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(54) Title: METHODS AND COMPOSITIONS RELATED TO B CELL ASSAYS

(57) Abstract: The present invention relates to novel methods for treating diseases and monitoring B cell levels in subjects and kit and compositions relating thereto by measuring serum BAFF levels in the subjects.

METHODS AND COMPOSITIONS RELATED TO B CELL ASSAYS

FIELD OF THE INVENTION

The present invention relates to novel methods for treating diseases and monitoring B cell levels in subjects and kit and compositions relating thereto.

BACKGROUND OF THE INVENTION

Therapies targeted to deplete B cells have been shown to be useful in treating a wide variety of B cell mediated diseases. For example, rituximab, the RITUXAN® antibody, which is a genetically engineered chimeric murine/human monoclonal antibody directed against human CD20 antigen (commercially available from Genentech, Inc., South San Francisco, California, U.S.) is used for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell non-Hodgkin's lymphoma. Results from rituximab clinical trials and case studies (Biogen Idec, Cambridge, MA, USA and Genentech, South San Francisco, CA, USA) report therapeutic benefits not only in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS), but also in patients with less common autoimmune diseases such as refractory dermatomyositis, type II mixed cryoglobulinemia, Wegener's granulomatosis, autoimmune hemolytic anemia, idiopathic thrombocytopenia, and immunoglobulin M (IgM) polyneuropathies (Gorman C, et al., (2003) *Arthritis Res Ther* 5:S17-S21; Somer BG, et al., (2003) *Arthritis Rheum* 49:394-398).

Currently, the activity of B cell depleting therapies in subjects is sometimes monitored by measuring actual B cell levels in the blood during B cell depletion and repletion (recovery). Alternatively or additionally, the activity of B cell depleting therapies have been evaluated by monitoring markers in blood traditionally associated with the disease. For example, for certain autoimmune diseases, autoantibodies such as double-stranded DNA antibodies have been monitored. None of these methods give a clear, contemporaneous view of the B cell population in other areas of the subject.

Obtaining biopsies of tissues (e.g., spleen, lymph nodes and joints) of patients or evaluating other bodily fluid (e.g., spinal fluid, synovial fluid) is often not an option, or at the very least, inconvenient.

One polypeptide that is elevated in several autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome, is the BAFF polypeptide (Cheema, G. S, et al., (2001) *Arthritis Rheum.* 44:1313-1319; Groom, J., et al, (2002) *J. Clin. Invest.* 109:59-68; Zhang, J., et al., (2001) *J. Immunol.* 166:6-10). BAFF (also known as BLyS, TALL-1, THANK, TNFSF13B, or zTNF4) is a member of the TNF ligand superfamily that is essential for B cell survival and maturation (reviewed in Mackay & Browning (2002) *Nature Rev. Immunol.* 2:465-475). BAFF can be found in secreted from or on the cell-surface of monocytes, macrophages, dendritic cells, and neutrophils, but not B cells (Nardelli B, et al. (2000) *Blood* 97: 198–204; Scapini P, et al. (2003) *J Exp Med* 197:297–302). BAFF overexpression in transgenic mice leads to B cell hyperplasia and development of severe autoimmune disease (Mackay, et al. (1999) *J. Exp. Med.* 190:1697-1710; Gross, et al. (2000) *Nature* 404:995-999; Khare, et al. (2000) *Proc. Natl. Acad. Sci. U.S.A.* 97:3370-33752-4).

Furthermore, BAFF levels correlate with disease severity, suggesting that BAFF may play a direct role in the pathogenesis of these illnesses. BAFF binds to three members of the TNF receptor superfamily, TACI, BCMA, and BR3 (also known as BAFF-R) (Gross, et al., *supra*; Thompson, J. S., et al., (2001) *Science* 293, 2108-2111; Yan, M., et al. (2001) *Curr. Biol.* 11:1547-1552; Yan, M., et al., (2000) *Nat. Immunol.* 1:37-41; Schiemann, B., et al., (2001) *Science* 293:2111-2114). Of the three, only BR3 is specific for BAFF; the other two receptors also bind the related TNF family member, APRIL. Comparison of the phenotypes of BAFF and receptor knockout or mutant mice indicates that signaling through BR3 mediates the B cell survival functions of BAFF (Thompson, et al., *supra*; Yan, (2002), *supra*; Schiemann, *supra*). In contrast, TACI appears to act as an inhibitory receptor (Yan, M., (2001) *Nat. Immunol.* 2, 638-643), while the role of BCMA is less clear (Schiemann, *supra*).

Currently, a blocking mAb targeting BAFF (Lymphostat-B™, Human Genome Sciences, Rockville, MD) is in clinical trials in RA and SLE patients, TACI-Fc (ZymoGenetics, Seattle, WA and Serono, Geneva, CH) is in clinical trials in SLE patients and BAFF-R:Fc (also called BR3-Fc) (Biogen Idec, Cambridge, MA and

Genentech, South San Francisco, CA) is in clinical development. Reports of the data from the phase II trial with Lymphostat-B™ in rheumatoid arthritis stated that patients experienced a reduction in select B cell populations (McKay, J., et al., 69th Annual Scientific Meeting of the American College of Rheumatology/Association of Rheumatology Health Professionals. Oral Presentation #1920 (November 16, 2005)).

The rationale for using inhibitors of BAFF to treat B cell mediated diseases is clear. However, understanding the scope of the use of BAFF as a marker, not as a target for a therapeutic agent, and understanding when and how to use it as a marker in treatment regimens is less clear. The answer to these questions and others are described below.

SUMMARY OF THE INVENTION

The present invention relates to the discovery that serum BAFF levels is an indicator of B cell levels in subjects, including an early indicator of tissue B cell levels in subjects treated with B cell depletion or proliferating therapeutic agents, and use therefore in kits or in any methods of treatment or evaluation of subjects that would benefit from knowing the B cell levels in the subject. Furthermore, the present invention relates to the discovery that serum BAFF levels are inversely related to the levels of B cells in the tissue in a patient after treatment with a B cell therapeutic agent and the use of that knowledge in treating patients.

The present invention provides methods for monitoring B cell levels in a subject comprising the steps of determining the serum BAFF levels in a test sample of the subject, determining the serum BAFF levels in a control sample, and calculating the B cell levels in the subject relative to the control, which calculation comprises the step of comparing the serum BAFF level in the test sample to the serum BAFF level in the control sample (e.g., dividing the serum BAFF level in the test sample to the serum BAFF level in the control sample). In one embodiment, the control sample is from the subject before treatment with a therapeutic agent and the test sample is from the subject after treatment with the therapeutic agent. In another embodiment, the test sample is from the subject who is suffering from a disease and the control sample is from a subject that is not suffering from the disease. According to one embodiment, the B cells are CD19 positive and/or CD20 positive B cells. This method is useful for determining B cell levels in any subject for whom the knowledge of the B cell levels

in the subject would be helpful to treat a disease. Therefore, this method can be useful for monitoring or treating subjects for any disease in which B cells are affected or should be monitored or in which the disease is treated with a B cell promoting agent or a B cell depleting agent. Thus, this method is useful for monitoring B cells in a variety of subjects, including those subjects who are not suffering from an autoimmune disease immunodeficiency, a lymphoma or a leukemia.

The present invention provides methods for treating a subject suffering from a disease comprising the steps of (1) administering a therapeutically effective amount of a therapeutic agent to the subject, (2) determining the serum BAFF levels in a test sample of the subject, (3) calculating the B cell level in the test sample relative to a control sample and (3) administering a therapeutically effective amount of the same or different therapeutic agent at a time point dependent on the serum BAFF level in the subject. In another embodiment, the invention provides methods for treating a subject suffering from a disease comprising the steps of (1) administering a therapeutically effective amount of a therapeutic agent to the subject, (2) determining the serum BAFF levels in a test sample of the subject, and (3) administering a therapeutically effective amount of the same or different therapeutic agent at a time point dependent on the serum BAFF level in the test sample. According to one embodiment, the time point is during or after the phase of maximum B cell depletion. According to another embodiment, the time point is during the B cell recovery phase. According to one preferred embodiment, the time point is before or during tissue B cell recovery that is prior to peripheral blood B cell recovery. According to one specific embodiment, the B cell recovery phase is characterized by decreasing serum BAFF levels. According to one specific embodiment, the maximum B cell depletion phase is characterized by maximum levels of BAFF in the sera of a subject.

The present invention provides methods of maintenance therapy for a subject previously treated with a B cell depletion agent comprising the step of determining the serum BAFF levels in the subject and treating the subject with a B cell depletion agent (same or different agent) or another therapeutic agent at a time point dependent on the serum BAFF level in the test sample, e.g., at maximum B cell depletion or after maximum B cell depletion and while serum BAFF levels are decreasing. According to one preferred embodiment, the time point is before or during tissue B cell recovery that is prior to peripheral blood B cell recovery.

According to this some embodiments of this invention, the therapeutic agent is selected from the group consisting of B cell promoting agent and a B cell depletion agent. According preferred embodiments, the therapeutic agent is not a BAFF antagonist that binds to BAFF. According to other embodiments, the therapeutic agent does not block BAFF from binding to BCMA, TACI or BR3 by binding to BAFF to block the interaction. According to one embodiment, the therapeutic agent is a B cell depletion agent that targets a B cell surface antigen selected from the group consisting of CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD40, CD52, D53, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD79b, CD80, CD81, CD82, CD83, CDw84, CD85, CD86, CD180 (RP105), FcRH2 (IRTA4), CD79A, C79B, CR2, CCR6, CD72, P2X5, HLA-DOB, CXCR5 (BLR1), FCER2, BR3 (aka BAFF-R), TACI, BTLA, NAG14 (aka LRRC4), SLGC16270 (ala LOC283663), FcRH1 (IRTA5), FcRH5 (IRTA2), ATWD578 (aka MGC15619), FcRH3 (IRTA3), FcRH4 (IRTA1), FcRH6 (aka LOC343413) and BCMA (aka TNFRSF17), HLA-DO, HLA-Dr10 and MHC ClassII. According to one embodiment, the B cell depleting agent that targets a B cell surface antigen is a monoclonal antibody or a peptibody. According to one specific embodiment, the monoclonal antibody is a human, humanized, chimeric or otherwise engineered antibody.

According to one embodiment of this invention, the disease is an immunological disorder or a cancer. According to another embodiment, the immunological disorder is a lymphoma, leukemia or multiple myeloma. In another embodiment, the disease is a B cell lymphoma or leukemia. According to another embodiment of this invention, the disease is selected from the group consisting of an autoimmune disease, a B cell neoplasm, a B cell lymphoproliferative disorder or an immunodeficiency disease. According to one embodiment, the autoimmune disease is elected from the group consisting of rheumatoid arthritis including juvenile rheumatoid arthritis, lupus including systemic lupus erythematosus (SLE), Wegener's disease, inflammatory bowel disease, including Crohn's disease and ulcerative colitis, 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, glomerulonephritis, dermatomyositis/polymyositis, ANCA-associated vasculitis (AAV), Aplastic anemia, Autoimmune hemolytic anemia

(AIHA), factor VIII deficiency, hemophilia A, Autoimmune neutropenia, Castleman's syndrome, Goodpasture's syndrome, solid organ transplant rejection, graft versus host disease (GVHD), IgM mediated, thrombotic thrombocytopenic purpura (TTP), Hashimoto's Thyroiditis, autoimmune hepatitis, lymphoid interstitial pneumonitis (LIP), bronchiolitis obliterans (non-transplant) vs. NSIP, Guillain-Barre Syndrome, large vessel vasculitis, giant cell (Takayasu's) arteritis, medium vessel vasculitis, Kawasaki's Disease, polyarteritis nodosa, Neuromyelitis Optica (NMO), IgG neuropathy and Myasthenia Gravis and pemphigus vulgaris. According to another embodiment, the lymphoma or leukemia is a B cell lymphoma or leukemia. According to one specific embodiment, the disease is selected from the group consisting of non-Hodgkin's lymphoma (NHL) or lymphocyte predominant Hodgkin's disease (LPHD), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), small lymphocytic lymphoma (SLL), and multiple myeloma.

