI (CD64), FcyRII (CD32) and FcyRIII (CD16) so as to focus cellular defense mechanisms to the B cell. Bispecific antibodies may also be used to localize cytotoxic agents to the B cell. These antibodies possess a B cell marker-binding arm and an arm which binds the cytotoxic agent (e. g. saporin, anti-interferon-, vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten).

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e. g. F (ab')₂ bispecific antibodies). Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., *Nature*, 305: 537-539 (1983)).

Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO93/08829, and in Traunecker et al., *EMBO J.*, 10: 3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs-encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., *Methods in Enzymology*, 121: 210 (1986). According to another approach described in U.S. Pat. No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody

molecule are replaced with larger side chains (e. g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e. g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Pat. No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al, *Science*, 229: 81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.*, 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.*, 148 (5): 1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion.

The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers.

The "diabody" technology described by Hollinger et al, *Proc. Natl. Acad. Sci. USA*, 90: 6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VH and VL domains of one fragment are forced to pair with the complementary VL and VH domains of another fragment, thereby forming two antigen-binding sites.

Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., *J. Immunology*, 152: 5368 (1994). Antibodies with more than two valencies are also contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147: 60(1991).

Diagnostic Assays

The invention further provides methods for detecting the presence of and/or a level of BCMA mRNA in a biological sample; and methods for detecting the presence of and/or a level of BCMA polypeptide in a biological sample.

In other embodiments, a method is provided for detecting a level of BCMA mRNA in a biological sample derived from an individual, comprising analyzing a polynucleotide sample from an individual for the level of BCMA polypeptide-encoding mRNA. The level of BCMA mRNA may be associated with autoimmune disease.

In still other embodiments, a method is provided for detecting the presence of and/or the level of a BCMA polypeptide in a biological sample.

A number of methods are available for determining the expression level of a BCMA nucleic acid molecule, e.g., a BCMA mRNA, or BCMA polypeptide in a particular sample. Diagnosis may be performed by a number of methods to determine the absence or presence or altered amounts of normal or abnormal BCMA mRNA in a patient sample. For example, detection may utilize staining of cells or histological sections with labeled antibodies, performed in accordance with conventional methods. Cells are permeabilized to stain cytoplasmic molecules. The antibodies of interest are added to the cell sample, and incubated for a period of time sufficient to allow binding to the epitope, usually at least about 10 minutes. The antibody may be labeled with radioisotopes, enzymes, fluorescers, chemiluminescers, or other labels for direct detection. Alternatively, a second stage antibody or reagent is used to amplify the signal. Such reagents are well known in the art. For example, the primary antibody may be conjugated to biotin, with horseradish peroxidase-conjugated avidin added as a second stage reagent. Alternatively, the secondary antibody conjugated to a fluorescent compound, e.g. fluorescein, rhodamine, Texas red, etc. Final detection uses a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding may be determined by various methods, including flow cytometry of dissociated cells, microscopy, radiography, scintillation counting, etc. The presence and/or the level of a BCMA polypeptide may also be detected and/or quantitated in any way known to one of ordinary skill.

In addition, a test can include measurements of the expression of BCMA mRNA. Biochemical studies may be performed to determine whether a sequence polymorphism in a BCMA coding region or control regions is associated with disease. Disease associated polymorphisms may include deletion or truncation of the gene, mutations that alter expression level, that affect the activity of the protein, etc.

Changes in the promoter or enhancer sequence that may affect expression levels of BCMA can be compared to expression levels of the normal allele by various methods known in the art. Methods for determining promoter or enhancer strength include quantitation of the expressed natural protein; insertion of the variant control element into a vector with a reporter gene such as β -galactosidase, luciferase, chloramphenicol acetyltransferase, etc. that provides for convenient quantitation; and the like.

Diagnostic methods of the subject invention in which the level of BCMA gene expression is of interest will typically involve comparison of the BCMA nucleic acid or protein abundance of a sample of interest with that of a control value to determine any relative differences, where the difference may be measured qualitatively and/or quantitatively, which differences are then related to the presence or absence of an abnormal BCMA gene expression pattern. A variety of different methods for determine the nucleic acid abundance in a sample are known to those of skill in the art, where particular methods of interest include those described in: Pietu et al., *Genome Res.* (June 1996) 6: 492-503; Zhao et al., *Gene* (Apr. 24, 1995) 156: 207-213; Soares, *Curr. Opin. Biotechnol.* (October 1997) 8: 542-546; Raval, J. *Pharmacol Toxicol Methods* (November 1994) 32: 125-127; Chalifour et al., *Anal. Biochem* (Feb. 1, 1994) 216: 299-304; Stolz & Tuan, *Mol. Biotechnol.* (December 1996) 6: 225-230; Hong et al., *Bioscience Reports* (1982) 2: 907; and McGraw, *Anal. Biochem.* (1984) 143: 298. Also of interest are the methods disclosed in WO 97/27317, the disclosure of which is herein incorporated by reference.

By a gene whose expression level is "correlated with" or "associated with" a particular physiologic state, it is intended a gene whose expression shows a statistically significant correlation with the physiologic state. The strength of the correlation between the expression level of a differentially expressed gene and the presence or absence of a particular physiologic state may be determined by a statistical test of significance. Methods for determining the strength of a correlation between the expression level of a differentially-expressed gene and a particular physiologic state by assigning a statistical score to the correlation are reviewed in Holloway et al. (2002) *Nature Genetics Suppl.* 32:481-89, Churchill (2002) *Nature Genetics Suppl.* 32:490-95, Quackenbush (2002) *Nature Genetics Suppl.* 32: 496-501; Slonim (2002) *Nature Genetics Suppl.* 32:502-08; and Chuaqui et al. (2002) *Nature Genetics Suppl.* 32:509-514; each of which is herein incorporated by reference in its entirety.

Additional tests that have been associated with autoimmune disease severity or progression can be combined with the BCMA test described above to render a full diagnosis or outlook result.

For example, the American College of Rheumatology has developed 11 criteria to diagnose SLE, which span the clinical spectrum of SLE in aspects of skin, systemic, and laboratory tests. These criteria include malar rash, discoid rash, sensitivity to sun light, oral ulcers, arthritis, serositis, kidney and central nervous system inflammation, blood alterations, and the presence of antinuclear antibodies. A patient must meet four of these criteria in order to be classified as a SLE patient. (Tan et al. (1982) *Arthritis Rheumatol.* 25:1271-1277). SLE is usually confirmed by tests including, but not limited to, blood tests to detect anti-nuclear antibodies; blood and urine tests to assess kidney function; complement tests to detect the presence of low levels of complement that are often associated with SLE; a sedimentation rate (ESR) or C-reactive protein (CRP) to measure inflammation levels; X-rays to assess lung damage and EKGs to assess heart damage.

Monitoring Effects of Drug Treatment

Monitoring the influence of agents (e.g., drugs, compounds) on the expression or BCMA protein (e.g., modulation of transcriptional activation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to decrease BCMA gene expres-

sion, or protein levels, can be monitored in clinical trials of subjects exhibiting decreased BCMA gene expression or protein levels. In such clinical trials, the expression or activity of a BCMA gene, and preferably, other genes that have been implicated in, for example, a disorder associated with levels of BCMA protein can be used as a "read out" or markers of the phenotype of a particular cell, in the present case, B cells.

In some embodiments, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a BCMA protein or mRNA, in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject, (iv) detecting the level of expression or activity of the BCMA protein or mRNA in the post-administration samples; (v) comparing the level of expression or activity of the BCMA protein or mRNA in the pre-administration sample with the BCMA protein or mRNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. According to such an embodiment, BCMA expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

The basal expression level of BCMA in different tissue may be determined by analysis of tissue samples from individuals typed for the presence or absence of a specific polymorphism. Any convenient method may be use, e.g. ELISA, RIA, etc. for protein quantitation, northern blot or other hybridization analysis, quantitative RT-PCR, etc. for mRNA quantitation. The tissue specific expression is correlated with the genotype.

The alteration of BCMA expression in response to a modifier is determined by administering or combining the candidate modifier with an expression system, e.g. animal, cell, in vitro transcription assay, etc. The effect of the modifier on BCMA transcription and/or steady state mRNA levels is determined. As with the basal expression levels, tissue specific interactions are of interest. Correlations are made between the ability of an expression modifier to affect BCMA levels, and the presence of the provided polymorphisms. A panel of different modifiers, cell types, etc. may be screened in order to determine the effect under a number of different conditions.

Treatment Methods

The present invention provides a method of treating an individual clinically diagnosed with a condition associated with increased BCMA levels on the B cell surface. The methods generally comprises analyzing a biological sample to measure BCMA levels and comparing such levels to those present in healthy controls. A treatment plan that is most effective for individuals clinically diagnosed as having a condition associated with increased BCMA levels, such as autoimmune disease, is then selected. Thus, the invention further provides a method for predicting a patient's likelihood to respond to a drug treatment for a condition associated with increased BCMA levels, comprising determining a patient's expression of a BCMA gene, wherein the presence of a increased BCMA levels associated with an autoimmune condition, such as SLE, and is predictive of the patient's likelihood to respond to a drug treatment for the condition.

Thus, another aspect of the invention provides methods for tailoring an individual's therapeutic treatment with BCMA expression according to that individual's drug response. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

Autoimmune Diseases

The following is a non-limiting list of the possible autoimmune diseases that treatment thereof could be aided by the use of the BCMA measuring assay presently disclosed. B-cell regulated autoimmune diseases include arthritis (rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), psoriasis, dermatitis including atopic dermatitis; chronic autoimmune urticaria, polymyositis/dermatomyositis, toxic epidermal necrolysis, systemic scleroderma and sclerosis, responses associated with inflammatory bowel disease (IBD) (Crohn's disease, ulcerative colitis), respiratory distress syndrome, adult respiratory distress syndrome (ARDS), meningitis, allergic rhinitis, encephalitis, uveitis, colitis, glomerulonephritis, allergic conditions, eczema, asthma, conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, autoimmune myocarditis, leukocyte adhesion deficiency, systemic lupus erythematosus (SLE), lupus (including nephritis, non-renal, discoid, alopecia), juvenile onset diabetes, multiple sclerosis, allergic encephalomyelitis, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, tuberculosis, sarcoidosis, granulomatosis including Wegener's granulomatosis, agranulocytosis, vasculitis (including ANCA), aplastic anemia, Coombs positive anemia, Diamond Blackfan anemia, immune hemolytic anemia including autoimmune hemolytic anemia (AIHA), pernicious anemia, pure red cell aplasia (PRCA), Factor VIII deficiency, hemophilia A, autoimmune neutropenia, pancytopenia, leukopenia, diseases involving leukocyte diapedesis, CNS inflammatory disorders, multiple organ injury syndrome, myasthenia gravis, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, allergic neuritis, Bechet disease, Castleman's syndrome, Goodpasture's Syndrome, Lambert-Eaton Myasthenic Syndrome, Reynaud's syndrome, Sjorgen's syndrome, Stevens-Johnson syndrome, solid organ transplant rejection (including pretreatment for high panel reactive antibody titers, IgA deposit in tissues, etc), graft versus host disease (GVHD), pemphigoid bullous, pemphigus (all including vulgaris, foliaceus), autoimmune polyendocrinopathies, Reiter's disease, stiff-man syndrome, giant cell arteritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or IgM mediated neuropathy, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism; autoimmune endocrine diseases including autoimmune thyroiditis, chronic thyroiditis (Hashimoto's Thyroiditis), subacute thyroiditis, idiopathic hypothyroidism, Addison's disease, Grave's disease, autoimmune polyglandular syndromes (or polyglandular endocrinopathy syndromes), Type I diabetes also referred to as insulin-dependent diabetes mellitus (IDDM) and Sheehan's syndrome; autoimmune hepatitis, Lymphoid interstitial pneumonitis (HIV), bronchiolitis obliterans (non-transplant) vs NSIP, Guillain-Barre' Syndrome, Large Vessel Vasculitis (including Polymyalgia Rheumatica and Giant Cell (Takayasu's) Arteritis), Medium