According to some embodiments, the B cell depleting agent is selected from the group consisting of an anti-CD20 antibody, an anti-BR3 antibody, an anti-CD22 antibody and an anti-CD52 antibody. In any of the embodiments of the methods, compositions and articles of manufacture of the invention, the anti-CD20 antibody can be a chimeric, human, humanized otherwise engineered antibody. According to one embodiment, the anti-BR3 antibody comprises a VH and a VL domain described herein.

Specific embodiments of the anti-CD20 antibody include rituximab (RITUXAN®), m2H7 (murine 2H7), hu2H7 (humanized 2H7) and all its functional variants, hu2H7.v16 (v stands for version), v31, v96, v114 and v115, (e.g., see, WO 2004/056312). According to other embodiments, the B cell promoting agent is selected from the group consisting of a cytokine or antibody that stimulates B cell proliferation or survival. The B cell promoting agent is preferably not BAFF.

The present invention also provides kits and articles of manufacture comprising instructions for assaying serum BAFF levels in a subject after administration of a therapeutic agent and uses of the assay results for setting up retreatment regimes. The present invention also provides kits comprising instructions for assaying serum BAFF levels in a subject and uses of the assay results to monitor both the efficiency of B cell depletion and/or the kinetics of B cell repletion in the subject after administration of a therapeutic agent. A kit comprising a BAFF binding

reagent and a package insert comprising instructions for determining serum BAFF levels using the BAFF binding reagent and for relating serum BAFF levels to B cell levels in the patient after treatment with a B cell depleting or promoting agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Serum BAFF is upregulated after B cell depletion in mice.

Figure 2: Serum BAFF upregulation correlates with the extent of anti-CD20 tissue B cell depletion in mice.

Figure 3. Serum BAFF is an indicator of anti-BR3 tissue B cell repletion in normal mice.

Figure 4. Anti-BR3 peripheral B cell depletion and soluble BAFF level in cyno blood.

Figure 5. Anti-BR3 peripheral CD20 B cell depletion and soluble BAFF level in cyno blood – individual kinetics in two representative cyno.

Figure 6. Schematic diagram illustrating the delay in peripheral B cell recovery compared to tissue B cell recovery.

DETAILED DESCRIPTION OF THE INVENTION

The clinical response of a subject to therapeutic agents that effect B cells is often measured by evaluating B cell depletion in the subject's blood. However, the results do not fully correlate with levels of B cell depletion observed in the tissue (spleen, lymph node, autoimmune sites like joints, spinal fluid etc). In actuality, clinical response for B cell depletion therapies correlates more with target organ B cell depletion than blood B cell depletion, especially in oncology. Therefore, searching for a better marker to indicate tissue B cell depletion as well as B cell recovery (repletion) is important for optimizing B cell depleting therapies.

The present application discloses that serum BAFF levels are more appropriate markers for reflecting the total B cell load in a subject. As such, evaluation of serum

BAFF levels can be used to determine B cell levels in subjects, regardless of whether the therapeutic agent targets B cells for inhibition or stimulation of cell growth or survival. Evaluation of serum BAFF levels in patients can be particularly useful in monitoring the efficacy of B cell therapies such as B cell depleting agents or B cell promoting agents. Further, reevaluation of serum BAFF levels during B cell recovery after B cell depletion can be useful for determining retreatment regimes for the B cell depletion agent or when to resume treatment with any other therapeutic agent that modulates the immune system (e.g., DMARDs, T cell depleting agents, immunosuppressive agents, vaccines, etc.). Serum BAFF levels can also be an early marker for determining patients who respond well to B cell therapy versus those who do not and need immediate alternative treatment. Evaluation of serum BAFF levels can be useful in maintenance therapies, wherein the therapy is carried out to maintain the status of a disease after treatment with a therapeutic agent. For example, maintenance therapy can be desired to maintain the remission stage of an autoimmune disease or a cancer.

The term "BAFF" refers to a polypeptide, also known as BLyS, TALL-1, THANK, TNFSF13B, or zTNF4 (e.g., SEQ ID NO:102), that is a member of the TNF ligand superfamily having a role in B cell survival, and homologs, isoforms, fragments and variants thereof having BAFF activity. The term BAFF includes those polypeptides described in Shu et al., *J. Leukocyte Biol.*, 65:680 (1999); GenBank Accession No. AF136293; WO98/18921 published May 7, 1998; EP 869,180 published October 7, 1998; WO98/27114 published June 25, 1998; WO99/12964 published March 18, 1999; WO99/33980 published July 8, 1999; Moore et al., *Science*, 285:260-263 (1999); Schneider et al., *J. Exp. Med.*, 189:1747-1756 (1999); Mukhopadhyay et al., *J. Biol. Chem.*, 274:15978-15981 (1999).

A receptor for BAFF according to this invention includes TACI, BR43X2, hTACI(265), BCMA and BR3, and any homologs, isoforms, fragments and variants thereof having BAFF-binding activity and through which BAFF can cell signal. "BR3" is also sometimes referred to as BAFF-R in the art. Examples of BR3, include those described in PCT Publications WO 02/24909 and WO 03/014294 e.g., human BR3 (SEQ ID NO:103), human BR3 extracellular domain (SEQ ID NO:104), and mouse BR3 extracellular domain (SEQ ID NO:105). Examples of TACI, BR43X2, hTACI(265), include those described in Gross et al., (200) *Nature* 404:995-999, WO

98/39361, WO 00/40716 and WO 01/60397. Examples of BCMA include those described in Laabi et al., (1992) EMBO J. 11(11):3897-3904.

The term "anti-BAFF receptor antibody" or "BAFF receptor binding antibody" refers to any antibody that specifically binds to at least one epitope of a receptor for BAFF. Examples of anti-BR3 antibodies include, but are not limited to, those described in WO 02/24909 (e.g., 9.1 and 2.1) and WO 2006/073941 (e.g., . Examples of anti-TACI antibodies include, but are not limited to, those described in WO 2004/011611. Examples of anti-BCMA antibodies include, but are not limited to, those described in Thompson et al., (2001) 293(5537):2108 – 2111 (e.g., C4.E2.1) and the Vicky-1 antibody (Abcam, Inc., Cambridge, Ma). The anti-BAFF receptor antibodies are preferably monoclonal antibodies. The use of either anti-BAFF receptor antibodies that inhibit the binding of BAFF to a receptor or anti-BAFF receptor antibodies that do not inhibit the binding of BAFF to a receptor as therapeutics are contemplated as in the methods of this invention. Human, humanized, chimerized or otherwise enhanced forms of anti-BAFF receptor antibodies useful for treatment in humans, including enhanced forms of those listed above, are contemplated as therapeutics in the methods of this invention. In one preferred embodiment, the anti-BAFF receptor antibody will bind a BAFF receptor with a K_d of $< 10\text{nM}$. In other preferred embodiments, the binding is at a K_d of $< 7.5\text{nM}$, more preferably $< 5\text{nM}$, even more preferably at between $1\text{-}5\text{nM}$, most preferably, $< 1\text{nM}$.

The term "BAFF antagonist" as used herein is used in the broadest sense, and includes any molecule that (1) binds a BAFF polypeptide or binds a receptor of BAFF to partially or fully block BAFF interaction with a BAFF receptor, and (2) partially or fully blocks or inhibits BAFF signaling through the BAFF receptor. BAFF antagonists may be proteinaceous (e.g., antibodies, receptor fusion proteins, peptides, peptibodies, dominant negative BAFF mutants) or non proteinaceous molecules (e.g., small organic molecules ($\leq 500\text{ Da}$)), including siRNA and aptamers, etc. Methods for assessing neutralizing biological activity of BAFF antagonists include, those are known described in the art. Examples of BAFF antagonists include polypeptides comprising a BAFF-binding portion of a BAFF receptor or a BAFF-binding variant thereof (e.g., WO 01/12812, WO 02/24909, WO 00/40716, WO 03/024991), anti-BAFF antibodies (e.g., WO 03/33658), BAFF-binding peptibodies (e.g., WO 02/092620), anti-BAFF-R antibodies (e.g., WO 02/24909) and BAFF-binding

peptides (e.g., WO 02/16412). According to one embodiment, the BAFF antagonist is selected from the group consisting of BCMA-Fc (e.g., WO 01/12812), BAFF-R-Fc (e.g., WO 02/24909), TACI-Ig (e.g., WO 00/40716), an anti-BAFF antibody (e.g., WO 03/33658), an anti-BAFF-R antibody (e.g., WO 02/24909), a BAFF-binding peptibodies (e.g., WO 02/092620), a dominant negative BAFF (e.g., WO 04/081043). According a further embodiment, anti-BAFF antibodies and anti-BAFF receptor antibodies are human, humanized, chimerized or otherwise enhanced for treatment in humans. Examples of an anti-BAFF antibody include belimumab and BAFF-binding antibodies described in WO02/02641 and WO 03/55979. Examples of BAFF-binding peptide-Fc fusion protein include BAFF-binding fusion proteins described in WO 02/24909.

A "B cell surface marker" or "B cell surface antigen" herein is an antigen expressed on the surface of a B cell which can be targeted with an antagonist which binds thereto. Exemplary B cell surface markers include, but are not limited to, CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD40, CD52, D53, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD79b, CD80, CD81, CD82, CD83, CDw84, CD85, CD86, CD180 (RP105), FcRH2 (IRTA4), CD79A, C79B, CR2, CCR6, CD72, P2X5, HLA-DOB, CXCR5 (BLR1), FCER2, BR3 (aka BAFF-R), TACI, BTLA, NAG14 (aka LRRC4), SLGC16270 (ala LOC283663), FcRH1 (IRTA5), FcRH5 (IRTA2), ATWD578 (aka MGC15619), FcRH3 (IRTA3), FcRH4 (IRTA1), FcRH6 (aka LOC343413) and BCMA (aka TNFRSF17), HLA-DO, HLA-Dr10 and MHC ClassII.

In one preferred embodiment, the B cell surface marker of particular interest is expressed on B cells compared to other non-B cell tissues of a mammal and may be expressed on both precursor B cells and mature B cells. Examples of preferred B cell surface markers include, but are not limited to, CD19, CD20 and CD22.

The "CD19" antigen refers to an antigen identified, for example, by the HD237-CD19 or B4 antibody (Kiesel et al. *Leukemia Research II*, 12: 1119 (1987)). CD19 is found on Pro-B, pre-B, immature and mature, activated and memory B cells, up to a point just prior to terminal differentiation into plasma cells. Neither CD19 nor CD20 is expressed on hematopoietic stem cell or plasma cell. Binding of an antagonist to CD19 may cause internalization of the CD19 antigen. The amino acid sequence of human CD19 is shown in *The Leukocyte Antigen Facts Book*, Barclay et

al. supra, page 180, and also EMBL Genbank accession no. M28170 and Swissprot P11836.

The "CD22" antigen, also known as BL-CAM or Lyb8, is a type 1 integral membrane glycoprotein with molecular weight of about 130 (reduced) to 140kD (unreduced). It is expressed in both the cytoplasm and cell membrane of B-lymphocytes. CD22 antigen appears early in B-cell lymphocyte differentiation at approximately the same stage as the CD19 antigen. Unlike other B-cell markers, CD22 membrane expression is limited to the late differentiation stages comprised between mature B cells (CD22+) and plasma cells (CD22-). The CD22 antigen is described, for example, in Wilson et al. *J. Exp. Med.* 173:137 (1991) and Wilson et al. *J. Immunol.* 150:5013 (1993).

The "CD20" antigen is a non-glycosylated, transmembrane phosphoprotein with a molecular weight of approximately 35 kD that is found on the surface of greater than 90% of B cells from peripheral blood or lymphoid organs. CD20 is expressed during early pre-B cell development and remains until plasma cell differentiation; it is not found on human stem cells, lymphoid progenitor cells or normal plasma cells. CD20 is present on both normal B cells as well as malignant B cells. Other names for CD20 in the literature include "B-lymphocyte-restricted differentiation antigen" and "Bp35". The CD20 antigen is described in, for example, Clark and Ledbetter, *Adv. Can. Res.* 52:81-149 (1989) and Valentine *et al. J. Biol. Chem.* 264(19):11282-11287 (1989).

CD20 binding antibody and anti-CD20 antibody are used interchangeably herein and encompass all antibodies that bind CD20 with sufficient affinity such that the antibody is useful as a therapeutic agent in targeting a cell expressing the antigen, and do not significantly cross-react with other proteins such as a negative control protein in the assays described below. Bispecific antibodies wherein one arm of the antibody binds CD20 are also contemplated. Also encompassed by this definition of CD20 binding antibody are functional fragments of the preceding antibodies. The CD20 binding antibody will bind CD20 with a Kd of < 10nM. In preferred embodiments, the binding is at a Kd of < 7.5nM, more preferably < 5nM, even more preferably at between 1-5nM, most preferably, <1nM.

Examples of antibodies which bind the CD20 antigen include: "C2B8" which is now called "Rituximab" ("RITUXAN®") (US Patent No. 5,736,137, expressly

incorporated herein by reference); the yttrium-[90]-labeled 2B8 murine antibody designated "Y2B8" or "Ibritumomab Tiuxetan" ZEVALIN® (US Patent No. 5,736,137, expressly incorporated herein by reference); murine IgG2a "B1," also called "Tositumomab," (Beckman Coulter) optionally labeled with ¹³¹I to generate the "131I-B1" antibody (iodine I131 tositumomab, BEXXAR™) (US Patent No. 5,595,721, expressly incorporated herein by reference); murine monoclonal antibody "1F5" (Press et al. Blood 69(2):584-591 (1987) and variants thereof including "framework patched" or humanized 1F5 (WO03/002607, Leung, S.); ATCC deposit HB-96450); murine 2H7 and chimeric 2H7 antibody (US Patent No. 5,677,180, expressly incorporated herein by reference); humanized 2H7; huMax-CD20 (Genmab, Denmark); AME-133 (Applied Molecular Evolution); A20 antibody or variants thereof such as chimeric or humanized A20 antibody (cA20, hA20, respectively) (US 2003/0219433, Immunomedics); and monoclonal antibodies L27, G28-2, 93-1B3, B-C1 or NU-B2 available from the International Leukocyte Typing Workshop (Valentine et al., In: Leukocyte Typing III (McMichael, Ed., p. 440, Oxford University Press (1987))).

The terms "rituximab" or "RITUXAN®" herein refer to the genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen and designated "C2B8" in US Patent No. 5,736,137 expressly incorporated herein by reference, including fragments thereof which retain the ability to bind CD20.

In a specific embodiment, the anti-CD20 antibodies bind human and primate CD20. In specific embodiments, the antibodies that bind CD20 are humanized or chimeric. CD20 binding antibodies include rituximab (RITUXAN®), m2H7 (murine 2H7), hu2H7 (humanized 2H7) and all its functional variants, including without limitation, hu2H7.v16 (v stands for version), v31, v73, v75, as well as fucose deficient variants, and other 2H7 variants described in WO2004/056312.

Unless indicated, the sequences disclosed herein of the humanized 2H7v.16 and variants thereof are of the mature polypeptide, i.e., without the leader sequence.

Patents and patent publications concerning CD20 antibodies include US Patent Nos. 5,776,456, 5,736,137, 5,843,439, 6,399,061, and 6,682,734, as well as US patent appln nos. US 2002/0197255A1, US 2003/0021781A1, US 2003/0082172 A1, US 2003/0095963 A1, US 2003/0147885 A1 (Anderson *et al.*); US Patent No. 6,455,043B1 and WO00/09160 (Grillo-Lopez, A.); WO00/27428 (Grillo-Lopez and

White); WO00/27433 (Grillo-Lopez and Leonard); WO00/44788 (Braslowsky *et al.*); WO01/10462 (Rastetter, W.); WO01/10461 (Rastetter and White); WO01/10460 (White and Grillo-Lopez); US2001/0018041A1, US2003/0180292A1, WO01/34194 (Hanna and Hariharan); US appln no. US2002/0006404 and WO02/04021 (Hanna and Hariharan); US appln no. US2002/0012665 A1 and WO01/74388 (Hanna, N.); US appln no. US 2002/0058029 A1 (Hanna, N.); US appln no. US 2003/0103971 A1 (Hariharan and Hanna); US appln no. US2002/0009444A1, and WO01/80884 (Grillo-Lopez, A.); WO01/97858 (White, C.); US appln no. US2002/0128488A1 and WO02/34790 (Reff, M.); WO02/060955 (Braslowsky *et al.*); WO2/096948 (Braslowsky *et al.*); WO02/079255 (Reff and Davies); US Patent No. 6,171,586B1, and WO98/56418 (Lam *et al.*); WO98/58964 (Raju, S.); WO99/22764 (Raju, S.); WO99/51642, US Patent No. 6,194,551B1, US Patent No. 6,242,195B1, US Patent No. 6,528,624B1 and US Patent No. 6,538,124 (Idusogie *et al.*); WO00/42072 (Presta, L.); WO00/67796 (Curd *et al.*); WO01/03734 (Grillo-Lopez *et al.*); US appln no. US 2002/0004587A1 and WO01/77342 (Miller and Presta); US appln no. US2002/0197256 (Grewal, I.); US Appln no. US 2003/0157108 A1 (Presta, L.); US Patent Nos. 6,565,827B1, 6,090,365B1, 6,287,537B1, 6,015,542, 5,843,398, and 5,595,721, (Kaminski *et al.*); US Patent Nos. 5,500,362, 5,677,180, 5,721,108, 6,120,767, 6,652,852B1 (Robinson *et al.*); US Pat No. 6,410,391B1 (Raubitschek *et al.*); US Patent No. 6,224,866B1 and WO00/20864 (Barbera-Guillem, E.); WO01/13945 (Barbera-Guillem, E.); WO00/67795 (Goldenberg); US Appl No. US 2003/0133930 A1 and WO00/74718 (Goldenberg and Hansen); WO00/76542 (Golay *et al.*); WO01/72333 (Wolin and Rosenblatt); US Patent No. 6,368,596B1 (Ghetie *et al.*); US Patent No. 6,306,393 and US Appln no. US2002/0041847 A1, (Goldenberg, D.); US Appln no. US2003/0026801A1 (Weiner and Hartmann); WO02/102312 (Engleman, E.); US Patent Application No. 2003/0068664 (Albitar *et al.*); WO03/002607 (Leung, S.); WO 03/049694, US2002/0009427A1, and US 2003/0185796 A1 (Wolin *et al.*); WO03/061694 (Sing and Siegall); US 2003/0219818 A1 (Bohen *et al.*); US 2003/0219433 A1 and WO 03/068821 (Hansen *et al.*); US2003/0219818A1 (Bohen *et al.*); US2002/0136719A1 (Shenoy *et al.*); WO2004/032828 (Wahl *et al.*), each of which is expressly incorporated herein by reference. See, also, US Patent No. 5,849,898 and EP appln no. 330,191 (Seed *et al.*);

US Patent No. 4,861,579 and EP332,865A2 (Meyer and Weiss); USP 4,861,579 (Meyer *et al.*); WO95/03770 (Bhat *et al.*); US 2003/0219433 A1 (Hansen *et al.*).

The CD20 antibodies can be naked antibody or conjugated to a cytotoxic compound such as a radioisotope, or a toxin. Such antibodies include the antibody Zevalin™ which is linked to the radioisotope, Yttrium-90 (IDEC Pharmaceuticals, San Diego, CA), and Bexxar™ which is conjugated to I-131 (Corixa, WA). The humanized 2H7 variants include those that have amino acid substitutions in the FR and affinity maturation variants with changes in the grafted CDRs. The substituted amino acids in the CDR or FR are not limited to those present in the donor or acceptor antibody. In other embodiments, the anti-CD20 antibodies of the invention further comprise changes in amino acid residues in the Fc region that lead to improved effector function including enhanced CDC and/or ADCC function and B-cell killing (also referred to herein as B-cell depletion). In particular, three mutations have been identified for improving CDC and ADCC activity: S298A/E333A/K334A (also referred to herein as a triple Ala mutant or variant; numbering in the Fc region is according to the EU numbering system; Kabat *et al.*, *supra*) as described (Idusogie *et al.*, *supra* (2001); Shields *et al.*, *supra*).

Other anti-CD20 antibodies of the invention include those having specific changes that improve stability. In one embodiment, the chimeric anti-CD20 antibody has murine V regions and human C region. One such specific chimeric anti-CD20 antibody is Rituxan® (Rituximab®; Genentech, Inc.). Rituximab and hu2H7 can mediate lysis of B-cells through both complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). Antibody variants with altered Fc region amino acid sequences and increased or decreased C1q binding capability are described in US patent No. 6,194,551B1 and WO99/51642. The contents of those patent publications are specifically incorporated herein by reference. See, also, Idusogie *et al. J. Immunol.* 164: 4178-4184 (2000).

“Therapeutic agents” refers to agents that are useful in alleviating a disease or the symptoms of a disease. Therapeutic agents can be proteinaceous (e.g., antibodies, receptor fusion proteins, peptides, peptibodies, immunoadhesins) or non proteinaceous molecules (e.g., small organic molecules (≤ 500 Da)), including siRNA and aptamers, etc.

“B cell promoting agents” refers to agents that stimulate B cell proliferation or survival. Examples of B cell promoting agents include cytokines and antibodies that stimulate B cell proliferation or survival. Examples of cytokines that are B cell promoting agents include, but are not limited to, IL-2, IL-4, IL-5, IL-6, IL-10, IL-14, IL-15 and IL-21.

As used herein, “B cell depletion” refers to a reduction in peripheral blood B cell levels in an animal or human after drug or antibody treatment, as compared to the level before treatment. B cell levels are measurable using well known assays such as by getting a complete blood count or by FACS analysis for known B cell markers (e.g., B220 or CD19 in mice, or CD19 and CD20 in humans). B cell depletion can be partial or complete. In one embodiment, the depletion of CD20 expressing peripheral B cells is at least 25%. In another embodiment, the depletion of CD20 expressing peripheral B cells is at least 30%, 40%, 50%, 60%, 70%, 80% or 90%. Not to be limited by any one mechanism, possible mechanisms of B cell depletion include ADCC, CDC, apoptosis, modulation of calcium flux or a combination of two or more of the preceding.

“B cell depletion agents” or “B cell depleting agents” refers to agents that reduce peripheral B cells by at least 25%. In another embodiment, the depletion of peripheral B cells is at least 30%, 40%, 50%, 60%, 70%, 80% or 90%. In one preferred embodiment, the B cell depletion agent specifically binds to a white blood cell and not other cells types. In another embodiment, the B cell depletion specifically binds to a B cell and not other cell types. In one embodiment, the B cell depletion agent is an antibody. In one preferred embodiment, the antibody is a monoclonal antibody. In another embodiment, the antibody is conjugated to a chemotherapeutic agent or a cytotoxic agent. Specific examples of B cell depletion agents include, but are not limited to, the aforementioned anti-CD20 antibodies, Alemtuzumab (anti-CD52 antibody), and Epratuzumab or CMC-544 (Wyeth) (anti-CD22 antibodies) or anti-BR3 antibodies described herein.

“B cell recovery phase” is the stage of B cell repletion in a subject after treatment with a therapeutic agent has reduced B cells levels in the subject to its lowest levels. “Tissue B cell recovery phase” is the stage of B cell repletion in the tissue in a subject after treatment with a therapeutic agent has reduced tissue B cells levels in the subject to its lowest levels. “Peripheral B cell recovery phase” is the

stage of B cell repletion in the peripheral blood in a subject after treatment with a therapeutic agent has reduced peripheral blood B cells levels in the subject to its lowest levels.

“Maximum B cell depletion phase” is the stage of maximum B cell depletion in a subject after treatment with a therapeutic agent that reduces B cells levels.