Vessel Vasculitis (including Kawasaki's Disease and Polyarteritis Nodosa), ankylosing spondylitis, Berger's Disease (IgA nephropathy), Rapidly Progressive Glomerulonephritis, Primary biliary cirrhosis, Celiac sprue (gluten enteropathy), Cryoglobulinemia, ALS, and coronary artery disease. BLYS and/or APRIL Antagonists

If high levels of BCMA on a B cell surface of a patient suffering from an autoimmune disease are seen, this suggests the likelihood that the patient will respond favorably to inhibition of BLYS and/or APRIL. Thus, the present invention also comprises BLYS and/or APRIL antagonists that are used for the treatment of autoimmune diseases wherein the patient has elevated levels of BCMA protein expression on the surface of their B cells. The following are representative examples of BLYS and/or APRIL antagonists that could be utilized to treat such patients. For the purposes of functioning as a BLYS and/or APRIL antagonist, the extracellular domain of any of the TNFR family receptors is a polypeptide essentially free of the transmembrane or cytoplasmic domains that generally retains the ability to bind BLYS. Specifically, the extracellular domain of TACI can comprise amino acids 1 to 154 of the TACI polypeptide sequence (SEQ ID NO: 2). Additionally, the ECD can be fragments or variants of this sequence, such as ECD forms of TACI as described in von Bulow et al., supra, WO 98/39361, WO 00/40716, WO 01/85782, WO 01/87979, and WO 01/81417. In particular, these ECD forms can comprise amino acids 1-106 of SEQ ID NO:2, amino acids 1-142 of SEQ ID NO:2, amino acids 30-154 of SEQ ID NO:2, amino acids 30-106 of SEQ ID NO:2, amino acids 30-110 of SEQ ID NO:2, amino acids 30-119 of SEQ ID NO:2, amino acids 1-166 of SEQ ID NO:2, amino acids 1-165 of SEQ ID NO:2, amino acids 1-114 of SEQ ID NO: 2, amino acids 1-119 of SEQ ID NO:2, amino acids 1-120 of SEQ ID NO:2, and amino acids 1-126 of SEQ ID NO:2. In addition, the TACI ECD can comprise those molecules having only one cysteine rich domain.

ECD forms of BAFF-R include those comprising amino acids 1-71 of the BAFF-R polypeptide sequence (SEQ ID NO: 4). Additionally, the ECD can be fragments or variants of this sequence such as ECD forms of BAFF-R as described in WO 02/24909, WO 03/14294, and WO 02/38766. In particular, these ECD forms can comprise amino acids 1-77 of SEQ ID NO: 4, amino acids 7-77 of SEQ ID NO:4, amino acids 1-69 of SEQ ID NO:4, amino acids 7-69 of SEQ ID NO:4, amino acids 2-62 of SEQ ID NO:4, amino acids 2-71 of SEQ ID NO:4, amino acids 1-61 of SEQ ID NO:4 and amino acids 2-63 of SEQ ID NO:4, amino acids 1-45 of SEQ ID NO:4, amino acids 1-39 of SEQ ID NO:4, amino acids 7-39 of SEQ ID NO:4, amino acids 1-17 of SEQ ID NO:4, amino acids 39-64 of SEQ ID NO:4, amino acids 19-35 of SEQ ID NO:4, and amino acids 17-42 of SEQ ID NO:4. In addition, the BAFF-R ECD can comprise those molecules having a cysteine rich domain.

ECD forms of BCMA include those comprising amino acids 1-48 of the BCMA polypeptide sequence (SEQ ID NO: 6). Additionally, the ECD can be fragments or variants of this sequence, such as ECD forms of BCMA as described in WO 00/40716 and WO 05/075511. In particular, these ECD forms can comprise amino acids 1-150 of SEQ ID NO:6, amino acids 1-48 of SEQ ID NO:6, amino acids 1-41 of SEQ ID NO:6, amino acids 8-41 of SEQ ID NO:6, amino acids 8-37 of SEQ ID NO:6, amino acids 8-88 of SEQ ID NO:6, amino acids 41-88 of SEQ ID NO:6, amino acids 1-54 of SEQ ID NO:6, amino acids 4-55 of SEQ ID NO:6, amino acids 4-51 of SEQ ID NO:6, and amino acids 21-53 of SEQ

ID NO:6. In addition, the BCMA ECD can comprise those molecules having only a partial cysteine rich domain.

In a further embodiment, the BLYS binding region of a BLYS receptor (e. g., an extracellular domain or fragment thereof of BAFF-R, BCMA or TACI) can be fused to an Fc portion of an immunoglobulin molecule to facilitate its solubility in vivo. According to one embodiment, the BLYS and/or APRIL antagonist binds to a BLYS polypeptide with a binding affinity of 100 nM or less. According to another embodiment, the BLYS and/or APRIL antagonist binds to a BLYS polypeptide with a binding affinity of 10 nM or less. According to yet another embodiment, the BLYS and/or APRIL antagonist binds to a BLYS polypeptide with a binding affinity of 1 nM or less.

In another example, BLYS and/or APRIL antagonists include BLYS binding polypeptides that are not native sequences or variants thereof. Some examples of such polypeptides are those having the sequence of Formula I, Formula II, Formula III as described in WO 05/000351. In particular, some binding polypeptides include ECFDLL-VRAWVPCSVLK (SEQ ID NO:13), ECFDLL-VRHWVPCGLLR (SEQ ID NO:14), ECFDLL-VRRWVPCMLG (SEQ ID NO:15), ECFDLLVRSWVPCMLR (SEQ ID NO:16), ECFDLL-VRHWVACGLLR (SEQ ID NO:17), or sequences listed in FIG. 32 of WO 05/000351.

Alternatively, the BLYS and/or APRIL antagonist can bind an extracellular domain of native sequence TACI, BAFF-R, or BCMA at its BLYS binding region to partially or fully block, inhibit or neutralize BLYS binding in vitro, in situ, or in vivo. For example, such indirect antagonist is a TACI antibody that binds in a region of TACI such that the binding of BLYS is sterically hindered. For example, binding at amino acids 72-109 or a neighboring region is believed to block BLYS binding. It could also be advantageous to block APRIL binding to this molecule, which is believed to occur in the region of amino acids 82-222. Another BLYS and/or APRIL antagonist is a BAFF-R antibody that binds in a region of BAFF-R such that binding of human BAFF-R to BLYS is sterically hindered. For example, binding at amino acids 23-38 or amino acids 17-42 or a neighboring region is believed to block BLYS binding. Finally, a further indirect antagonist would be a BCMA antibody that binds in a region of BCMA such that the binding of BLYS is sterically hindered. For example, binding at amino acids 5-43 or a neighboring region is believed to block BLYS (or APRIL) binding.

In some embodiments, a BLYS and/or APRIL antagonist according to this invention includes BLYS antibodies. The term "antibody" when referring to is used in the broadest sense and specifically covers, for example, monoclonal antibodies, polyclonal antibodies, antibodies with polyeptopic specificity, single chain antibodies, and fragments of antibodies. According to some embodiments, a polypeptide of this invention is fused into an antibody framework, for example, in the variable region or in a CDR such that the antibody can bind to and inhibit BLYS binding to TACI, BAFF-R, or BCMA or inhibits BLYS signaling. The antibodies comprising a polypeptide of this invention can be chimeric, humanized, or human. The antibodies comprising a polypeptide of this invention can be an antibody fragment. Alternatively, an antibody of this invention can be produced by immunizing an animal with a polypeptide of this invention. Thus, an antibody directed against a polypeptide of this invention is contemplated.

In particular, antibodies specific for BLYS that bind within a region of human BLYS (SEQ ID NO: 8) comprising

residues 162-275 and/or a neighboring amino acid of amino acids selected from the group consisting of 162, 163, 206, 211, 231, 233, 264 and 265 of human BLYS are contemplated. The binding of the antibodies are such that the antibody sterically hinders BLYS binding to one or more of its receptors. Such antibodies are described in WO 02/02641 and WO 03/055979. A particularly preferred antibody is the one described as Lymphostat-B (Baker et al. (2003) *Arthritis Rheum*, 48, 3253-3265).

10 Other Immunosuppressive Drugs

The present method contemplates the use of other immunosuppressive drugs either singly or in combination with a BLYS, APRIL or BCMA inhibitor. These other drugs include, but are not limited to, immunosuppressive agents such as calcineurin inhibitors (e.g., cyclosporin A or FK506), steroids (e.g., methyl prednisone or prednisone), or immunosuppressive agents that arrest the growth of immune cells (e.g., rapamycin), anti-CD40 pathway inhibitors (e.g., anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway), transplant salvage pathway inhibitors (e.g., mycophenolate mofetil (MMF)), IL-2 receptor antagonists (e.g., Zeonpax© from Hoffmann-1a Roche Inc., and Simulet from Novartis, Inc.), or analogs thereof, cyclophosphamide, thalidomide, azathioprine, monoclonal antibodies (e.g., Daclizumab (anti-interleukin (IL)-2), Infliximab (anti-tumor necrosis factor), MEDI-205 (anti-CD2), abx-cb1 (anti-CD147)), and polyclonal antibodies (e.g., ATG (anti-thymocyte globulin)).

In one embodiment, a therapeutically effective amount of a BCMA antagonist (such as an antibody that binds the extracellular domain of BCMA) can be administered to a subject in combination with a therapeutically effective amount of rituximab. Such methods allow for the improved depletion and/or neutralization of B cells from said subject. Co-administration of such compounds can occur simultaneously or consecutively and through any effective route of administration.

As used herein, "a therapeutically effective amount" of an agent of interest is an amount which, when administered to a subject, is sufficient to achieve a desired effect, such as the depletion and/or neutralization of B-cells in a subject being treated with that composition.

In some embodiments a "therapeutically effective amount" or "effective amount" of a pharmaceutical composition containing a BCMA antagonist or an anti-CD 20 agent such as rituximab is from about 0.1 to about 200 mg/kg body weight in single or divided doses; for example from about 1 to about 100 mg/kg, from about 2 to about 50 mg/kg, from about 3 to about 25 mg/kg, or from about 5 to about 10 mg/kg. When animal assays are used, a dosage is administered to provide a target tissue concentration similar to that which has been shown to be effective in the animal assays. It is recognized that the method of treatment may comprise a single administration of a therapeutically effective amount or multiple administrations of a therapeutically effective amount of the BCMA antagonist (such as an antibody that binds the extracellular domain of BCMA) and the anti-CD 20 agent such as rituximab.

The term "anti-CD 20 agent" encompasses any molecule that binds to CD-20 and in the most preferred embodiment targets the cell associated with the CD-20 protein for killing. Such molecules include anti-CD-20 antibodies, such as RITUXAN® and follow-on versions of that agent such as ocrelizumab, a humanized version of that antibody, ofatumumab (HuMax-CD20® a fully human anti-CD 20 agent), DXL625 (a second generation anti-CD20 monoclonal), GA101 (a third generation anti-CD20 agent that has an

altered Fc region), the anti-CD20 molecules described in U.S. Application No. 20060121032, the anti-CD20 molecules described in U.S. Application No. 200700202059, the anti-CD20 molecules described in U.S. Application No. 20070014720, the anti-CD20 molecules described in U.S. Application No. 20060251652, the anti-CD20 molecules described in U.S. Application No. 20050069545, the anti-CD20 molecules described in U.S. Application No. 20040167319, TRU-015 (a small molecule immunopharmaceutical molecule that targets CD 20), as well as conjugated molecules such as ibritumomab (ZEVALIN®).