“T cell depletion agents” refers to agents that reduce T cells by at least 25% in the peripheral blood. In another embodiment, the depletion of peripheral T cells is at least 30%, 40%, 50%, 60%, 70%, 80% or 90%. In one preferred embodiment, the T cell depletion agent specifically binds to a T cell and not other cells types. In one embodiment, the T cell depletion agent is an antibody or a chemical compound. In one preferred embodiment, the antibody is a monoclonal antibody. In another embodiment, the antibody is conjugated to a chemotherapeutic agent or a cytotoxic agent.

“DMARDS” or “disease-modifying anti-rheumatic drugs” are drugs that slow down the biological processes that are the driving force behind persistent inflammation. DMARDS include, but are not limited to, methotrexate, hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, etanercept, infliximab, azathioprine, D-penicillamine, Gold (oral), Gold (intramuscular), minocycline, cyclosporine, Staphylococcal protein A immunoabsorption.

“Immunosuppressive agent” as used herein refers to substances that act to suppress or mask the immune system of a patient. Such agents would include substances that suppress cytokine production, down regulate or suppress self-antigen expression, or mask the MHC antigens. Examples of such agents include steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone; 2-amino-6-aryl-5-substituted pyrimidines (see U.S. Pat. No. 4,665,077), azathioprine (or cyclophosphamide, if there is an adverse reaction to azathioprine); bromocryptine; glutaraldehyde (which masks the MHC antigens, as described in U.S. Pat. No. 4,120,649); anti-idiotypic antibodies for MHC antigens and MHC fragments; cyclosporin A; cytokine or cytokine receptor antagonists including anti-interferon- γ , - β , or - α antibodies; anti-tumor necrosis factor- α antibodies; anti-tumor necrosis factor- β antibodies; anti-interleukin-2 antibodies and anti-IL-2 receptor antibodies; anti-L3T4 antibodies; heterologous anti-lymphocyte globulin; pan-T antibodies, preferably anti-CD3 or anti-CD4/CD4a antibodies; soluble peptide

containing a LFA-3 binding domain (WO 90/08187 published 7/26/90); streptokinase; TGF- β ; streptodornase; RNA or DNA from the host; FK506; RS-61443; deoxyspergualin; rapamycin; T-cell receptor (U.S. Pat. No. 5,114,721); T-cell receptor fragments (Offner *et al.*, *Science* 251:430-432 (1991); WO 90/11294; and WO 91/01133); and T cell receptor antibodies (EP 340,109) such as T10B9.

The term "immunological disorder" refers to disorders and conditions in which an immune response is aberrant. The aberrant response can be due to (a) abnormal proliferation, maturation, survival, differentiation, or function of immune cells such as, for example, T and/or B cells. Examples of immunological disorders include, but are not limited to, hyperproliferative immune disorders, antibody mediated pathologies, autoimmune disorders, B cell disorders including plasma cell disorders, B cell lymphoproliferative disorders such as B cell neoplasias and B cell hyperplasias, antibody mediated pathologies, transplant rejection, allergies. According to one embodiment, the immunological disorder exhibits, in part, elevated serum BAFF levels or decreased serum BAFF levels compared to a control (e.g., compared to serum BAFF levels of a normal, healthy subject).

An "immunodeficiency disease" is a disorder or condition where the immune response is reduced (e.g., severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA). Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia, thymic aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia telangiectasia (cerebellar ataxia, oculocutaneous telangiectasia and

immunodeficiency), short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleotide phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency,) or conditions associated with an immunodeficiency, Janus Associated Kinase 3 (JAK3) deficiency, DiGeorge's syndrome (isolated T cell deficiency) and Associated syndromes e.g., Down syndrome, chronic mucocutaneous candidiasis, hyper-IgE syndrome, chronic granulomatous disease, partial albinism and WHIM syndrome (warts, hypogammaglobulinemia, infection, and myelokathexis [retention of leukocytes in a hypercellular marrow]).

An "autoimmune disease" herein is a disease or disorder arising from and directed against an individual's own tissues or organs or a co-segregate or manifestation thereof or resulting condition therefrom. In many of these autoimmune and inflammatory disorders, a number of clinical and laboratory markers may exist, including, but not limited to, hypergammaglobulinemia, high levels of autoantibodies, antigen-antibody complex deposits in tissues, benefit from corticosteroid or immunosuppressive treatments, and lymphoid cell aggregates in affected tissues. Without being limited to any one theory regarding B-cell mediated autoimmune disease, it is believed that B cells demonstrate a pathogenic effect in human autoimmune diseases through a multitude of mechanistic pathways, including autoantibody production, immune complex formation, dendritic and T-cell activation, cytokine synthesis, direct chemokine release, and providing a nidus for ectopic neolymphogenesis. Each of these pathways may participate to different degrees in the pathology of autoimmune diseases.

"Autoimmune disease" can be an organ-specific disease (*i.e.*, the immune response is specifically directed against an organ system such as the endocrine system, the hematopoietic system, the skin, the cardiopulmonary system, the gastrointestinal and liver systems, the renal system, the thyroid, the ears, the neuromuscular system, the central nervous system, *etc.*) or a systemic disease which can affect multiple organ systems (for example, systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyositis, *etc.*). Preferred such diseases include autoimmune rheumatologic disorders (such as, for example, rheumatoid arthritis, Sjögren's syndrome,

scleroderma, lupus such as SLE and lupus nephritis, polymyositis/dermatomyositis, cryoglobulinemia, anti-phospholipid antibody syndrome, and psoriatic arthritis), autoimmune gastrointestinal and liver disorders (such as, for example, inflammatory bowel diseases (e.g., ulcerative colitis and Crohn's disease), autoimmune gastritis and pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and celiac disease), vasculitis (such as, for example, ANCA-associated vasculitis, including Churg-Strauss vasculitis, Wegener's granulomatosis, and polyarteriitis), autoimmune neurological disorders (such as, for example, multiple sclerosis, opsoclonus myoclonus syndrome, myasthenia gravis, neuromyelitis optica, Parkinson's disease, Alzheimer's disease, and autoimmune polyneuropathies), renal disorders (such as, for example, glomerulonephritis, Goodpasture's syndrome, and Berger's disease), autoimmune dermatologic disorders (such as, for example, psoriasis, urticaria, hives, pemphigus vulgaris, bullous pemphigoid, and cutaneous lupus erythematosus), hematologic disorders (such as, for example, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, post-transfusion purpura, and autoimmune hemolytic anemia), atherosclerosis, uveitis, autoimmune hearing diseases (such as, for example, inner ear disease and hearing loss), Behcet's disease, Raynaud's syndrome, organ transplant, and autoimmune endocrine disorders (such as, for example, diabetic-related autoimmune diseases such as insulin-dependent diabetes mellitus (IDDM), Addison's disease, and autoimmune thyroid disease (e.g., Graves' disease and thyroiditis)). More preferred such diseases include, for example, rheumatoid arthritis, ulcerative colitis, ANCA-associated vasculitis, lupus, multiple sclerosis, Sjögren's syndrome, Graves' disease, IDDM, pernicious anemia, thyroiditis, and glomerulonephritis.

Specific examples of other autoimmune diseases as defined herein, which in some cases encompass those listed above, include, but are not limited to, arthritis (acute and chronic, rheumatoid arthritis including juvenile-onset rheumatoid arthritis and stages such as rheumatoid synovitis, gout or gouty arthritis, acute immunological arthritis, chronic inflammatory arthritis, degenerative arthritis, type II collagen-induced arthritis, infectious arthritis, Lyme arthritis, proliferative arthritis, psoriatic arthritis, Still's disease, vertebral arthritis, osteoarthritis, arthritis chronica progrediente, arthritis deformans, polyarthritis chronica primaria, reactive arthritis, menopausal arthritis, estrogen-depletion arthritis, and ankylosing

spondylitis/rheumatoid spondylitis), autoimmune lymphoproliferative disease, inflammatory hyperproliferative skin diseases, psoriasis such as plaque psoriasis, guttate psoriasis, pustular psoriasis, and psoriasis of the nails, atopy including atopic diseases such as hay fever and Job's syndrome, dermatitis including contact dermatitis, chronic contact dermatitis, exfoliative dermatitis, allergic dermatitis, allergic contact dermatitis, hives, dermatitis herpetiformis, nummular dermatitis, seborrheic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, and atopic dermatitis, x-linked hyper IgM syndrome, allergic intraocular inflammatory diseases, urticaria such as chronic allergic urticaria and chronic idiopathic urticaria, including chronic autoimmune urticaria, myositis, polymyositis/dermatomyositis, juvenile dermatomyositis, toxic epidermal necrolysis, scleroderma (including systemic scleroderma), sclerosis such as systemic sclerosis, multiple sclerosis (MS) such as spino-optical MS, primary progressive MS (PPMS), and relapsing remitting MS (RRMS), progressive systemic sclerosis, atherosclerosis, arteriosclerosis, sclerosis disseminata, ataxic sclerosis, neuromyelitis optica (NMO), inflammatory bowel disease (IBD) (for example, Crohn's disease, autoimmune-mediated gastrointestinal diseases, gastrointestinal inflammation, colitis such as ulcerative colitis, colitis ulcerosa, microscopic colitis, collagenous colitis, colitis polyposa, necrotizing enterocolitis, and transmural colitis, and autoimmune inflammatory bowel disease), bowel inflammation, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, respiratory distress syndrome, including adult or acute respiratory distress syndrome (ARDS), meningitis, inflammation of all or part of the uvea, iritis, choroiditis, an autoimmune hematological disorder, graft-versus-host disease, angioedema such as hereditary angioedema, cranial nerve damage as in meningitis, herpes gestationis, pemphigoid gestationis, pruritis scroti, autoimmune premature ovarian failure, sudden hearing loss due to an autoimmune condition, IgE-mediated diseases such as anaphylaxis and allergic and atopic rhinitis, encephalitis such as Rasmussen's encephalitis and limbic and/or brainstem encephalitis, uveitis, such as anterior uveitis, acute anterior uveitis, granulomatous uveitis, nongranulomatous uveitis, phacoantigenic uveitis, posterior uveitis, or autoimmune uveitis, glomerulonephritis (GN) with and without nephrotic syndrome such as chronic or acute glomerulonephritis such as primary GN, immune-mediated GN, membranous GN (membranous nephropathy), idiopathic membranous GN or idiopathic

membranous nephropathy, membrano- or membranous proliferative GN (MPGN), including Type I and Type II, and rapidly progressive GN (RPGN), proliferative nephritis, autoimmune polyglandular endocrine failure, balanitis including balanitis circumscripta plasmacellularis, balanoposthitis, erythema annulare centrifugum, erythema dyschromicum perstans, erythema multiform, granuloma annulare, lichen nitidus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen spinulosus, lichen planus, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant keratosis, pyoderma gangrenosum, allergic conditions and responses, food allergies, drug allergies, insect allergies, rare allergic disorders such as mastocytosis, allergic reaction, eczema including allergic or atopic eczema, asteatotic eczema, dyshidrotic eczema, and vesicular palmoplantar eczema, asthma such as asthma bronchiale, bronchial asthma, and auto-immune asthma, conditions involving infiltration of T cells and chronic inflammatory responses, immune reactions against foreign antigens such as fetal A-B-O blood groups during pregnancy, chronic pulmonary inflammatory disease, autoimmune myocarditis, leukocyte adhesion deficiency, lupus, including lupus nephritis, lupus cerebritis, pediatric lupus, non-renal lupus, extra-renal lupus, discoid lupus and discoid lupus erythematosus, alopecia lupus, SLE, such as cutaneous SLE or subacute cutaneous SLE, neonatal lupus syndrome (NLE), and lupus erythematosus disseminatus, juvenile onset (Type I) diabetes mellitus, including pediatric IDDM, adult onset diabetes mellitus (Type II diabetes), autoimmune diabetes, idiopathic diabetes insipidus, diabetic retinopathy, diabetic nephropathy, diabetic colitis, diabetic large-artery disorder, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, tuberculosis, sarcoidosis, granulomatosis including lymphomatoid granulomatosis, Wegener's granulomatosis, agranulocytosis, vasculitides, including vasculitis, large-vessel vasculitis (including polymyalgia rheumatica and giant-cell (Takayasu's) arteritis), medium-vessel vasculitis (including Kawasaki's disease and polyarteritis nodosa/periarteritis nodosa), microscopic polyarteritis, immunovasculitis, CNS vasculitis, cutaneous vasculitis, hypersensitivity vasculitis, necrotizing vasculitis such as systemic necrotizing vasculitis, and ANCA-associated vasculitis, such as Churg-Strauss vasculitis or syndrome (CSS) and ANCA-associated small-vessel vasculitis, temporal arteritis, aplastic anemia, autoimmune aplastic anemia, Coombs positive anemia, Diamond Blackfan anemia, hemolytic anemia or immune hemolytic anemia

including autoimmune hemolytic anemia (AIHA), pernicious anemia (anemia perniciosa), Addison's disease, pure red cell anemia or aplasia (PRCA), Factor VIII deficiency, hemophilia A, autoimmune neutropenia(s), cytopenias such as pancytopenia, leukopenia, diseases involving leukocyte diapedesis, CNS inflammatory disorders, Alzheimer's disease, Parkinson's disease, multiple organ injury syndrome such as those secondary to septicemia, trauma or hemorrhage, antigen-antibody complex-mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, motoneuritis, allergic neuritis, Behçet's disease/syndrome, Castleman's syndrome, Goodpasture's syndrome, Reynaud's syndrome, Sjögren's syndrome, Stevens-Johnson syndrome, pemphigoid such as pemphigoid bullous and skin pemphigoid, pemphigus (including pemphigus vulgaris, pemphigus foliaceus, pemphigus mucus-membrane pemphigoid, and pemphigus erythematosus), autoimmune polyendocrinopathies, Reiter's disease or syndrome, thermal injury due to an autoimmune condition, preeclampsia, an immune complex disorder such as immune complex nephritis, antibody-mediated nephritis, neuroinflammatory disorders, polyneuropathies, chronic neuropathy such as IgM polyneuropathies or IgM-mediated neuropathy, thrombocytopenia (as developed by myocardial infarction patients, for example), including thrombotic thrombocytopenic purpura (TTP), post-transfusion purpura (PTP), heparin-induced thrombocytopenia, and autoimmune or immune-mediated thrombocytopenia including, for example, idiopathic thrombocytopenic purpura (ITP) including chronic or acute ITP, scleritis such as idiopathic cerato-scleritis, episcleritis, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism, hypoparathyroidism, autoimmune endocrine diseases including thyroiditis such as autoimmune thyroiditis, Hashimoto's disease, chronic thyroiditis (Hashimoto's thyroiditis), or subacute thyroiditis, autoimmune thyroid disease, idiopathic hypothyroidism, Grave's disease, polyglandular syndromes such as autoimmune polyglandular syndromes, for example, type I (or polyglandular endocrinopathy syndromes), paraneoplastic syndromes, including neurologic paraneoplastic syndromes such as Lambert-Eaton myasthenic syndrome or Eaton-Lambert syndrome, stiff-man or stiff-person syndrome, encephalomyelitis such as allergic encephalomyelitis or encephalomyelitis allergica and experimental allergic encephalomyelitis (EAE), myasthenia gravis such as thymoma-associated myasthenia

gravis, cerebellar degeneration, neuromyotonia, opsoclonus or opsoclonus myoclonus syndrome (OMS), and sensory neuropathy, multifocal motor neuropathy, Sheehan's syndrome, autoimmune hepatitis, chronic hepatitis, lupoid hepatitis, giant-cell hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis, pneumonitis such as lymphoid interstitial pneumonitis (LIP), bronchiolitis obliterans (non-transplant) vs NSIP, Guillain-Barré syndrome, Berger's disease (IgA nephropathy), idiopathic IgA nephropathy, linear IgA dermatosis, acute febrile neutrophilic dermatosis, subcorneal pustular dermatosis, transient acantholytic dermatosis, cirrhosis such as primary biliary cirrhosis and pneumonocirrhosis, autoimmune enteropathy syndrome, Celiac or Coeliac disease, celiac sprue (gluten enteropathy), refractory sprue, idiopathic sprue, cryoglobulinemia such as mixed cryoglobulinemia, amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), coronary artery disease, autoimmune ear disease such as autoimmune inner ear disease (AIED), autoimmune hearing loss, polychondritis such as refractory or relapsed or relapsing polychondritis, pulmonary alveolar proteinosis, Cogan's syndrome/nonsyphilitic interstitial keratitis, Bell's palsy, Sweet's disease/syndrome, rosacea autoimmune, zoster-associated pain, amyloidosis, a non-cancerous lymphocytosis, a primary lymphocytosis, which includes monoclonal B cell lymphocytosis (e.g., benign monoclonal gammopathy and monoclonal gammopathy of undetermined significance, MGUS), peripheral neuropathy, paraneoplastic syndrome, channelopathies such as epilepsy, migraine, arrhythmia, muscular disorders, deafness, blindness, periodic paralysis, and channelopathies of the CNS, autism, inflammatory myopathy, focal or segmental or focal segmental glomerulosclerosis (FSGS), endocrine ophthalmopathy, uveoretinitis, chorioretinitis, autoimmune hepatological disorder, fibromyalgia, multiple endocrine failure, Schmidt's syndrome, adrenalitis, gastric atrophy, presenile dementia, demyelinating diseases such as autoimmune demyelinating diseases and chronic inflammatory demyelinating polyneuropathy, Dressler's syndrome, alopecia areata, alopecia totalis, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), male and female autoimmune infertility, e.g., due to anti-spermatozoan antibodies, mixed connective tissue disease, Chagas' disease, rheumatic fever, recurrent abortion, farmer's lung, erythema multiforme, post-cardiotomy syndrome, Cushing's syndrome, bird-fancier's lung, allergic granulomatous angiitis, benign lymphocytic angiitis, Alport's syndrome,

alveolitis such as allergic alveolitis and fibrosing alveolitis, interstitial lung disease, transfusion reaction, leprosy, malaria, parasitic diseases such as leishmaniasis, kypanosomiasis, schistosomiasis, ascariasis, aspergillosis, Sampter's syndrome, Caplan's syndrome, dengue, endocarditis, endomyocardial fibrosis, diffuse interstitial pulmonary fibrosis, interstitial lung fibrosis, fibrosing mediastinitis, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, endophthalmitis, erythema elevatum et diutinum, erythroblastosis fetalis, eosinophilic faciitis, Shulman's syndrome, Felty's syndrome, flariasis, cyclitis such as chronic cyclitis, heterochronic cyclitis, iridocyclitis (acute or chronic), or Fuch's cyclitis, Henoch-Schonlein purpura, human immunodeficiency virus (HIV) infection, SCID, acquired immune deficiency syndrome (AIDS), echovirus infection, sepsis (systemic inflammatory response syndrome (SIRS)), endotoxemia, pancreatitis, thyroxicosis, parvovirus infection, rubella virus infection, post-vaccination syndromes, congenital rubella infection, Epstein-Barr virus infection, mumps, Evan's syndrome, autoimmune gonadal failure, Sydenham's chorea, post-streptococcal nephritis, thromboangitis ubiterans, thyrotoxicosis, tabes dorsalis, chorioiditis, giant-cell polymyalgia, chronic hypersensitivity pneumonitis, conjunctivitis, such as vernal catarrh, keratoconjunctivitis sicca, and epidemic keratoconjunctivitis, idiopathic nephritic syndrome, minimal change nephropathy, benign familial and ischemia-reperfusion injury, transplant organ reperfusion, retinal autoimmunity, joint inflammation, bronchitis, chronic obstructive airway/pulmonary disease, silicosis, aphthae, aphthous stomatitis, arteriosclerotic disorders (cerebral vascular insufficiency) such as arteriosclerotic encephalopathy and arteriosclerotic retinopathy, aspermiogenese, autoimmune hemolysis, Boeck's disease, cryoglobulinemia, Dupuytren's contracture, endophthalmia phacoanaphylactica, enteritis allergica, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, Hamman-Rich's disease, sensoneural hearing loss, haemoglobinuria paroxysmatica, hypogonadism, ileitis regionalis, leucopenia, mononucleosis infectiosa, traverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia symphatica, orchitis granulomatosa, pancreatitis, polyradiculitis acuta, pyoderma gangrenosum, Quervain's thyreoiditis, acquired spenic atrophy, non-malignant thymoma, lymphofollicular thymitis, vitiligo, toxic-shock syndrome, food poisoning, conditions involving infiltration of T cells, leukocyte-adhesion deficiency, immune responses associated

with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, diseases involving leukocyte diapedesis, multiple organ injury syndrome, antigen-antibody complex-mediated diseases, antiglomerular basement membrane disease, autoimmune polyendocrinopathies, oophoritis, primary myxedema, autoimmune atrophic gastritis, sympathetic ophthalmia, rheumatic diseases, mixed connective tissue disease, nephrotic syndrome, insulinitis, polyendocrine failure, autoimmune polyglandular syndromes, including polyglandular syndrome type I, adult-onset idiopathic hypoparathyroidism (AOIH), cardiomyopathy such as dilated cardiomyopathy, epidermolysis bullosa acquisita (EBA), hemochromatosis, myocarditis, nephrotic syndrome, primary sclerosing cholangitis, purulent or nonpurulent sinusitis, acute or chronic sinusitis, ethmoid, frontal, maxillary, or sphenoid sinusitis, allergic sinusitis, an eosinophil-related disorder such as eosinophilia, pulmonary infiltration eosinophilia, eosinophilia-myalgia syndrome, Loeffler's syndrome, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia, bronchopneumonic aspergillosis, aspergilloma, or granulomas containing eosinophils, anaphylaxis, spondyloarthropathies, seronegative spondyloarthritides, polyendocrine autoimmune disease, sclerosing cholangitis, sclera, episclera, chronic mucocutaneous candidiasis, Bruton's syndrome, transient hypogammaglobulinemia of infancy, Wiskott-Aldrich syndrome, ataxia telangiectasia syndrome, angiectasis, autoimmune disorders associated with collagen disease, rheumatism such as chronic arthrorheumatism, lymphadenitis, reduction in blood pressure response, vascular dysfunction, tissue injury, cardiovascular ischemia, hyperalgesia, renal ischemia, cerebral ischemia, and disease accompanying vascularization, allergic hypersensitivity disorders, glomerulonephritides, reperfusion injury, ischemic reperfusion disorder, reperfusion injury of myocardial or other tissues, lymphomatous tracheobronchitis, inflammatory dermatoses, dermatoses with acute inflammatory components, multiple organ failure, bullous diseases, renal cortical necrosis, acute purulent meningitis or other central nervous system inflammatory disorders, ocular and orbital inflammatory disorders, granulocyte transfusion-associated syndromes, cytokine-induced toxicity, narcolepsy, acute serious inflammation, chronic intractable inflammation, pyelitis, endarterial hyperplasia, peptic ulcer, valvulitis, and endometriosis.

Examples of hyperproliferative immune disorders include, but are not limited to, non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), mantle cell lymphoma, marginal zone related tumors, follicular lymphoma (FL), large cell lymphoma such as diffuse large B-cell lymphoma, Burkitt's lymphoma, plasma cell disorders such as multiple myeloma.

Examples of antibody mediated pathologies include, but are not limited to, ITP, myasthenia gravis, autoimmune hemolytic anemia (erythrocyte autoantibodies), Hashimoto's thyroiditis (thyroid autoantibodies), myasthenia gravis (acetylcholine receptor autoantibodies), Grave's disease characterized by diffuse goiter and hyperthyroidism (thyrotropin receptor autoantibodies) and Goodpasture's syndrome comprising anti-GBM autoantibodies.