Pharmaceutical Formulations

Therapeutic formulations of the BLyS and/or APRIL antagonists such as BLyS-binding antibodies used in accordance with the present invention are prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Science 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyltrimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e. g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN, PLURONICS™ or polyethylene glycol (PEG)).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide a cytotoxic agent, chemotherapeutic agent, cytokine or immunosuppressive agent (e. g. one which acts on T cells, such as cyclosporin or an antibody that binds T cells, e. g. one which binds LFA-1). The effective amount of such other agents depends on the amount of antibody present in the formulation, the type of disease or disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein or about from 1 to 99% of the heretofore employed dosages.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing

the antagonist, which matrices are in the form of shaped articles, e. g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl-alcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and L-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

EXPERIMENTAL

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric.

EXAMPLE 1

Measurement of BCMA Levels on B Cells of Autoimmune Patients

Peripheral blood B cells were obtained by negative selection from 16 healthy controls (HC) and 15 SLE patients with whose disease activity was assessed by analysis of disease activity by SLEDAI. B cells were sub-grouped as CD19+CD27- (naïve), CD19+CD27+ (memory) and CD19+CD27high (plasmablasts). BAFF-R, TACI, and BCMA expression were compared by flow cytometry on each subset of B cells from SLE and healthy controls (HC) were compared by flow cytometry. The levels of serum BAFF-BLyS, APRIL and autoantibodies were quantified by ELISAs. In some experiments, BCMA-positive and -negative B cells were separated by flow cytometric sorting.

Expression Pattern of BAFF-R, TACI and BCMA in the Human Peripheral Blood B Cells

Peripheral blood B cells were stained with anti-BAFF-R, anti-TACI and anti-BCMA antibodies. It has been shown that the expressions of BAFF receptors change with B cell maturation; hence, naïve (CD27-), memory B cells (CD27+) and plasmablasts (CD27high) were all analyzed separately. BAFF-R and TACI are detected in all the subsets but BAFF-R expression is low in plasmablasts and TACI expression is lower in naïve B cells (FIG. 1A). Even though it has been reported that BCMA expression is limited only in the plasma cells and germinal center B cells, we could also see the BCMA+ population in naïve and memory B cells from peripheral blood (FIG. 1A). This difference might be due to the different specificity of antibodies to the various transcript variants because BCMA was reported as having five transcript variants which are results of alternative splicing. Average of BCMA+ B cells are 24% in naïve B cells and

20.8% in memory B cells, which is lower than that of plasmablasts (37.9%) (FIG. 6A)

Expression of BAFF-R, TACI and BCMA on the B Cells in Controls and SLE Patients

B cells from 15 patients with SLE and 16 non-autoimmune individuals were examined for expression of BAFF receptors. In the analysis of BAFF-R expression of the SLE and control groups, SLE patients showed significantly decreased BAFF-R expression in all three B cell subsets (MFI of control vs SLE, naïve=1387 vs 929, $p=0.002$; memory=1290 vs 840, $p=0.003$; plasmablasts=130 vs 85, $p=0.077$, FIG. 1B). TACI expressions of both two groups are not significantly different in all three subsets (MFI of control vs SLE, naïve=18.8 vs 24.4, $p=0.144$; memory=73.2 vs 60.4, $p=0.121$; plasmablasts=39.0 vs 32.1, $p=0.110$, FIG. 1C).

The B cells from SLE had higher surface BCMA expression than normal controls (MFI of control vs SLE—17.8 vs 27.9, $p=0.038$; FIG. 1D). The BCMA expression of SLE in memory B cells is higher than that of normal controls (BCMA MFI of naïve B cells=19.5 vs 29.5, $p=0.008$, FIG. 1D). But the BCMA expression of naïve and plasmablasts are not significantly different.

Relationships of BAFF Receptors and Serum BAFF/APRIL Level, Auto-Antibodies, Disease Activity.

There was an inverse correlation between BAFF-R expression of total B cells and serum BAFF ($p=0.0491$) but there was no significant correlation between BAFF-R expression and serum APRIL (FIG. 2). BAFF-R expression was inversely correlated with anti-dsDNA weakly ($p=0.064$) but not statistically significant. There was no correlation between BAFF-R and disease activity assessed by SLEDAI score ($p=0.342$, FIG. 2). MFI of BCMA positive memory cell is inversely correlated with serum IgG anti-dsDNA antibody levels ($p=0.0119$, FIG. 2) even though there's no significant correlation between BCMA and disease activity (SLEDAI) or serum BAFF level.

Characteristics of BCMA Positive B Cells

Lupus patients have increased BCMA expression on the naïve and memory B cells. We examined the characteristics of BCMA+ B cells to see the relations with autoimmunity. Mean FSC of BCMA+ and BCMA- cells in the each B cell subset was analyzed at first. Notably, lupus patients have the higher mean FSC than normal control indicating that the increased proportion of activated B cells in lupus as expected. BCMA+ B cells had higher mean FSC than BCMA- B cells in naïve B cells from both lupus and healthy controls (FIG. 3A). In memory B cells, BCMA+ B cells from healthy controls and lupus patients had significantly higher mean FSC than BCMA- B cells (FIG. 3A). These data might indicate that BCMA positive B cells in naïve and memory B cells are more activated B cells than BCMA negative B cells. This was true in both normal and SLE patients and there were no differences between them.

We also analyzed BCMA expression on the CD19high population which was reported as increased in the lupus patients. We couldn't find significant differences between healthy controls and lupus patients in CD19high population in our study (Sup. FIG. 2) but CD19high B cells have much higher BCMA expressions than CD19low B cells in both healthy controls and lupus patients (FIG. 3B). Higher CD19 expression in BCMA+ B cells might be related with higher sensitivity to many immunologic responses including BCR signaling because CD19 is a BCR co-receptor that augments BCR signaling and partner of multiple receptors like CD21, CD40, CD38, CD72, VLA-4 and FcγRIIB.

Most of the BCMA+ B cells are IgD+ and IgM+ in both lupus and healthy people, which means BCMA+ B cells are not class switched (FIG. 4A). Therefore, CD27- BCMA+ B cells might be included into the naïve B cell population. CD27+BCMA+ B cells also shows IgD+ and these cells could be un-class-switched memory B cells. Furthermore, lupus patients have higher percentage of IgD+ B cells than healthy control (FIG. 4B).

B cells of lupus patients are usually more activated than healthy people and it was reported that CD86 expression is much higher in lupus B cells. CD80 and CD86 expression of BCMA+ B cells were examined in lupus and healthy people. Lupus patients have much higher CD86 expressions and the percentage of CD86+ cells on the BCMA+ cells are higher than BCMA- cells. Healthy controls have lower CD86 expressions but percentage of CD86+ cells on the BCMA+ cells are higher than BCMA- cells. CD80 expressions were not high in both lupus and healthy controls (FIG. 4A). BAFF and APRIL plus CPG increased BCMA expression on all the subsets of B cells and induced expansion of plasmablasts and naïve B cells.

B cells isolated from PBMC of lupus patient and healthy control were labeled with CFSE (Carboxy-fluorescein diacetate) and incubated with CPG (oligodeoxynucleotides containing a CpG motif) with or without BAFF, APRIL or HT. After 4 day incubation, BCMA expression on each subset of B cells and their proliferation were analyzed (FIG. 5A and FIG. 5C). CPG alone didn't increase BCMA expression. BCMA expressions on all the subsets of B cells were increased significantly by CPG+BAFF and CPG+HT, especially on CD27high plasmablasts. CPG+APRIL also increased BCMA expression slightly. BAFF, APRIL, and HT induced strong proliferation of CD27 high B cells and moderate proliferation of CD27- B cells (FIG. 5B). But CD27+ population was not expanded. Decrease of CD27+ memory B population could be due to CD27+ cells were differentiated to CD27high plasma cells or due to the lack of proliferation CD27+ B cells.

Ig Secretion and Auto-Antibody Production by BCMA+ and BCMA- B Cells

B cells are isolated from PBMC of lupus and healthy people by magnetic sorting (B cell enrichment kit. Stemcell, British Columbia, Canada). BCMA+ B cells are sorted from isolated B cells by FACS sorting. The sorted BCMA+ B cells are incubated with or without anti-CD40/IL4, anti-CD40/IL4/CPG, anti-CD40/IL4/BCR for 5 days in the 96-well culture plate. The IgM and IgG concentration and anti-dsDNA activity of supernatants were analyzed by ELISA.

Summary of Results:

Whereas BAFF-R expression on SLE B cells was significantly lower compared to its levels on HC B cells (MFI of control vs SLE, naïve=1387 vs 929, $p=0.002$; memory=1290 vs 840, $p=0.003$), BCMA expression was substantially higher on SLE B cells (MFI of control vs SLE: 18 vs 28, $p=0.038$). This was most pronounced in the memory B cell subset (MFI of control vs SLE=19 vs 29, $p=0.008$). BCMA levels were not correlated with either disease severity (SLEDAI) or with serum BlyS or APRIL levels. BCMA+ cells also tended to be larger than BCMA-negative cells, and had higher CD19 and CD86 expression, indicating a greater degree of activation. To examine the functional implications of differential BCMA expression, purified BCMA-positive or BCMA-negative B cells were incubated with BlyS, APRIL or BlyS/APRIL heterotrimers (HT) with or without the TLR9 stimulator, CpG. Whereas none of the ligands induced proliferation of the BCMA+ B

cells on their own, the combination of CpG with each individual ligand induced substantial BCMA+ B cell proliferation.

Conclusions:

BCMA expression on B cells from patients with SLE is significantly increased, especially on memory B cells. BCMA positive cells have a more activated phenotype and produce higher amounts of immunoglobulin and autoantibodies. All 3 ligands, BLYS, APRIL or HT potently activate BCMA positive cells in the presence of CpG. These findings may help to explain the observed expansion of DNA reactive SLE B cells in the presence of BLYS and APRIL.

EXAMPLE 2

Combination Treatment with BCMA Antibodies and Rituximab in Human CD20 Transgenic Mice for the Depletion and/or Neutralization of B Cells

BCMA expression is important for the survival of plasma cells. Gene targeting has confirmed that survival of long lived bone marrow derived from plasma cells was reduced in BCMA deficient mice. Since CD20 is not expressed on long lived plasma cells in the bone marrow, targeting these cells with blocking or cytotoxic antibodies to BCMA should deplete these cells which may contribute a significant component of the anti-CD20 resistant autoantibody producing cells in patients with SLE. Combining such treatment with rituximab will provide further beneficial results.

Rituximab does not bind to mouse CD20 and therefore cannot be used to deplete B cells in normal mice. Also, there are no commercially available anti-mouse CD20 mAbs effective for in vivo B cell depletion. Gong et al. (*J. Immunol* 174:817-826; 2005) utilized a strain of human CD20 transgenic mice (generated using bacterial artificial chromosome/BAC technology) that they could treat with anti-human CD20 mAbs (rituximab and ocrelizumab) and induce B cell depletion or neutralization similar to that observed in humans treated with these mAbs. This example utilizes a strain of hCD20 Tg mice disclosed in Ahuja et al., *J. Immunol* 179:3351-3361; 2007.