B cell neoplasms include Hodgkin's disease including lymphocyte predominant Hodgkin's disease (LPHD); non-Hodgkin's lymphoma (NHL); follicular center cell (FCC) lymphomas; acute lymphocytic leukemia (ALL); chronic lymphocytic leukemia (CLL); and Hairy cell leukemia. The non-Hodgkins lymphoma include low grade/follicular non-Hodgkin's lymphoma (NHL), small lymphocytic (SL) NHL, intermediate grade/follicular NHL, intermediate grade diffuse NHL, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, plasmacytoid lymphocytic lymphoma, mantle cell lymphoma, AIDS- related lymphoma and Waldenstrom's macroglobulinemia. Treatment of relapses of these cancers are also contemplated. LPHD is a type of Hodgkin's disease that tends to relapse frequently despite radiation or chemotherapy treatment. CLL is one of four major types of leukemia. A cancer of mature B-cells called lymphocytes, CLL is manifested by progressive accumulation of cells in blood, bone marrow and lymphatic tissues. Indolent lymphoma is a slow-growing, incurable disease in which the average patient survives between six and 10 years following numerous periods of remission and relapse.

The term "non-Hodgkin's lymphoma" or "NHL", as used herein, refers to a cancer of the lymphatic system other than Hodgkin's lymphomas. Hodgkin's lymphomas can generally be distinguished from non-Hodgkin's lymphomas by the presence of Reed-Sternberg cells in Hodgkin's lymphomas and the absence of said cells in non-Hodgkin's lymphomas. Examples of non-Hodgkin's lymphomas encompassed by the term as used herein include any that would be identified as such

by one skilled in the art (e.g., an oncologist or pathologist) in accordance with classification schemes known in the art, such as the Revised European-American Lymphoma (REAL) scheme as described in Color Atlas of Clinical Hematology, Third Edition; A. Victor Hoffbrand and John E. Pettit (eds.) (Harcourt Publishers Limited 2000) (see, in particular Fig. 11.57, 11.58 and/or 11.59). More specific examples include, but are not limited to, relapsed or refractory NHL, front line low grade NHL, Stage III/IV NHL, chemotherapy resistant NHL, precursor B lymphoblastic leukemia and/or lymphoma, small lymphocytic lymphoma, B cell chronic lymphocytic leukemia and/or prolymphocytic leukemia and/or small lymphocytic lymphoma, B-cell prolymphocytic lymphoma, immunocytoma and/or lymphoplasmacytic lymphoma, marginal zone B cell lymphoma, splenic marginal zone lymphoma, extranodal marginal zone - MALT lymphoma, nodal marginal zone lymphoma, hairy cell leukemia, plasmacytoma and/or plasma cell myeloma, low grade/follicular lymphoma, intermediate grade/follicular NHL, mantle cell lymphoma, follicle center lymphoma (follicular), intermediate grade diffuse NHL, diffuse large B-cell lymphoma, aggressive NHL (including aggressive front-line NHL and aggressive relapsed NHL), NHL relapsing after or refractory to autologous stem cell transplantation, primary mediastinal large B-cell lymphoma, primary effusion lymphoma, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, Burkitt's lymphoma, precursor (peripheral) T-cell lymphoblastic leukemia and/or lymphoma, adult T-cell lymphoma and/or leukemia, T cell chronic lymphocytic leukemia and/or prolymphocytic leukemia, large granular lymphocytic leukemia, mycosis fungoides and/or Sezary syndrome, extranodal natural killer/T-cell (nasal type) lymphoma, enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma, subcutaneous panniculitis like T-cell lymphoma, skin (cutaneous) lymphomas, anaplastic large cell lymphoma, angiocentric lymphoma, intestinal T cell lymphoma, peripheral T-cell (not otherwise specified) lymphoma and angioimmunoblastic T-cell lymphoma.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer,

adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; multiple myeloma and post-transplant lymphoproliferative disorder (PTLD).

As used herein, the term "immunoadhesin" designates molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with a desired binding specificity, which amino acid sequence is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence (e.g., CH₂ and/or CH₃ sequence of an IgG). Exemplary adhesin sequences include contiguous amino acid sequences that comprise a portion of a receptor or a ligand that binds to a protein of interest. Adhesin sequences can also be sequences that bind a protein of interest, but are not receptor or ligand sequences (e.g., adhesin sequences in peptibodies). Such polypeptide sequences can be selected or identified by various methods, include phage display techniques and high throughput sorting methods. The immunoglobulin constant domain sequence in the immunoadhesin 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.

The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an

amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of an antibody or immunoadhesin, or by recombinantly engineering the Fc region to to remove the K447. Accordingly, a composition of antibodies or immunoadhesins, e.g., as recited herein, may comprise populations with all K447 residues removed, populations with no K447 residues removed, and populations having a mixture of antibodies with and without the K447 residue.

Unless indicated otherwise, herein the numbering of the residues in an immunoglobulin heavy chain is that of the EU index as in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991), expressly incorporated herein by reference. The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody.

The term "antibody" is used in the broadest sense and specifically covers, for example, single monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), antibody compositions with polyepitopic specificity, polyclonal antibodies, single chain anti- antibodies, and fragments of antibodies (see below) as long as they specifically bind a native polypeptide and/or exhibit a biological activity or immunological activity of this invention. According to one embodiment, the antibody binds to an oligomeric form of a target protein, e.g., a trimeric form. According to another embodiment, the antibody specifically binds to a protein, which binding can be inhibited by a monoclonal antibody of this invention (e.g., a deposited antibody of this invention, etc.). The phrase "functional fragment or analog" of an antibody is a compound having a qualitative biological activity in common with an antibody to which it is being referred. For example, a functional fragment or analog of an antibody of this invention can be one which can specifically bind to a B cell surface antigen. The term "immunoglobulin" (Ig) is used interchangeably with "antibody" herein.

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 can 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 basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_{H1}). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of

their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , γ , ϵ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and define specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L , and around about 31-35B (H1), 50-65 (H2) and 95-102 (H3) in the V_H (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in

the V_L, and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

The term "monoclonal antibody" as used herein refers to an antibody from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical and/or bind the same epitope(s), except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. Such monoclonal antibody typically includes an antibody comprising a polypeptide sequence that binds a target, wherein the target-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones or recombinant DNA clones. It should be understood that the selected target binding sequence can be further altered, for example, to improve affinity for the target, to humanize the target binding sequence, to improve its production in cell culture, to reduce its immunogenicity *in vivo*, to create a multispecific antibody, *etc.*, and that an antibody comprising the altered target binding sequence is also a monoclonal antibody of this invention. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. In addition to their specificity, the monoclonal antibody preparations are advantageous in that they are typically 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 a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler *et al.*, *Nature*, 256:495 (1975); Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling *et al.*, in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681, (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567), phage display technologies (see, *e.g.*, Clackson *et al.*, *Nature*, 352:624-628 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991); Sidhu *et*

al., *J. Mol. Biol.* 338(2):299-310 (2004); Lee *et al.*, *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat. Acad. Sci. USA* 101(34):12467-12472 (2004); and Lee *et al.* *J. Immunol. Methods* 284(1-2):119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, e.g., WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:2551 (1993); Jakobovits *et al.*, *Nature*, 362:255-258 (1993); Bruggemann *et al.*, *Year in Immuno.*, 7:33 (1993); U.S. Patent Nos. 5,545,806; 5,569,825; 5,591,669 (all of GenPharm); 5,545,807; WO 1997/17852; U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology*, 10: 779-783 (1992); Lonberg *et al.*, *Nature*, 368: 856-859 (1994); Morrison, *Nature*, 368: 812-813 (1994); Fishwild *et al.*, *Nature Biotechnology*, 14: 845-851 (1996); Neuberger, *Nature Biotechnology*, 14: 826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.*, 13: 65-93 (1995).

The monoclonal antibodies herein include "chimeric" antibodies 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 a biological activity of this invention (see U.S. Patent No. 4,816,567; and Morrison *et al.*, *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (*e.g.* Old World Monkey, Ape etc), and human constant region sequences.

An "intact" antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, C_H1, C_H2 and C_H3. The constant domains can be native sequence constant domains (*e.g.* human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody

fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata et al., *Protein Eng.* 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments or other techniques.

The expression "linear antibodies" generally refers to the antibodies described in Zapata et al., *Protein Eng.*, 8(10):1057-1062 (1995). Briefly, these antibodies comprise a pair of tandem Fd segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H1). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large F(ab')₂ fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The Fc fragment comprises the carboxy-terminal portions of both H chains held together by di sulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the

H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

"Humanized" forms of non-human (*e.g.*, rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine 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 FRs are those of a human immunoglobulin sequence. The humanized antibody optionally 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); Riechmann et al., Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992).

A "species-dependent antibody" is an antibody which has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

An agent "which binds" an antigen of interest is one that binds the antigen with sufficient affinity such that a polypeptide, antibody, antagonist or composition is useful as a diagnostic and/or therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins (unless otherwise specified). In such embodiments, the extent of binding of the agent to a "non-target" protein will be less than about 10% of the binding of the polypeptide, antibody, antagonist or composition to its particular target protein, which can be determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of a polypeptide agent to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar

structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term “specific binding” or “specifically binds to” or is “specific for” a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a K_d for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In one embodiment, the term “specific binding” refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

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: C1q 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 $Fc\gamma RIII$ only, whereas monocytes express $Fc\gamma RI$, $Fc\gamma RII$ and $Fc\gamma RIII$. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. 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 US Patent No. 5,500,362 or 5,821,337 can 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 can be assessed in vivo, e.g., in a animal model such as that disclosed in Clynes et al. (USA) 95:652-656 (1998).

"Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

"Human effector cells" are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least FcγRIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells can be isolated from a native source, e.g., from blood.

"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), can be performed.

A subject to be treated according to this invention is a mammal. The mammal could be, for example, a primate (e.g., a human), a rodent (e.g., a rat or a mouse), or a mammal of another species. In each one of the above methods, the mammal may be one that suffers from an immunological disorder.

A mammal "in need" of treatment can include, but are not limited to, mammals that have immunological disorders, mammals that have had immunological disorders, mammals with symptoms of immunological disorders or mammals that have elevated or decreased BAFF levels.

An "effective amount" of an agent as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and by known methods relating to the stated purpose.

The term "therapeutically effective amount" refers to an amount of a therapeutic agent of this invention effective to "treat" a disease or disorder in a mammal (aka patient). In one instance, the therapeutically effective amount may be a growth inhibitory amount or a cytotoxic amount for one or several cell types. In autoimmune diseases, a therapeutically effective amount may be the amount that alleviates one or more symptoms of the disease or the amount necessary to keep a disease in remission. In the case of cancer, the therapeutically effective amount of the drug active for any one of the following: reducing the number of cancer cells; reducing the tumor size; inhibiting (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibiting (i.e., slow to some extent and preferably stop) tumor metastasis; inhibiting, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug can prevent growth and/or kill existing cancer cells, it can be cytostatic and/or cytotoxic. A "treatment" or a "therapeutically effective amount" refers to a course of administration of the therapeutic agent, which course may include several dosings spread over a period of time to achieve a desired effect.

A "growth inhibitory amount" of a therapeutic agent an amount capable of inhibiting the growth of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "growth inhibitory amount" of a polypeptide, antibody, antagonist or composition of this invention can be determined empirically or for example, by methods known in the art.

A "cytotoxic amount" of a therapeutic agent is an amount capable of causing the destruction of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "cytotoxic amount" of therapeutic agent can be determined empirically or, for example, by methods known in the art.

The term "determining" is intended to include any method for evaluating the amounts of a substance. In general, the particular technique used for detection is not critical for practice of the invention.

Examples of comparative controls include, but are not limited to, sera from normal healthy patients, non-malignant tissue and pre-treatment or post-treatment samples. In one embodiment, BAFF polypeptide levels in sera from mammals with immunological disorders are compared to sera from normal mammals.

Production of antibodies

(i) Polyclonal antibodies

Polyclonal antibodies can be raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen to a protein that is immunogenic in the species to be immunized, e.g., keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. For example, the animal can be boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions.