General approach: Use optimal doses of each therapeutic (BCMA antibody antagonists which binds to the extracellular domain of BCMA and rituximab), either sequentially or in combination and evaluate B cell depletion and/or neutral-

ization. Assess B cell depletion at an optimal timepoint (3 weeks), but include additional groups to evaluate B cell recovery following treatment cessation (~20 weeks).

Materials and Methods

TABLE 1

Treatment	Concentration	Final dose solution (mg/mL)	Volume/mouse (mL)	Route	Schedule
PBS	—	—	0.2	SC	M/W/F × 3 weeks
BCMA antibody	Therapeutically effective dose	—	—	SC	M/W/F × 3 weeks (9 doses/mouse)
Rituxan (Rituximab)	stock = 10 mg/mL	10.0	0.2-0.25	IP	once a week for 2 or 3 weeks (three weekly doses for Groups 3 and 4; two weekly doses for Group 5)

Animal Care, Acclimation, and Housing

Room temperature is maintained at 70-74° F. and humidity maintained at 30%-70%. A light/dark cycle of 12 hours is used, except when room lights may be turned on during the dark cycle to accommodate study-related activities. Each animal is offered rodent chow (irradiated 5056, Pico Lab, Richmond, Ind.) and water ad libitum. Procedures in this study are designed to avoid or minimize discomfort, distress, or pain to animals. Treatment of study animals is in accordance with conditions specified in the Guide for the Care and Use of Laboratory Animals (ILAR publication, 1996, National Academy Press). The animals are randomly assigned to the various treatment groups.

Treatment Groups: The period of dosing is designated as the dosing phase. The first day of dosing is designated "Day 1." The day prior to Day 1 is "Day -1." The day following the dosing phase terminal sacrifice is the first day of the recovery phase.

TABLE 2

Group	1 st Treatment (route)	2 nd Treatment (route)	Dose schedule	Sac Day 23	Sac Week ~20
1	PBS (SC)	PBS (SC)	3 times weekly	5	6
2	BCMA antibody Therapeutically effective dose (SC)	—	3 times weekly for 3 weeks (total of 9 doses)	5	5
3	Rituximab 10 mg/kg (IP)	—	once weekly for 3 weeks (total of 3 doses)	5	5
4	Rituximab 10 mg/kg (IP)	BCMA antibody (SC) Therapeutically effective dose	Stagger treatments by 2 days; continue both treatments for 3 wks	5	6
5	BCMA antibody (SC) Therapeutically effective dose	Rituximab 10 mg/kg (IP)	BCMA antibody for 3 weeks (9 doses), Rituximab for last 2 weeks of BCMA antibody dosing period (2 doses)	5	6

35

Rituximab is administered intraperitoneally (IP). The BCMA antibody and vehicle (PBS) is administered via subcutaneous (SC) injection within the subscapular region three times weekly (9 total doses). The first dose is administered on Day 1 (D1). In combination treatment groups, and where relevant, all animals receive the IP injection first, followed by administration of the SC injection within a period of 60 minutes. GROUP 4: rituximab 1st, then BCMA antibody; GROUP 5: BCMA antibody 1st, then rituximab. Dose volumes are adjusted weekly according to individual animal body weights.

Summary of Study Endpoints:

Whole blood (150 μ L; EDTA) is collected and flow cytometry analysis performed for T and B cell subsets. Serum (~100 μ L whole blood placed in serum separator tubes) is collected at various timepoints for later analysis of total IgG₁, IgG_{2a}, IgM, IgE and IgA by Luminex assay.

At sac, spleens are collected and processed for flow analysis and later IHC/histology. Splenectomy is performed under isoflurane anesthesia prior to blood collection. Whole spleen is weighed and recorded before sectioning.

At sac, major peripheral lymph nodes (inguinal, axillary, brachial, cervical, and mesenteric) are collected for possible future IHC and histology. The lymph nodes are fixed with formalin or Zinc Tris buffer and stored in 70% alcohol for possible future use.

For histology: $\frac{1}{3}$ spleen and 1 LLN (left LN) are placed into ZnTris and the same tissues (right LN) is collected into 10% NBF.

All animals in Groups 1-5 have serum (100 μ L blood in serum separator tubes) and whole blood (150 μ L in EDTA tubes) collected on day -5 via retro-orbital vein. Serum Collection: A minimum of 100 μ L of whole blood is placed into serum separator tubes and allowed to clot for a minimum of 15 minutes. Blood is then spun at 4000 rpm for 10 minutes. A minimum of 50 μ L of serum is aliquoted into a second container. Aliquots of serum are stored at $\leq 60^\circ$ C.

Whole Blood in EDTA Collection: A minimum of 150 μ L of blood is placed into a microtainer tube containing EDTA. The tubes are gently inverted a minimum of 20 times. Whole blood in EDTA samples are stored at room temperature until processed for flow cytometry.

All animals that are sacrificed are anesthetized with isoflurane. All sacrificed animals have blood, serum, spleen and major peripheral lymph nodes collected. The spleen is collected under isoflurane anesthesia prior to the blood sample to avoid altering splenocyte subsets. The whole spleen is weighed. The spleen is cut into 3 sections (cranial, middle & caudal), to be processed as shown in Table 3.

TABLE 3

Collection of Spleen Samples			
Spleen section ¹	Media	Use	Storage
Cranial	Zinc-Tris Buffer	IHC	Room Temperature
Middle	RPMI + 10% FBS	Flow Cytometry	4 degrees Celsius
Caudal	10% NBF	Histology	Room Temperature

Lymph Node Collection: Major peripheral lymph nodes (inguinal, axillary, brachial, cervical and mesenteric) are collected for histology/IHC in cassettes.

36

- Cassettes containing Left Lymph Nodes (excluding mesenteric LN) for IHC are placed into Zinc Tris buffer.
- Cassettes containing Right Lymph Nodes (excluding mesenteric LN) for histology are placed into 10% NBF.
- Cassettes containing Mesenteric Lymph Nodes are collected into 10% NBF by taking the entire intestinal tract (from stomach to just above the rectum) whole and unflushed.

All samples are stored at room temperature.

TABLE 4

Collection of Lymph Nodes			
LN ¹	Media	Potential Use	Storage
Left LNs	Zinc-Tris Buffer	IHC	Room Temperature
Mesenteric	10% NBF	Histology	Room Temperature
Right LNs	10% NBF	Histology	Room Temperature

Whole Blood Immunophenotyping: Briefly, whole blood is collected into BD Microtainer™ tubes containing K₂EDTA anticoagulant. A 50 μ L aliquot of whole blood is incubated with the appropriate working antibody cocktail (see Table 5) and red blood cells are lysed. Prior to sample acquisition on the flow cytometer, Flow Count™ fluorescent microspheres are added to each sample tube for calculating absolute cell concentrations. Data acquisition is conducted on a BD FACSCalibur flow cytometer equipped with a 15 mW air-cooled Argon ion laser with 488 nm emission and a red-diode laser with 635 nm emission.

TABLE 5

Whole blood four-color monoclonal antibody panel		
Antibody Panel	Cell Type Identified	
CD45/B220/ IgD/IgM	Total lymphocytes	[CD45+]
	Total B lymphocyte	[CD45+/B220+]
	Mature B lymphocytes	[CD45+/B220+/IgD+/IgM-]
	Immature B lymphocytes	[CD45+/B220+/IgD-/IgM+]
CD3/B220/ CD19/hu CD20	Mature Naïve B lymphocytes	[CD45+/B220+/IgD+/IgM+]
	Total T lymphocytes	[CD3+]
	Total B lymphocyte	[CD3-/B220+]
	B lymphocytes ¹	[B220+/CD19+/huCD20-]
	B lymphocytes ²	[B220+/CD19+/huCD20+]

¹The phenotype [B220+/CD19+/huCD20-] describes a population of B cells expressing both B220 and murine CD19 surface antigen but not the human CD20 transgene.

²The phenotype [B220+/CD19+/huCD20+] describes a population of B cells expressing both B220 and murine CD19 surface antigen including the human CD20 transgene.

Spleen Immunophenotyping: Briefly, single cells are isolated and incubated with the appropriate antibody cocktails (see Table 6). Instrument calibration and data acquisition is conducted as for whole blood immunophenotyping.

TABLE 6

Spleen four-color monoclonal antibody panel		
ANTIBODY PANEL	B CELL SUBSET IDENTIFIED	
IgD/IgM/B220/ hCD20	F(I) Mature	[B220+/IgM ^{low} /IgD+]
	F(II) Less Mature	[B220+/IgM+/IgD+]
	F(III) Less Mature	[B220+/IgM+/IgD ^{low}]
CD23/CD21/B220/ CD45	MZ (marginal zone)	[B220+/CD21+/CD23 ^{low}]
	FO (follicular)	[B220+/CD21 ^{low} /CD23+]
	NF Newly Formed	[B220+/CD21-/CD23-]

TABLE 6-continued

Spleen four-color monoclonal antibody panel		
ANTIBODY PANEL	B CELL SUBSET IDENTIFIED	
IgM/CD21/B220/ CD45	M (Mature)	[B220+/IgM ^{low} /CD21 ^{low}]
	T2 (Transitional 2)/ MZ	[B220+/IgM+/CD21+]
	T1 (Transitional 1)	[B220+/IgM+/CD21-]

IHC Analysis

Tissues: Test tissues includes samples from both spleens and lymph nodes. For the spleen samples, transverse sections of spleen (cranial and caudal pieces) from each animal is included. The cranial spleen sections (Zinc Tris-fixed) are stained with rat monoclonal antibody to CD45R/B220, CD138, or CD5 alone. A subset of tissue sections will also be stained with rat isotype IgG as a negative control. The caudal spleen sections (formalin-fixed) is stained with biotinylated PNA (if necessary to visualize GC; H&E may suffice) and H&E. A subset of tissue sections is also stained with biotinylated parathyroid hormone-related protein (PTHrP) as a negative control.

The lymph nodes examined from each animal include the inguinal, axillary, brachial, cervical, and mesenteric. The lymph nodes are fixed with formalin or zinc Tris and held in 70% alcohol for possible future use.

Antibodies: The antibodies used included three rat monoclonal antibodies to mouse CD45R/B220 (clone RA3-6B2,

isotype: rat IgG2a, k; 0.5 mg/mL, #557390, BD Biosciences, San Jose, Calif.), CD5 (Ly-1, clone 53-7.3, 0.5 mg/mL, #553017, BD Biosciences), and CD138 (clone Syndecan-1, 0.5 mg/mL, #553712, BD Biosciences).

5 Statistical Analyses: Statistical analyses of group differences in organ weights, B cell counts, and immunoglobulin levels were conducted using analysis of variance (ANOVA).

10 Collection of the data outlined above will allow the percent change in absolute concentration of B cells in the mouse peripheral blood samples at various time points for the stated treatment group to be determined. Alternatively, the data can be expressed as a change in the percent of positive lymphocytes or B220+ cells. Such data will demonstrate that the combination of anti-CD 20 agents and BCMA antagonists, such as RITUXAN® and a BCMA antibody, result in a depletion (in some embodiments a synergistic depletion) and/or neutralization of B cells levels compared to the level of reduction with RITUXAN® and BCMA antagonists alone at many time points.