Also, aggregating agents such as alum are suitably used to enhance the immune response.

(ii) *Monoclonal antibodies*

Monoclonal antibodies are 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 may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies.

For example, the monoclonal antibodies may be made using the hybridoma method first described by Kohler *et al.*, *Nature*, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that may contain one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

In one embodiment, the myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred myeloma cell lines include murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Maryland USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of

human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur *et al.*, *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. In one embodiment, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson *et al.*, *Anal. Biochem.*, 107:220 (1980).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a one source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra *et al.*, *Curr. Opinion in Immunol.*, 5:256-262 (1993) and Plückthun, *Immunol. Revs.*, 130:151-188 (1992).

In a further embodiment, antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in e.g., McCafferty *et al.*, *Nature*, 348:552-554 (1990). Clackson *et al.*, *Nature*, 352:624-628 (1991) and Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks *et al.*, *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse *et al.*, *Nuc. Acids. Res.*, 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *et al.*, *Proc. Natl Acad. Sci. USA*, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

(iii) *Humanized antibodies*

Examples of methods for humanizing non-human antibodies have been described. Generally, a humanized antibody has one or more amino acid residues in it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain (e.g., Jones *et al.*, *Nature*, 321:522-525 (1986); Riechmann *et al.*, *Nature*, 332:323-327 (1988); Verhoeyen *et al.*, *Science*, 239:1534-1536 (1988)). Often, humanized antibodies are human antibodies in which some hypervariable region residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework region (FR) for the humanized antibody (Sims *et al.*, *J. Immunol.*, 151:2296 (1993); Chothia *et al.*, *J. Mol. Biol.*, 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter *et al.*, *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); Presta *et al.*, *J. Immunol.*, 151:2623 (1993)).

It is often important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

(iv) *Human antibodies*

As an alternative to humanization, human antibodies can be generated. For example, it is possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in

chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:2551 (1993); Jakobovits *et al.*, *Nature*, 362:255-258 (1993); Bruggermann *et al.*, *Year in Immuno.*, 7:33 (1993); and US Patent Nos. 5,591,669, 5,589,369 and 5,545,807.

Alternatively, phage display technology (e.g., McCafferty *et al.*, *Nature* 348:552-553 (1990)) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. In one embodiment, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B cell. Phage display can be performed in a variety of formats; for their review see, e.g., Johnson, Kevin S. and Chiswell, David J., *Current Opinion in Structural Biology* 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson *et al.*, *Nature*, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks *et al.*, *J. Mol. Biol.* 222:581-597 (1991), or Griffith *et al.*, *EMBO J.* 12:725-734 (1993). See, also, US Patent Nos. 5,565,332 and 5,573,905.

Human antibodies may also be generated by *in vitro* activated B cells (see US Patents 5,567,610 and 5,229,275).

(v) *Antibody fragments*

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto *et al.*, *Journal of Biochemical and Biophysical Methods* 24:107-117 (1992) and Brennan *et al.*, *Science*, 229:81 (1985)). However,

these fragments can now be produced directly by recombinant host cells. For example, the antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter *et al.*, Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; US Patent No. 5,571,894; and US Patent No. 5,587,458. The antibody fragment may also be a "linear antibody", *e.g.*, as described in US Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

(vi) *Bispecific antibodies*

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 (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (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).

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 WO 93/08829, 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 can be with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. According to one embodiment, the first heavy-chain constant region (CH1) containing the site necessary for light chain binding is 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 one 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 US Patent 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 interface can comprise at least a part of the C_H3 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 (US Patent 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 US Patent 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 (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H 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. Immunol.*, 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.* *J. Immunol.* 147: 60 (1991).

Amino acid sequence modification(s) of protein or peptide antagonists and antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the original molecule (e.g., B cell depleting agent, etc.). Amino acid sequence variants of the antagonist are prepared by introducing appropriate nucleotide changes into the antagonist nucleic acid, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antagonist. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antagonist, such as changing the number or position of glycosylation sites.

A useful method for identification of certain residues or regions that are preferred locations for mutagenesis is called "alanine scanning mutagenesis" as

described by Cunningham and Wells *Science*, 244:1081-1085 (1989). Here, a residue or group of target residues are identified (*e.g.*, charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most often preferably alanine or polyalanine) to affect the interaction of the amino acids with antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* need not be predetermined. For example, to analyze the performance of a mutation at a given site, alanine scanning or random mutagenesis is conducted at the target codon or region and the expressed variants are screened for the desired activity.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include a polypeptide with an N-terminal methionyl residue or polypeptides fused to a cytotoxic polypeptide. Other insertional variants include the fusion of an enzyme or a polypeptide which increases the serum half-life of a molecule to the N- or C-terminus of the original molecule.

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the original molecule replaced by different residue. The sites of greatest interest for substitutional mutagenesis of antibody antagonists include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 1, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys

Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

Substantial modifications in the biological properties of the original molecule are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

Any cysteine residue not involved in maintaining the proper conformation of the original molecule also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the original molecule to improve its stability (particularly where the original molecule is an antibody fragment such as an Fv fragment).

One preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody. Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants is affinity maturation using phage display. Briefly, several hypervariable region sites (*e.g.* 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (*e.g.* binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or in addition, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Another type of amino acid variant alters the original glycosylation pattern of the antagonist. By altering is meant deleting one or more carbohydrate moieties found in the original molecule, and/or adding one or more glycosylation sites that are not present in the original molecule.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine

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

Addition of glycosylation sites to the original molecule is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original molecule (for O-linked glycosylation sites).

Nucleic acid molecules encoding amino acid sequence variants of the original molecule can be prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the original molecule.

It may be desirable to modify an antibody of the invention with respect to effector function, *e.g.* so as to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the original molecule. This may be achieved by introducing one or more amino acid substitutions in an Fc region of an antibody. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, *J. Exp Med.* 176:1191-1195 (1992) and Shopes, B. *J. Immunol.* 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* *Cancer Research* 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual

Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.* *Anti-Cancer Drug Design* 3:219-230 (1989).

To increase the serum half life of the original molecule, one may incorporate a salvage receptor binding epitope into the original molecule (especially an antibody fragment) as described in US Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (*e.g.*, IgG₁, IgG₂, IgG₃, or IgG₄) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

Dosing

Depending on the indication to be treated and factors relevant to the dosing that a physician of skill in the field would be familiar with, the therapeutic agents of the invention will typically be administered at a dosage that is efficacious for the treatment of that indication while minimizing toxicity and side effects. As necessary, treatment sessions can be intermittent. For example, patients can receive weekly doses followed by cessation for a period of time and then treatment can be resumed. Treatment for oncological diseases with B cell depletion agents can be combined with chemotherapy such as with CHOP or fludarabine and cytoxan. Treatment of autoimmune diseases with depletion agents can be combined with therapeutic agents useful in those diseases, *e.g.*, methotrexate.

In one example, the treatment of patients suffering from B-cell neoplasm such as non-Hodgkins lymphoma, the anti-CD20 antibodies of the invention can be administered to a human patient at a dosage range of 1mg/kg to 20mg/kg body weight, preferably at 2.5mg/kg to 10mg/kg. In one embodiment for treating an NHL, the anti-CD20 antibody is administered at a dosage of 10mg/kg or 375mg/m².

According to one embodiment, for treating autoimmune diseases, anti-CD20 therapies are administered at 250-1000mg per dose for 2-4 doses every other week or every third week. For example, for treating rheumatoid arthritis, in one embodiment, Rituxan[™] which is a chimeric antibody is administered at 500mg per dose every other week for a total of 2 doses. A humanized anti-CD20 antibody, *e.g.*, hu2H7v.16 or any other variant of hu 2H7 as disclosed herein, can be administered at less than 500mg per dose such as at between about 200-500mg per dose, between about

250mg-450mg, or 300-400mg per dose, for 2-4 doses every other week or every 3rd week.

According to one embodiment, anti-BR3 therapies are administered at 100mg/m² – 1500mg/m² weekly or 1m/kg to 20mg/kg body weight as necessary.

The treatment methods of the invention comprises a combination of concurrently and sequentially administering the anti-CD20 antibody and the BAFF antagonist (both referred to herein as the drugs). In sequential administration, the drugs can be administered in either order, i.e., BAFF antagonist first followed by anti-CD20 antibody. The patient is treated with one drug and monitored for efficacy before treatment with the one drug. Alternatively, the patient can be initially administered both drugs and subsequent dosing can be with only one or the other drug.

To condition the patient to tolerate the drugs and/or to reduce the occurrence of adverse effects such as infusion-related symptoms which arise from the initial and subsequent administrations of the therapeutic compound, the mammal in need thereof can be administered a first or initial conditioning dose of one or both drugs and then administered at least a second therapeutically effective dose of one or both drugs wherein the second and any subsequent doses are higher than the first dose. The first dose serves to condition the mammal to tolerate the higher second therapeutic dose. In this way, the mammal is able to tolerate higher doses of the therapeutic compound than could be administered initially. A “conditioning dose” is a dose which attenuates or reduces the frequency or the severity of first dose adverse side effects associated with administration of a therapeutic compound. The conditioning dose may be a therapeutic dose, a sub-therapeutic dose, a symptomatic dose or a sub-symptomatic dose. A therapeutic dose is a dose which exhibits a therapeutic effect on the patient and a sub-therapeutic dose is a dose which does not exhibit a therapeutic effect on the patient treated. A symptomatic dose is a dose which induces at least one adverse effect on administration and a sub-symptomatic dose is a dose which does not induce an adverse effect. Some adverse effects are fever, headache, nausea, vomiting, breathing difficulties, myalgia, and chills.

Route of administration

The B cell depleting or promoting agents and other therapeutic agents can be administered to a human patient by a variety of methods, such as by intravenous

administration, *e.g.*, as a bolus or by continuous infusion over a period of time, by subcutaneous, intramuscular, intraperitoneal, intracerebrospinal, intra-articular, intrasynovial, intrathecal, or inhalation routes. The anti-CD20 antibody will generally be administered by intravenous or subcutaneous administration. The drugs can be administered by the same or different route.

Kits

Another embodiment of the invention is a kit comprising a BAFF binding reagent, such as an anti-BAFF antibody or other polypeptide that can bind BAFF for use in determining serum BAFF levels, and a label or package insert instructing how serum BAFF levels relate to total B cells levels or tissue B cell levels in a patient after treatment with a B cell promoting or depleting agent. Optionally, the kit comprises the B cell promoting or B cell depleting agent. In a further embodiment, the kit further comprises instructions for retreating the patient with the B cell depleting agent or other therapeutic agent based on the patient's serum BAFF levels. The package insert can contain instructions to retreat the patient when serum BAFF levels are highest or as serum BAFF levels are decreasing (*e.g.*, B cell recovery phase). The instructions can indicate retreatment at or before the tissue B cell recovery phase before the peripheral B cell recovery phase.

The kit comprises at least one container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container can have a sterile access port for extracting a therapeutic agent (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The label or package insert can indicate that the composition is used for treating the particular condition, *e.g.*, non-Hodgkin's lymphoma or rheumatoid arthritis. Additionally, the kit may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Examples of Specific Anti-BR3 Antibodies

Antibodies of this invention specifically include antibodies comprising the variable heavy chain sequence of any one of the antibodies disclosed in Table 2 (below), and BR3-binding fragments thereof that has not been produced by a hybridoma cell. Antibodies of this invention specifically include antibodies comprising a variable heavy chain sequence of any one of the antibodies in Table 2, anti-BR3 antibodies that can be competitively inhibited by an antibody in Table 2, and BR3-binding fragments thereof. According to a further embodiment, an antibody of this invention comprises the variable heavy and the variable light chain region of any one of the antibodies disclosed in Table 2, and BR3-binding fragments thereof.