20 While the present invention has been described with reference to the specific embodiments thereof, it is to be understood by those skilled in the art that various changes may be made and an equivalence may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the object, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

SEQUENCE LISTING

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agc c g t g t g g a c c a g g a g g a g c g c t t t c c a c a g g g c c t g t g g a c g g g g 97
Ser Arg Val Asp Gln Glu Glu Arg Phe Pro Gln Gly Leu Trp Thr Gly
15 20 25

g t g g c t a t g a g a t c c t g c c c g a a g a g c a g t a c t g g g a t c c t c t g c t g 145
Val Ala Met Arg Ser Cys Pro Glu Glu Gln Tyr Trp Asp Pro Leu Leu
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g g t a c c t g c a t g t c c t g c a a a a c c a t t t g c a a c c a t c a g a g c c a g c g c 193
Gly Thr Cys Met Ser Cys Lys Thr Ile Cys Asn His Gln Ser Gln Arg
45 50 55 60

a c c t g t g c a g c c t t c t g c a g g t c a c t c a g c t g c c g c a a g g a g c a a g g c 241
Thr Cys Ala Ala Phe Cys Arg Ser Leu Ser Cys Arg Lys Glu Gln Gly
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a a g t t c t a t g a c c a t c t c c t g a g g a c t g c a t c a g c t g t g c c t c c a t c 289
Lys Phe Tyr Asp His Leu Leu Arg Asp Cys Ile Ser Cys Ala Ser Ile
80 85 90

t g t g g a c a g c a c c c t a a g c a a t g t g c a t a c t t c t g t g a g a a c a a g c t c 337
Cys Gly Gln His Pro Lys Gln Cys Ala Tyr Phe Cys Glu Asn Lys Leu
95 100 105

a g g a g c c c a g t g a a c c t t c c a c c a g a g c t c a g g a g a c a g c g g a g t g g a 385

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Glu	Val	Glu	Asn	Asn	Ser	Asp	Asn	Ser	Gly	Arg	Tyr	Gln	Gly	Leu	Glu	
125					130					135					140	
cac aga ggc tca gaa gca agt cca gct ctc ccg ggg ctg aag ctg agt 481																
His	Arg	Gly	Ser	Glu	Ala	Ser	Pro	Ala	Leu	Pro	Gly	Leu	Lys	Leu	Ser	
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gca gat cag gtg gcc ctg gtc tac agc acg ctg ggg ctc tgc ctg tgt 529																
Ala	Asp	Gln	Val	Ala	Leu	Val	Tyr	Ser	Thr	Leu	Gly	Leu	Cys	Leu	Cys	
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Ala	Val	Leu	Cys	Cys	Phe	Leu	Val	Ala	Val	Ala	Cys	Phe	Leu	Lys	Lys	
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Arg	Gly	Asp	Pro	Cys	Ser	Cys	Gln	Pro	Arg	Ser	Arg	Pro	Arg	Gln	Ser	
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ccg gcc aag tct tcc cag gat cac gcg atg gaa gcc ggc agc cct gtg 673																
Pro	Ala	Lys	Ser	Ser	Gln	Asp	His	Ala	Met	Glu	Ala	Gly	Ser	Pro	Val	
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tgc agg gcg ccc acg cag gag agc gca gtc acg cct ggg acc ccc gac 769																
Cys	Arg	Ala	Pro	Thr	Gln	Glu	Ser	Ala	Val	Thr	Pro	Gly	Thr	Pro	Asp	
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ccc act tgt gct gga agg tgg ggg tgc cac acc agg acc aca gtc ctg 817																
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Ser Cys Pro Glu Glu Gln Tyr Trp Asp Pro Leu Leu Gly Thr Cys Met																
		35					40					45				

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

Asn Leu Pro Pro Glu Leu Arg Arg Gln Arg Ser Gly Glu Val Glu Asn
115 120 125

Asn Ser Asp Asn Ser Gly Arg Tyr Gln Gly Leu Glu His Arg Gly Ser
130 135 140

Glu Ala Ser Pro Ala Leu Pro Gly Leu Lys Leu Ser Ala Asp Gln Val
145 150 155 160

Ala Leu Val Tyr Ser Thr Leu Gly Leu Cys Leu Cys Ala Val Leu Cys
165 170 175

Cys Phe Leu Val Ala Val Ala Cys Phe Leu Lys Lys Arg Gly Asp Pro
180 185 190

Cys Ser Cys Gln Pro Arg Ser Arg Pro Arg Gln Ser Pro Ala Lys Ser
195 200 205

Ser Gln Asp His Ala Met Glu Ala Gly Ser Pro Val Ser Thr Ser Pro
210 215 220

Glu Pro Val Glu Thr Cys Ser Phe Cys Phe Pro Glu Cys Arg Ala Pro
225 230 235 240

Thr Gln Glu Ser Ala Val Thr Pro Gly Thr Pro Asp Pro Thr Cys Ala
245 250 255

Gly Arg Trp Gly Cys His Thr Arg Thr Thr Val Leu Gln Pro Cys Pro
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Gly Arg Asp Ala Pro Ala Pro Thr Pro Cys Val Pro Ala Glu Cys Phe
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gac ctg ctg gtc cgc cac tgc gtg gcc tgc ggg ctc ctg cgc acg ccg 149
Asp Leu Leu Val Arg His Cys Val Ala Cys Gly Leu Leu Arg Thr Pro
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cgg ccg aaa ccg gcc ggg gcc agc agc cct gcg ccc agg acg gcg ctg 197
Arg Pro Lys Pro Ala Gly Ala Ser Ser Pro Ala Pro Arg Thr Ala Leu
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cag ccg cag gag tcg gtg ggc gcg ggg gcc ggc gag gcg gcg ctg ccc 245
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cgg cgg ctt cgc ggc gcg tcc tcc gca gag gcc ccc gac gga gac aag   389
Arg Arg Leu Arg Gly Ala Ser Ser Ala Glu Ala Pro Asp Gly Asp Lys
                110                115                120

gac gcc cca gag ccc ctg gac aag gtc atc att ctg tct ccg gga atc   437
Asp Ala Pro Glu Pro Leu Asp Lys Val Ile Ile Leu Ser Pro Gly Ile
                125                130                135

tct gat gcc aca gct cct gcc tgg cct cct cct ggg gaa gac cca gga   485
Ser Asp Ala Thr Ala Pro Ala Trp Pro Pro Pro Gly Glu Asp Pro Gly
                140                145                150

acc acc cca cct ggc cac agt gtc cct gtg cca gcc aca gag ctg ggc   533
Thr Thr Pro Pro Gly His Ser Val Pro Val Pro Ala Thr Glu Leu Gly
                155                160                165

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<212> TYPE: PRT
<213> ORGANISM: homo sapiens

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<400> SEQUENCE: 4

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      35      40      45

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

Ala Gly Ala Gly Glu Ala Ala Leu Pro Leu Pro Gly Leu Leu Phe Gly
      65      70      75      80

Ala Pro Ala Leu Leu Gly Leu Ala Leu Val Leu Ala Leu Val Leu Val
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Gly Leu Val Ser Trp Arg Arg Arg Gln Arg Arg Leu Arg Gly Ala Ser
      100      105      110

Ser Ala Glu Ala Pro Asp Gly Asp Lys Asp Ala Pro Glu Pro Leu Asp
      115      120      125

Lys Val Ile Ile Leu Ser Pro Gly Ile Ser Asp Ala Thr Ala Pro Ala
      130      135      140

Trp Pro Pro Pro Gly Glu Asp Pro Gly Thr Thr Pro Pro Gly His Ser
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agctgctctt gctgcatttg ctctggaatt cttgtagaga tattacttgt ccttccaggc      180
tgttctttct gtagctcctt tgttttcttt ttgtgatc atg ttg cag atg gct ggg      236
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                               1             5

cag tgc tcc caa aat gaa tat ttt gac agt ttg ttg cat gct tgc ata      284
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                10             15             20

cct tgt caa ctt cga tgt tct tct aat act cct cct cta aca tgt cag      332
Pro Cys Gln Leu Arg Cys Ser Ser Asn Thr Pro Pro Leu Thr Cys Gln
                25             30             35

cgt tat tgt aat gca agt gtg acc aat tca gtg aaa gga acg aat gcg      380
Arg Tyr Cys Asn Ala Ser Val Thr Asn Ser Val Lys Gly Thr Asn Ala
                40             45             50

att ctc tgg acc tgt ttg gga ctg agc tta ata att tct ttg gca gtt      428
Ile Leu Trp Thr Cys Leu Gly Leu Ser Leu Ile Ile Ser Leu Ala Val
                55             60             65             70

ttc gtg cta atg ttt ttg cta agg aag ata agc tct gaa cca tta aag      476
Phe Val Leu Met Phe Leu Leu Arg Lys Ile Ser Ser Glu Pro Leu Lys
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gac gag ttt aaa aac aca gga tca ggt ctc ctg ggc atg gct aac att      524
Asp Glu Phe Lys Asn Thr Gly Ser Gly Leu Leu Gly Met Ala Asn Ile
                90             95             100

gac ctg gaa aag agc agg act ggt gat gaa att att ctt ccg aga ggc      572
Asp Leu Glu Lys Ser Arg Thr Gly Asp Glu Ile Ile Leu Pro Arg Gly
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ctc gag tac acg gtg gaa gaa tgc acc tgt gaa gac tgc atc aag agc      620
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                120             125             130

aaa ccg aag gtc gac tct gac cat tgc ttt cca ctc cca gct atg gag      668
Lys Pro Lys Val Asp Ser Asp His Cys Phe Pro Leu Pro Ala Met Glu
                135             140             145             150

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Glu Gly Ala Thr Ile Leu Val Thr Thr Lys Thr Asn Asp Tyr Cys Lys
                155             160             165

agc ctg cca gct gct ttg agt gct acg gag ata gag aaa tca att tct      764
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                170             175             180

gct agg taattaacca tttcgactcg agcagtgcca ctttaaaaat cttttgtcag      820
Ala Arg

aatagatgat gtgtcagatc tctttaggat gactgtatctt ttcagttgcc gatacagctt      880
tttgtcctct aactgtggaa actctttatg ttagatatat ttctctaggt tactgttggg      940
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<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

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Val Lys Gly Thr Asn Ala Ile Leu Trp Thr Cys Leu Gly Leu Ser Leu			
	50	55	60
Ile Ile Ser Leu Ala Val Phe Val Leu Met Phe Leu Leu Arg Lys Ile			
	65	70	75
Ser Ser Glu Pro Leu Lys Asp Glu Phe Lys Asn Thr Gly Ser Gly Leu			
	85	90	95
Leu Gly Met Ala Asn Ile Asp Leu Glu Lys Ser Arg Thr Gly Asp Glu			
	100	105	110
Ile Ile Leu Pro Arg Gly Leu Glu Tyr Thr Val Glu Glu Cys Thr Cys			
	115	120	125
Glu Asp Cys Ile Lys Ser Lys Pro Lys Val Asp Ser Asp His Cys Phe			
	130	135	140
Pro Leu Pro Ala Met Glu Glu Gly Ala Thr Ile Leu Val Thr Thr Lys			
	145	150	155
Thr Asn Asp Tyr Cys Lys Ser Leu Pro Ala Ala Leu Ser Ala Thr Glu			
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Ile Glu Lys Ser Ile Ser Ala Arg			
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ccctgtggtc acttattcta aaggccccaa ccttcaaagt tcaagtagtg at atg gat	178
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aga gaa gaa atg aaa ctg aag gag tgt gtt tcc atc ctc cca cgg aag	274
Arg Glu Glu Met Lys Leu Lys Glu Cys Val Ser Ile Leu Pro Arg Lys	
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gaa agc ccc tct gtc cga tcc tcc aaa gac gga aag ctg ctg gct gca	322
Glu Ser Pro Ser Val Arg Ser Ser Lys Asp Gly Lys Leu Leu Ala Ala	
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acc ttg ctg ctg gca ctg ctg tct tgc tgc ctc acg gtg gtg tct ttc	370
Thr Leu Leu Leu Ala Leu Leu Ser Cys Cys Leu Thr Val Val Ser Phe	
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tac cag gtg gcc gcc ctg caa ggg gac ctg gcc agc ctc cgg gca gag	418
Tyr Gln Val Ala Ala Leu Gln Gly Asp Leu Ala Ser Leu Arg Ala Glu	
	70 75 80
ctg cag ggc cac cac gcg gag aag ctg cca gca gga gca gga gcc ccc	466
Leu Gln Gly His His Ala Glu Lys Leu Pro Ala Gly Ala Gly Ala Pro	
	85 90 95
aag gcc ggc ctg gag gaa gct cca gct gtc acc gcg gga ctg aaa atc	514

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Lys	Ala	Gly	Leu	Glu	Glu	Ala	Pro	Ala	Val	Thr	Ala	Gly	Leu	Lys	Ile		
	100					105					110						
ttt	gaa	cca	cca	gct	cca	gga	gaa	ggc	aac	tcc	agt	cag	aac	agc	aga		562
Phe	Glu	Pro	Pro	Ala	Pro	Gly	Glu	Gly	Asn	Ser	Ser	Gln	Asn	Ser	Arg		
115				120					125						130		
aat	aag	cgt	gcc	ggt	cag	ggt	cca	gaa	gaa	aca	gtc	act	caa	gac	tgc		610
Asn	Lys	Arg	Ala	Val	Gln	Gly	Pro	Glu	Glu	Thr	Val	Thr	Gln	Asp	Cys		
				135					140					145			
ttg	caa	ctg	att	gca	gac	agt	gaa	aca	cca	act	ata	caa	aaa	gga	tct		658
Leu	Gln	Leu	Ile	Ala	Asp	Ser	Glu	Thr	Pro	Thr	Ile	Gln	Lys	Gly	Ser		
			150					155					160				
tac	aca	ttt	ggt	cca	tgg	ctt	ctc	agc	ttt	aaa	agg	gga	agt	gcc	cta		706
Tyr	Thr	Phe	Val	Pro	Trp	Leu	Leu	Ser	Phe	Lys	Arg	Gly	Ser	Ala	Leu		
		165				170						175					
gaa	gaa	aaa	gag	aat	aaa	ata	ttg	gtc	aaa	gaa	act	ggt	tac	ttt	ttt		754
Glu	Glu	Lys	Glu	Asn	Lys	Ile	Leu	Val	Lys	Glu	Thr	Gly	Tyr	Phe	Phe		
	180					185					190						
ata	tat	ggt	cag	ggt	tta	tat	act	gat	aag	acc	tac	gcc	atg	gga	cat		802
Ile	Tyr	Gly	Gln	Val	Leu	Tyr	Thr	Asp	Lys	Thr	Tyr	Ala	Met	Gly	His		
195				200					205					210			
cta	att	cag	agg	aag	aag	gtc	cat	gtc	ttt	ggg	gat	gaa	ttg	agt	ctg		850
Leu	Ile	Gln	Arg	Lys	Lys	Val	His	Val	Phe	Gly	Asp	Glu	Leu	Ser	Leu		
				215					220					225			
gtg	act	ttg	ttt	cga	tgt	att	caa	aat	atg	cct	gaa	aca	cta	ccc	aat		898
Val	Thr	Leu	Phe	Arg	Cys	Ile	Gln	Asn	Met	Pro	Glu	Thr	Leu	Pro	Asn		
			230					235					240				
aat	tcc	tgc	tat	tca	gct	ggc	att	gca	aaa	ctg	gaa	gaa	gga	gat	gaa		946
Asn	Ser	Cys	Tyr	Ser	Ala	Gly	Ile	Ala	Lys	Leu	Glu	Glu	Gly	Asp	Glu		
		245				250						255					
ctc	caa	ctt	gca	ata	cca	aga	gaa	aat	gca	caa	ata	tca	ctg	gat	gga		994
Leu	Gln	Leu	Ala	Ile	Pro	Arg	Glu	Asn	Ala	Gln	Ile	Ser	Leu	Asp	Gly		
	260					265					270						
gat	gtc	aca	ttt	ttt	ggt	gca	ttg	aaa	ct	gctgtgacct	acttacacca						1043
Asp	Val	Thr	Phe	Phe	Gly	Ala	Leu	Lys									
275				280													
tgtctgtagc	tattttctc	cctttctctg	tacctctaag	aagaaagaat	ctaactgaaa												1103
ataccaaaaa	aaaaaaaaaa	aaaaaaaaaa	ccctcgagcg	gccgcc													1149

<210> SEQ ID NO 8

<211> LENGTH: 283

<212> TYPE: PRT

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 8

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

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Lys Ile Phe Glu Pro Pro Ala Pro Gly Glu Gly Asn Ser Ser Gln Asn
 115 120 125
 Ser Arg Asn Lys Arg Ala Val Gln Gly Pro Glu Glu Thr Val Thr Gln
 130 135 140
 Asp Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys
 145 150 155 160
 Gly Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser
 165 170 175
 Ala Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr
 180 185 190
 Phe Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met
 195 200 205
 Gly His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu
 210 215 220
 Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu
 225 230 235 240
 Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly
 245 250 255
 Asp Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu
 260 265 270
 Asp Gly Asp Val Thr Phe Phe Gly Ala Leu Lys
 275 280

<210> SEQ ID NO 9
 <211> LENGTH: 1680
 <212> TYPE: DNA
 <213> ORGANISM: mus musculus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (164)...(1093)

<400> SEQUENCE: 9

tactcactat agggctcgag cggccgcccc ggcaggtgct cctgggggaa cccagcctg 60
 ccatgctctg agggcagtct cccaggacac agatgacagg aaatgaccca cccctgtggt 120
 cacttactcc aaaggcctag accttcaaag tgctcctcgt gga atg gat gag tct 175
 Met Asp Glu Ser
 1
 gca aag acc ctg cca cca ccg tgc ctc tgt ttt tgc tcc gag aaa gga 223
 Ala Lys Thr Leu Pro Pro Pro Cys Leu Cys Phe Cys Ser Glu Lys Gly
 5 10 15 20
 gaa gat atg aaa gtg gga tat gat ccc atc act ccg cag aag gag gag 271
 Glu Asp Met Lys Val Gly Tyr Asp Pro Ile Thr Pro Gln Lys Glu Glu
 25 30 35
 ggt gcc tgg ttt ggg atc tgc agg gat gga agg ctg ctg gct gct acc 319
 Gly Ala Trp Phe Gly Ile Cys Arg Asp Gly Arg Leu Leu Ala Ala Thr
 40 45 50
 ctc ctg ctg gcc ctg ttg tcc agc agt ttc aca gcg atg tcc ttg tac 367
 Leu Leu Leu Ala Leu Leu Ser Ser Ser Phe Thr Ala Met Ser Leu Tyr
 55 60 65
 cag ttg gct gcc ttg caa gca gac ctg atg aac ctg cgc atg gag ctg 415
 Gln Leu Ala Ala Leu Gln Ala Asp Leu Met Asn Leu Arg Met Glu Leu
 70 75 80
 cag agc tac cga ggt tca gca aca cca gcc gcc gcg ggt gct cca gag 463
 Gln Ser Tyr Arg Gly Ser Ala Thr Pro Ala Ala Ala Gly Ala Pro Glu
 85 90 95 100
 ttg acc gct gga gtc aaa ctc ctg aca ccg gca gct cct cga ccc cac 511
 Leu Thr Ala Gly Val Lys Leu Leu Thr Pro Ala Ala Pro Arg Pro His

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	105	110	115	
aac tcc agc cgc ggc cac agg aac aga cgc gct ttc cag gga cca gag				559
Asn Ser Ser Arg Gly His Arg Asn Arg Arg Ala Phe Gln Gly Pro Glu				
	120	125	130	
gaa aca gaa caa gat gta gac ctc tca gct cct cct gca cca tgc ctg				607
Glu Thr Glu Gln Asp Val Asp Leu Ser Ala Pro Pro Ala Pro Cys Leu				
	135	140	145	
cct gga tgc cgc cat tct caa cat gat gat aat gga atg aac ctc aga				655
Pro Gly Cys Arg His Ser Gln His Asp Asp Asn Gly Met Asn Leu Arg				
	150	155	160	
aac atc att caa gac tgt ctg cag ctg att gca gac agc gac acg ccg				703
Asn Ile Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp Ser Asp Thr Pro				
	165	170	175	180
act ata cga aaa gga act tac aca ttt gtt cca tgg ctt ctc agc ttt				751
Thr Ile Arg Lys Gly Thr Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe				
	185	190	195	
aaa aga gga aat gcc ttg gag gag aaa gag aac aaa ata gtg gtg agg				799
Lys Arg Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys Ile Val Val Arg				
	200	205	210	
caa aca ggc tat ttc ttc atc tac agc cag gtt cta tac acg gac ccc				847
Gln Thr Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu Tyr Thr Asp Pro				
	215	220	225	
atc ttt gct atg ggt cat gtc atc cag agg aag aaa gta cac gtc ttt				895
Ile Phe Ala Met Gly His Val Ile Gln Arg Lys Lys Val His Val Phe				
	230	235	240	
ggg gac gag ctg agc ctg gtg acc ctg ttc cga tgt att cag aat atg				943
Gly Asp Glu Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met				
	245	250	255	260
ccc aaa aca ctg ccc aac aat tcc tgc tac tcg gct ggc atc gcg agg				991
Pro Lys Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Arg				
	265	270	275	
ctg gaa gaa gga gat gag att cag ctt gca att cct cgg gag aat gca				1039
Leu Glu Glu Gly Asp Glu Ile Gln Leu Ala Ile Pro Arg Glu Asn Ala				
	280	285	290	
cag att tca cgc aac gga gac gac acc ttc ttt ggt gcc cta aaa ctg				1087
Gln Ile Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly Ala Leu Lys Leu				
	295	300	305	
ctg taa ctcaacttgct ggagtgcgtg atccccttcc ctcgctcttct ctgtacctcc				1143
Leu *				
gagggagaaa cagacgactg gaaaaactaa aagatgggga aagccgtcag cgaaagtttt				1203
ctcgtgaccc gttgaatctg atccaaacca gaaatataa cagacagcca caaccgaagt				1263
gtgccatgtg agttatgaga aacggagccc gcgctcagaa agaccggatg aggaagaccg				1323
ttttctocag tcctttgcca acacgcaccg caaccttgct ttttgccttg ggtgacacat				1383
gttcagaatg cagggagatt tccttgtttt gcgatttgcc atgagaagag ggcccacaac				1443
tgcaggtcac tgaagcattc acgctaagtc tcaggattta ctctcccttc tcatgctaag				1503
tacacacacg ctcttttcca ggtaatacta tgggatacta tggaaagggt gtttgttttt				1563
aaatctagaa gtcttgaact ggcaatagac aaaaatcctt ataaattcaa gtgtaaaata				1623
aacttaatta aaaaggtaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa				1680

<210> SEQ ID NO 10

<211> LENGTH: 309

<212> TYPE: PRT

<213> ORGANISM: mus musculus

<400> SEQUENCE: 10

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Met Asp Glu Ser Ala Lys Thr Leu Pro Pro Pro Cys Leu Cys Phe Cys
 1 5 10 15
 Ser Glu Lys Gly Glu Asp Met Lys Val Gly Tyr Asp Pro Ile Thr Pro
 20 25 30
 Gln Lys Glu Glu Gly Ala Trp Phe Gly Ile Cys Arg Asp Gly Arg Leu
 35 40 45
 Leu Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Ser Ser Phe Thr Ala
 50 55 60
 Met Ser Leu Tyr Gln Leu Ala Ala Leu Gln Ala Asp Leu Met Asn Leu
 65 70 75 80
 Arg Met Glu Leu Gln Ser Tyr Arg Gly Ser Ala Thr Pro Ala Ala Ala
 85 90 95
 Gly Ala Pro Glu Leu Thr Ala Gly Val Lys Leu Leu Thr Pro Ala Ala
 100 105 110
 Pro Arg Pro His Asn Ser Ser Arg Gly His Arg Asn Arg Arg Ala Phe
 115 120 125
 Gln Gly Pro Glu Glu Thr Glu Gln Asp Val Asp Leu Ser Ala Pro Pro
 130 135 140
 Ala Pro Cys Leu Pro Gly Cys Arg His Ser Gln His Asp Asp Asn Gly
 145 150 155 160
 Met Asn Leu Arg Asn Ile Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp
 165 170 175
 Ser Asp Thr Pro Thr Ile Arg Lys Gly Thr Tyr Thr Phe Val Pro Trp
 180 185 190
 Leu Leu Ser Phe Lys Arg Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys
 195 200 205
 Ile Val Val Arg Gln Thr Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu
 210 215 220
 Tyr Thr Asp Pro Ile Phe Ala Met Gly His Val Ile Gln Arg Lys Lys
 225 230 235 240
 Val His Val Phe Gly Asp Glu Leu Ser Leu Val Thr Leu Phe Arg Cys
 245 250 255
 Ile Gln Asn Met Pro Lys Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala
 260 265 270
 Gly Ile Ala Arg Leu Glu Glu Gly Asp Glu Ile Gln Leu Ala Ile Pro
 275 280 285
 Arg Glu Asn Ala Gln Ile Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly
 290 295 300
 Ala Leu Lys Leu Leu
 305

<210> SEQ ID NO 11
 <211> LENGTH: 185
 <212> TYPE: PRT
 <213> ORGANISM: homo sapiens

<400> SEQUENCE: 11

Met Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Ala Pro
 1 5 10 15
 Thr Pro Cys Val Pro Ala Glu Cys Phe Asp Leu Leu Val Arg His Cys
 20 25 30
 Val Ala Cys Gly Leu Leu Arg Thr Pro Arg Pro Lys Pro Ala Gly Ala
 35 40 45
 Ala Ser Ser Pro Ala Pro Arg Thr Ala Leu Gln Pro Gln Glu Ser Val
 50 55 60

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Gly Ala Gly Ala Gly Glu Ala Ala Leu Pro Leu Pro Gly Leu Leu Phe
 65 70 75 80
 Gly Ala Pro Ala Leu Leu Gly Leu Ala Leu Val Leu Ala Leu Val Leu
 85 90 95
 Val Gly Leu Val Ser Trp Arg Arg Arg Gln Arg Arg Leu Arg Gly Ala
 100 105 110
 Ser Ser Ala Glu Ala Pro Asp Gly Asp Lys Asp Ala Pro Glu Pro Leu
 115 120 125
 Asp Lys Val Ile Ile Leu Ser Pro Gly Ile Ser Asp Ala Thr Ala Pro
 130 135 140
 Ala Trp Pro Pro Pro Gly Glu Asp Pro Gly Thr Thr Pro Pro Gly His
 145 150 155 160
 Ser Val Pro Val Pro Ala Thr Glu Leu Gly Ser Thr Glu Leu Val Thr
 165 170 175
 Thr Lys Thr Ala Gly Pro Glu Gln Gln
 180 185

<210> SEQ ID NO 12
 <211> LENGTH: 247
 <212> TYPE: PRT
 <213> ORGANISM: homo sapiens

<400> SEQUENCE: 12

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

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245

<210> SEQ ID NO 13
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: BLYS binding polypeptide

<400> SEQUENCE: 13

Glu Cys Phe Asp Leu Leu Val Arg Ala Trp Val Pro Cys Ser Val Leu
 1 5 10 15

Lys

<210> SEQ ID NO 14
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: BLYS binding polypeptide

<400> SEQUENCE: 14

Glu Cys Phe Asp Leu Leu Val Arg His Trp Val Pro Cys Gly Leu Leu
 1 5 10 15

Arg

<210> SEQ ID NO 15
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: BLYS binding polypeptide

<400> SEQUENCE: 15

Glu Cys Phe Asp Leu Leu Val Arg Arg Trp Val Pro Cys Glu Met Leu
 1 5 10 15

Gly

<210> SEQ ID NO 16
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: BLYS binding polypeptide

<400> SEQUENCE: 16

Glu Cys Phe Asp Leu Leu Val Arg Ser Trp Val Pro Cys His Met Leu
 1 5 10 15

Arg

<210> SEQ ID NO 17
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: BLYS binding polypeptide

<400> SEQUENCE: 17

Glu Cys Phe Asp Leu Leu Val Arg His Trp Val Ala Cys Gly Leu Leu
 1 5 10 15

Arg

<210> SEQ ID NO 18

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<211> LENGTH: 1214
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TACI-Fc fusion protein
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (17)...(1192)

<400> SEQUENCE: 18

tattaggccg gccacc atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg      52
      Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu
          1             5             10

ctg ctg tgt ggc gcc gtc ttc gtt tcg ctc agc cag gaa atc cat gcc      100
Leu Leu Cys Gly Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala
          15             20             25

gag ttg aga cgc ttc cgt aga gct atg aga tcc tgc ccc gaa gag cag      148
Glu Leu Arg Arg Phe Arg Arg Ala Met Arg Ser Cys Pro Glu Glu Gln
          30             35             40

tac tgg gat cct ctg ctg ggt acc tgc atg tcc tgc aaa acc att tgc      196
Tyr Trp Asp Pro Leu Leu Gly Thr Cys Met Ser Cys Lys Thr Ile Cys
          45             50             55             60

aac cat cag agc cag cgc acc tgt gca gcc ttc tgc agg tca ctc agc      244
Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg Ser Leu Ser
          65             70             75

tgc cgc aag gag caa ggc aag ttc tat gac cat ctc ctg agg gac tgc      292
Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu Arg Asp Cys
          80             85             90

atc agc tgt gcc tcc atc tgt gga cag cac cct aag caa tgt gca tac      340
Ile Ser Cys Ala Ser Ile Cys Gly Gln His Pro Lys Gln Cys Ala Tyr
          95             100            105

ttc tgt gag aac aag ctc agg agc cca gtg aac ctt cca cca gag ctc      388
Phe Cys Glu Asn Lys Leu Arg Ser Pro Val Asn Leu Pro Pro Glu Leu
          110            115            120

agg aga cag cgg agt gga gaa gtt gaa aac aat tca gac aac tcg gga      436
Arg Arg Gln Arg Ser Gly Glu Val Glu Asn Asn Ser Asp Asn Ser Gly
          125            130            135            140

agg tac caa gga ttg gag cac aga ggc tca gaa gca agt cca gct ctc      484
Arg Tyr Gln Gly Leu Glu His Arg Gly Ser Glu Ala Ser Pro Ala Leu
          145            150            155

cca ggt ctc aag gag ccc aaa tct tca gac aaa act cac aca tgc cca      532
Pro Gly Leu Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
          160            165            170

ccg tgc cca gca cct gaa gcc gag ggg gca ccg tca gtc ttc ctc ttc      580
Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe
          175            180            185

ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc      628
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
          190            195            200

aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc      676
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
          205            210            215            220

aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg      724
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
          225            230            235

cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc      772
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
          240            245            250

gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc      820
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
          255            260            265

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tcc aac aaa gcc ctc cca tcc tcc atc gag aaa acc atc tcc aaa gcc	868
Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala	
270 275 280	
aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg	916
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg	
285 290 295 300	
gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc	964
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly	
305 310 315	
ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg	1012
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro	
320 325 330	
gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc	1060
Glu Asn Asn Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser	
335 340 345	
ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag	1108
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln	
350 355 360	
ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac	1156
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His	
365 370 375 380	
tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa taatctagag	1202
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys	
385 390	
gcgcgccaat ta	1214

<210> SEQ ID NO 19

<211> LENGTH: 392

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: TACI-Fc fusion protein

<400> SEQUENCE: 19

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

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Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 195 200 205
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 210 215 220
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 225 230 235 240
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 245 250 255
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 260 265 270
 Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 275 280 285
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 290 295 300
 Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 305 310 315 320
 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 325 330 335
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 340 345 350
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 355 360 365
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 370 375 380
 Ser Leu Ser Leu Ser Pro Gly Lys
 385 390

<210> SEQ ID NO 20

<211> LENGTH: 1070

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: TACI-Fc fusion protein

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (17)...(1048)

<400> SEQUENCE: 20

tattaggccg gccacc atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg 52
 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu
 1 5 10
 ctg ctg tgt ggc gcc gtc ttc gtt tgc ctc agc cag gaa atc cat gcc 100
 Leu Leu Cys Gly Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala
 15 20 25
 gag ttg aga cgc ttc cgt aga gct atg aga tcc tgc ccc gaa gag cag 148
 Glu Leu Arg Arg Phe Arg Arg Ala Met Arg Ser Cys Pro Glu Glu Gln
 30 35 40
 tac tgg gat cct ctg ctg ggt acc tgc atg tcc tgc aaa acc att tgc 196
 Tyr Trp Asp Pro Leu Leu Gly Thr Cys Met Ser Cys Lys Thr Ile Cys
 45 50 55 60
 aac cat cag agc cag cgc acc tgt gca gcc ttc tgc agg tca ctc agc 244
 Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg Ser Leu Ser
 65 70 75
 tgc cgc aag gag caa ggc aag ttc tat gac cat ctc ctg agg gac tgc 292
 Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu Arg Asp Cys
 80 85 90
 atc agc tgt gcc tcc atc tgt gga cag cac cct aag caa tgt gca tac 340
 Ile Ser Cys Ala Ser Ile Cys Gly Gln His Pro Lys Gln Cys Ala Tyr

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95	100	105	
ttc tgt gag aac gag ccc aaa tct tca gac aaa act cac aca tgc cca			388
Phe Cys Glu Asn Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro			
110	115	120	
ccg tgc cca gca cct gaa gcc gag ggg gca ccg tca gtc ttc ctc ttc			436
Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe			
125	130	135	140
ccc cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc			484
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val			
145		150	155
aca tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc			532
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe			
160	165		170
aac tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg			580
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro			
175	180		185
cgg gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc			628
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr			
190	195		200
gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc			676
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val			
205	210	215	220
tcc aac aaa gcc ctc cca tcc tcc atc gag aaa acc atc tcc aaa gcc			724
Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala			
225		230	235
aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg			772
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg			
240	245		250
gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc			820
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly			
255	260		265
ttc tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg			868
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro			
270	275		280
gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc			916
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser			
285	290	295	300
ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag			964
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln			
305	310		315
ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac			1012
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His			
320	325		330
tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa taatctagag			1058
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys			
335	340		
gcgcgccaat ta			1070

<210> SEQ ID NO 21
 <211> LENGTH: 344
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: TACI-Fc fusion protein

<400> SEQUENCE: 21

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 1 5 10 15
 Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala Glu Leu Arg Arg
 20 25 30

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Phe Arg Arg Ala Met Arg Ser Cys Pro Glu Glu Gln Tyr Trp Asp Pro
 35 40 45
 Leu Leu Gly Thr Cys Met Ser Cys Lys Thr Ile Cys Asn His Gln Ser
 50 55 60
 Gln Arg Thr Cys Ala Ala Phe Cys Arg Ser Leu Ser Cys Arg Lys Glu
 65 70 75 80
 Gln Gly Lys Phe Tyr Asp His Leu Leu Arg Asp Cys Ile Ser Cys Ala
 85 90 95
 Ser Ile Cys Gly Gln His Pro Lys Gln Cys Ala Tyr Phe Cys Glu Asn
 100 105 110
 Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 115 120 125
 Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 130 135 140
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 145 150 155 160
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 165 170 175
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 180 185 190
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 195 200 205
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 210 215 220
 Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 225 230 235 240
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 245 250 255
 Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 260 265 270
 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 275 280 285
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 290 295 300
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 305 310 315 320
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 325 330 335
 Ser Leu Ser Leu Ser Pro Gly Lys
 340

<210> SEQ ID NO 22
 <211> LENGTH: 1082
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: TACI-Fc fusion protein
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (17)...(1060)

<400> SEQUENCE: 22

tattaggccg gccacc atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg 52
 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu
 1 5 10
 ctg ctg tgt ggc gcc gtc ttc gtt tcg ctc agc cag gaa atc cat gcc 100

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Leu	Leu	Cys	Gly	Ala	Val	Phe	Val	Ser	Leu	Ser	Gln	Glu	Ile	His	Ala		
		15					20				25						
gag	ttg	aga	cgc	ttc	cgt	aga	gct	atg	aga	tcc	tgc	ccc	gaa	gag	cag		148
Glu	Leu	Arg	Arg	Phe	Arg	Arg	Ala	Met	Arg	Ser	Cys	Pro	Glu	Glu	Gln		
	30					35					40						
tac	tgg	gat	cct	ctg	ctg	ggg	acc	tgc	atg	tcc	tgc	aaa	acc	att	tgc		196
Tyr	Trp	Asp	Pro	Leu	Leu	Gly	Thr	Cys	Met	Ser	Cys	Lys	Thr	Ile	Cys		
45					50					55					60		
aac	cat	cag	agc	cag	cgc	acc	tgt	gca	gcc	ttc	tgc	agg	tca	ctc	agc		244
Asn	His	Gln	Ser	Gln	Arg	Thr	Cys	Ala	Ala	Phe	Cys	Arg	Ser	Leu	Ser		
				65					70					75			
tgc	cgc	aag	gag	caa	ggc	aag	ttc	tat	gac	cat	ctc	ctg	agg	gac	tgc		292
Cys	Arg	Lys	Glu	Gln	Gly	Lys	Phe	Tyr	Asp	His	Leu	Leu	Arg	Asp	Cys		
			80					85					90				
atc	agc	tgt	gcc	tcc	atc	tgt	gga	cag	cac	cct	aag	caa	tgt	gca	tac		340
Ile	Ser	Cys	Ala	Ser	Ile	Cys	Gly	Gln	His	Pro	Lys	Gln	Cys	Ala	Tyr		
		95					100					105					
ttc	tgt	gag	aac	aag	ctc	agg	agc	gag	ccc	aaa	tct	tca	gac	aaa	act		388
Phe	Cys	Glu	Asn	Lys	Leu	Arg	Ser	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr		
	110					115					120						
cac	aca	tgc	cca	ccg	tgc	cca	gca	cct	gaa	gcc	gag	ggg	gca	ccg	tca		436
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Glu	Gly	Ala	Pro	Ser		
125					130					135					140		
gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	atc	tcc	cgg		484
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg		
				145					150					155			
acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	gaa	gac	cct		532
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro		
			160					165					170				
gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	cat	aat	gcc		580
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala		
		175					180					185					
aag	aca	aag	ccg	cgg	gag	gag	cag	tac	aac	agc	acg	tac	cgt	gtg	gtc		628
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val		
	190						195				200						
agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	aag	gag	tac		676
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr		
205					210						215				220		
aag	tgc	aag	gtc	tcc	aac	aaa	gcc	ctc	cca	tcc	tcc	atc	gag	aaa	acc		724
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr		
				225					230					235			
atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	gaa	cca	cag	gtg	tac	acc	ctg		772
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu		
			240					245					250				
ccc	cca	tcc	cgg	gat	gag	ctg	acc	aag	aac	cag	gtc	agc	ctg	acc	tgc		820
Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys		
		255						260				265					
ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	tgg	gag	agc		868
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser		
		270				275						280					
aat	ggg	cag	ccg	gag	aac	aac	tac	aag	acc	acg	cct	ccc	gtg	ctg	gac		916
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp		
285					290					295				300			
tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	acc	gtg	gac	aag	agc		964
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser		
				305					310					315			
agg	tgg	cag	cag	ggg	aac	gtc	ttc	tca	tgc	tcc	gtg	atg	cat	gag	gct		1012
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala		
			320					325						330			

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Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 340 345

<210> SEQ ID NO 24
 <211> LENGTH: 1109
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: TACI-Fc fusion protein
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (17)...(1090)

<400> SEQUENCE: 24

tattaggccg gccacc atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg 52
 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu
 1 5 10

ctg ctg tgt ggc gcc gtc ttc gtt tgc ctc agc cag gaa atc cat gcc 100
 Leu Leu Cys Gly Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala
 15 20 25

gag ttg aga cgc ttc cgt aga gct atg aga tcc tgc ccc gaa gag cag 148
 Glu Leu Arg Arg Phe Arg Arg Ala Met Arg Ser Cys Pro Glu Glu Gln
 30 35 40

tac tgg gat cct ctg ctg ggt acc tgc atg tcc tgc aaa acc att tgc 196
 Tyr Trp Asp Pro Leu Leu Gly Thr Cys Met Ser Cys Lys Thr Ile Cys
 45 50 55 60

aac cat cag agc cag cgc acc tgt gca gcc ttc tgc agg tca ctc agc 244
 Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg Ser Leu Ser
 65 70 75

tgc cgc aag gag caa ggc aag ttc tat gac cat ctc ctg agg gac tgc 292
 Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu Arg Asp Cys
 80 85 90

atc agc tgt gcc tcc atc tgt gga cag cac cct aag caa tgt gca tac 340
 Ile Ser Cys Ala Ser Ile Cys Gly Gln His Pro Lys Gln Cys Ala Tyr
 95 100 105

ttc tgt gag aac aag ctc agg agc cca gtg aac ctt cca cca gag ctc 388
 Phe Cys Glu Asn Lys Leu Arg Ser Pro Val Asn Leu Pro Pro Glu Leu
 110 115 120

agg gag ccc aaa tct tca gac aaa act cac aca tgc cca ccg tgc cca 436
 Arg Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 125 130 135 140

gca cct gaa gcc gag ggg gca ccg tca gtc ttc ctc ttc ccc cca aaa 484
 Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
 145 150 155

ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg 532
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 160 165 170

gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac 580
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 175 180 185

gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag 628
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 190 195 200

cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac 676
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 205 210 215 220

cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa 724
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 225 230 235

gcc ctc cca tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag 772
 Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 240 245 250

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ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg      820
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
      255                      260                      265

acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc      868
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
      270                      275                      280

agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac      916
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
285                      290                      295                      300

tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc      964
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      305                      310                      315

tac agc aag ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc      1012
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      320                      325                      330

ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac acg cag      1060
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      335                      340                      345

aag agc ctc tcc ctg tct ccg ggt aaa taa tctagaggcg cgccaatta      1109
Lys Ser Leu Ser Leu Ser Pro Gly Lys *
      350                      355

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<210> SEQ ID NO 25

<211> LENGTH: 357

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: TACI-Fc fusion protein

<400> SEQUENCE: 25

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Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
1          5          10          15

Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala Glu Leu Arg Arg
20          25          30

Phe Arg Arg Ala Met Arg Ser Cys Pro Glu Glu Gln Tyr Trp Asp Pro
35          40          45

Leu Leu Gly Thr Cys Met Ser Cys Lys Thr Ile Cys Asn His Gln Ser
50          55          60

Gln Arg Thr Cys Ala Ala Phe Cys Arg Ser Leu Ser Cys Arg Lys Glu
65          70          75          80

Gln Gly Lys Phe Tyr Asp His Leu Leu Arg Asp Cys Ile Ser Cys Ala
85          90          95

Ser Ile Cys Gly Gln His Pro Lys Gln Cys Ala Tyr Phe Cys Glu Asn
100         105         110

Lys Leu Arg Ser Pro Val Asn Leu Pro Pro Glu Leu Arg Glu Pro Lys
115         120         125

Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130         135         140

Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145         150         155         160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165         170         175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180         185         190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195         200         205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu

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210	215	220
Asn Gly Lys Glu Tyr 225	Lys Cys Lys Val 230	Ser Asn Lys Ala Leu Pro Ser 235 240
Ser Ile Glu Lys Thr 245	Ile Ser Lys Ala 250	Lys Gly Gln Pro Arg Glu Pro 255
Gln Val Tyr Thr 260	Leu Pro Pro Ser 265	Arg Asp Glu Leu Thr Lys Asn Gln 270
Val Ser Leu Thr Cys 275	Leu Val Lys Gly Phe Tyr 280	Pro Ser Asp Ile Ala 285
Val Glu Trp Glu Ser 290	Asn Gly Gln Pro 295	Glu Asn Asn Tyr Lys Thr Thr 300
Pro Pro Val Leu Asp 305	Ser Asp Gly Ser Phe 310	Phe Leu Tyr Ser Lys Leu 315 320
Thr Val Asp Lys Ser 325	Arg Trp Gln Gln 330	Gly Asn Val Phe Ser Cys Ser 335
Val Met His Glu Ala 340	Leu His Asn His 345	Tyr Thr Gln Lys Ser Leu Ser 350
Leu Ser Pro Gly Lys 355		

<210> SEQ ID NO 26
 <211> LENGTH: 311
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: BAFF-R-Fc fusion protein

<400> SEQUENCE: 26

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

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210	215	220
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 225	230	235 240
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 245	250	255
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 260	265	270
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser 275	280	285
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 290	295	300
Leu Ser Leu Ser Pro Gly Lys 305	310	

That which is claimed:

1. A method of reducing the systemic lupus erythematosus (SLE) disease activity of an individual clinically diagnosed with SLE, said method comprising:

analyzing peripheral blood B cells from an individual clinically diagnosed with SLE for the presence or absence of elevated BCMA protein expression levels on said peripheral blood B cells, said analyzing step comprising:

- (i) measuring a first level of BCMA protein expression on the surface of peripheral blood B cells from said individual clinically diagnosed with SLE;
- (ii) comparing the first level to a second level of BCMA protein expression on the surface of peripheral blood B cells from a healthy individual; and
- (iii) identifying an individual wherein the first level is elevated as compared to the second level; and administering a BlyS antagonist to said individual clinically diagnosed with SLE and having elevated

- 20 BCMA protein expression levels on said peripheral blood B cells, wherein the BlyS antagonist is a receptor extracellular domain/Fc domain fusion protein selected from the group consisting of TACI-Ig, BCMA-Ig, and BAFF-R-Ig,
- 25 wherein the SLE disease activity of said individual is reduced following said administration of the BlyS antagonist.
- 2. The method of claim 1 wherein said BlyS antagonist is also an APRIL antagonist.
- 3. The method of claim 1, wherein said receptor-extracellular domain/Fc domain fusion protein is TACI-Ig.
- 4. The method of claim 3, wherein said TACI-Ig is atacept.
- 35 5. *The method of claim 1, wherein said first level of BCMA protein expression is measured by flow cytometry.*
- 6. *The method of claim 1, wherein said second level of BCMA protein expression is measured by flow cytometry.*

* * * * *