Table 2. Examples of Anti-BR3 Antibody Sequences

ANTIBODY	VH domain of SEQ ID NO:	VL domain of SEQ ID NO:
9.1	1 (VL)	2 (VH)
Hu9.1-graft	3 (VL)	4 (VH)
Hu9.1-73	5 (VL)	6 (VH)
Hu9.1-70	7 (VL)	8 (VH)
Hu9.1-56	3 (VL)	9 (VH)
Hu9.1-51	3 (VL)	10 (VH)
Hu9.1-59	3 (VL)	11 (VH)
Hu9.1-61	3 (VL)	12 (VH)
Hu9.1-A	3 (VL)	13 (VH)
Hu9.1-B	3 (VL)	14 (VH)
Hu9.1-C	3 (VL)	15 (VH)
Hu9.1-66	3 (VL)	16 (VH)
Hu9.1-RF	3 (VL)	17 (VH)
Hu9.1-48	3 (VL)	18 (VH)
Hu9.1-RL	3 (VL)	19 (VH)
Hu9.1-91	3 (VL)	20 (VH)
Hu9.1-90	3 (VL)	21 (VH)
Hu9.1-75	3 (VL)	22 (VH)
Hu9.1-88	3 (VL)	23 (VH)
Hu9.1RL-9	3 (VL)	24 (VH)
Hu9.1RL-44	3 (VL)	25 (VH)
Hu9.1RL-13	3 (VL)	26 (VH)
Hu9.1RL-47	3 (VL)	27 (VH)
Hu9.1RL-28	3 (VL)	28 (VH)
Hu9.1RL-43	3 (VL)	29 (VH)

ANTIBODY	VH domain of SEQ ID NO:	VL domain of SEQ ID NO:
Hu9.1RL-16	3 (VL)	30 (VH)
Hu9.1RL-70	3 (VL)	31 (VH)
Hu9.1RL-30	3 (VL)	32 (VH)
Hu9.1RL-32	3 (VL)	33 (VH)
Hu9.1RL-37	3 (VL)	34 (VH)
Hu9.1RL-29	3 (VL)	35 (VH)
Hu9.1RL-10	3 (VL)	36 (VH)
Hu9.1RL-24	3 (VL)	37 (VH)
Hu9.1RL-39	3 (VL)	38 (VH)
Hu9.1RL-31	3 (VL)	39 (VH)
Hu9.1RL-18	3 (VL)	40 (VH)
Hu9.1RL-23	3 (VL)	41 (VH)
Hu9.1RL-41	3 (VL)	42 (VH)
Hu9.1RL-95	3 (VL)	43 (VH)
Hu9.1RL-14	3 (VL)	44 (VH)
Hu9.1RL-57	3 (VL)	45 (VH)
Hu9.1RL-15	3 (VL)	46 (VH)
Hu9.1RL-54	3 (VL)	47 (VH)
Hu9.1RL-12	3 (VL)	48 (VH)
Hu9.1RL-34	3 (VL)	49 (VH)
Hu9.1RL-25	3 (VL)	50 (VH)
Hu9.1RL-71	3 (VL)	51 (VH)
Hu9.1RL-5	3 (VL)	52 (VH)
Hu9.1RL-79	3 (VL)	53 (VH)
Hu9.1RL-66	3 (VL)	54 (VH)
Hu9.1RL-69	3 (VL)	55 (VH)
9.1RF-IgG	56 (LC)	57 (HC)
V3-Fab	58 (LC)	59 (HC)
V24	58 (LC)	60 (VH)
V44	58 (LC)	61 (VH)
V89	58 (LC)	62 (VH)
V96	58 (LC)	63 (VH)
V46	58 (LC)	64 (VH)
V51	58 (LC)	65 (VH)
V75	58 (LC)	66 (VH)
V58	58 (LC)	67 (VH)
V60	58 (LC)	68 (VH)
V3-1	69 (VL)	70 (VH)
V3-11	71 (VL)	72 (VH)
V3-12	73 (VL)	74 (VH)
V3-13	75 (VL)	76 (VH)
V3-3	77 (VL)	78 (VH)
V3-5	79 (VL)	80 (VH)

ANTIBODY	VH domain of SEQ ID NO:	VL domain of SEQ ID NO:
V3-9	81 (VL)	70 (VH)
V3-16	69 (VL)	81 (VH)
V3-19	69 (VL)	82 (VH)
V3-24	83 (VL)	84 (VH)
V3-27	85 (VL)	86 (VH)
V3-34	87 (VL)	88 (VH)
V3-35	89 (VL)	90 (VH)
V3-37	91 (VL)	92 (VH)
V3-41	93 (VL)	94 (VH)
V3-46	95 (VL)	96 (VH)
V3-46a	95 (VL)	97 (VH)
V3-46q	95 (VL)	98 (VH)
V3-46s	95 (VL)	99 (VH)
V3-46sFab	100 (LC)	101 (HC)
V3-46s-1	108 (LC)	99 (VH)
V3-46s-7	109 (LC)	99 (VH)
V3-46s-9	110 (LC)	99 (VH)
V3-46s-10	111 (LC)	99 (VH)
V3-46s-12	112 (LC)	107 (VH)
V3-46s-13	113 (LC)	99 (VH)
V3-46s-29	114 (LC)	99 (VH)
V3-46s-31	115 (LC)	99 (VH)
V3-46s-33	116 (LC)	99 (VH)
V3-46s-34	117 (LC)	99 (VH)
V3-46s-37	118 (LC)	99 (VH)
V3-46s-40	119 (LC)	99 (VH)
V3-46s-42	120 (LC)	99 (VH)
V3-46s-45	121 (LC)	99 (VH)

Antibodies of this invention include BR3-binding antibodies having an H3 sequence that is at least about 70% amino acid sequence identity, alternatively at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to the H3 sequence of any one of the sequences of Table 2, and BR3 binding fragments of those antibodies.

Antibodies of this invention include BR3-binding antibodies having H1, H2 and H3 sequences that are at least 70% identical to the CDRs of any one of the antibodies sequences described in the Table 2, or alternatively having at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%,

86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity. According to one embodiment the H1, H2 and H3 are each at least 70% identical to SEQ ID NOs: 124, 123 and 122, respectively, and the antibody optionally comprises a VL comprising SEQ ID NO:3 or a VL that is at least 70% identical to SEQ ID NO:3.

Antibodies of this invention include BR3-binding antibodies having L1, L2 and L3 sequences that are at least 70% identical to the CDRs of any one of the antibodies described in Table 2 or alternatively having at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity. According to one embodiment the L1, L2 and L3 are each at least 70% identical to SEQ ID NOs: 133, 134 and 135, respectively, and the antibody optionally comprises a VH comprising SEQ ID NO:17 or a VH that is at least 70% identical to SEQ ID NO:17.

Antibodies of this invention include BR3-binding antibodies having a VH domain with at least 70% homology to a VH domain of any one of the antibodies of Table 2, or alternatively having at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity. In a further embodiment, in addition to said VH domain sequence, said antibody further comprises a VL domain with at least 70% homology to the VL domain of the corresponding antibody of Table 2, or alternatively having at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity. In one embodiment, the antibody comprises the VH and VL of 9.1RF, or a anti-BR3 binding variant thereof that comprises a VH that is at least 70% identical to SEQ ID NO:17 and a VL that is at least 70% identical to SEQ ID NO:3.

According to one preferred embodiment, the antibodies of this invention specifically bind to a sequence of a native human BR3 polypeptide. According to yet another embodiment, an antibody of this invention has improved ADCC function in the presence of human effector cells compared to the antibody known as 9.1-RF Ig. According to yet another embodiment, an antibody of this invention has decreased

ADCC function in the presence of human effector cells compared to the antibody known as 9.1-RF Ig. According to another embodiment, the antibody made by the process of expressing nucleic acid sequences encoding an antibody of this invention from a cell selected from the group consisting of a mammalian cell, a bacterial cell, a fungal cell, a yeast cell, an insect cell and a plant cell.

It is understood that all antibodies of this invention include antibodies lacking a signal sequence and antibodies lacking the K447 residue of the Fc region.

Examples of Specific Anti-CD20 Antibodies

CD20 antibodies include: "C2B8," which is now called "rituximab" ("RITUXAN®") (US Patent No. 5,736,137); the yttrium-[90]-labelled 2B8 murine antibody designated "Y2B8" or "Ibritumomab Tiuxetan" (ZEVALIN®) commercially available from IDEC Pharmaceuticals, Inc. (US Patent No. 5,736,137; 2B8 deposited with ATCC under accession no. HB11388 on June 22, 1993); murine IgG2a "B1," also called "Tositumomab," optionally labelled with ¹³¹I to generate the "131I-B1" or "iodine I131 tositumomab" antibody (BEXXAR™) commercially available from Corixa (see, also, US Patent No. 5,595,721); murine monoclonal antibody "1F5" (Press *et al. Blood* 69(2):584-591 (1987) and variants thereof including "framework patched" or humanized 1F5 (WO 2003/002607, Leung, S.; ATCC deposit HB-96450); murine 2H7 and chimeric 2H7 antibody (US Patent No. 5,677,180); a humanized 2H7 (WO 2004/056312 Lowman *et al.*) and as set forth below); HUMAX-CD20™ fully human antibody (Genmab, Denmark; see, for example, Glennie and van de Winkel, *Drug Discovery Today* 8: 503-510 (2003) and Cragg *et al., Blood* 101: 1045-1052 (2003)); the human monoclonal antibodies set forth in WO 2004/035607 (Teeling *et al.*); the antibodies having complex N-glycoside-linked sugar chains bound to the Fc region described in US 2004/0093621 (Shitara *et al.*); CD20 binding molecules such as the AME series of antibodies, e.g., AME-133™ antibodies as set forth in WO 2004/103404 (Watkins *et al.*, Applied Molecular Evolution); A20 antibody or variants thereof such as chimeric or humanized A20 antibody (cA20, hA20, respectively) (US 2003/0219433, Immunomedics); and monoclonal antibodies L27, G28-2, 93-1B3, B-C1 or NU-B2 available from the International Leukocyte Typing Workshop (Valentine *et al.*, In: *Leukocyte Typing* III (McMichael, Ed., p. 440, Oxford University Press (1987)). The preferred CD20 antibodies herein are

humanized, chimeric, or human CD20 antibodies, more preferably, a humanized 2H7 antibody, rituximab, chimeric or humanized A20 antibody (Immunomedics), and HUMAX-CD20™ human CD20 antibody (Genmab).

For the purposes herein, "humanized 2H7" refers to an intact antibody or antibody fragment comprising the variable light (V_L) sequence:

DIQMTQSPSSLSASVGDRVTITCRASSSVSYMHYQQKPGKAPKPLIYAPSNL
ASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSFNPTFGGQTKVEIKR
(SEQ ID NO:136); and variable heavy (V_H) sequence:

EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHWVRQAPGKGLEWVGAI
YPGNGDTSYNQKFKGRFTISVDKSKNTLYLQMNSLRAEDTAVYYCARVVYY
SNSYWYFDVWGQGLVTVSS
(SEQ ID NO: 137)

Where the humanized 2H7 antibody is an intact antibody, preferably it comprises the v16 light chain amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCRASSSVSYMHYQQKPGKAPKPLIYAPSNL
ASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSFNPTFGGQTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
C (SEQ ID NO: 138); and

heavy chain amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYNMHWVRQAPGKGLEWVGAI
YPGNGDTSYNQKFKGRFTISVDKSKNTLYLQMNSLRAEDTAVYYCARVVYY
SNSYWYFDVWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN
HKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 139).

The V region of all other variants based on version 16 will have the amino acid sequences of v16 except at the positions of amino acid substitutions which are indicated in Table 3 below. Unless otherwise indicated, the 2H7 variants will have the same L chain as that of v16. Humanized antibody 2H7v.16 is also referred to as rhuMAb2H7 or Ocrelizumab.

TABLE 3

2H7 version	Light chain (V _L) changes	Heavy chain (V _H) changes	Fc changes
16 for reference			-
31	-	-	S298A, E333A, K334A
73	M32L	N100A	
75	M32L	N100A	S298A, E333A, K334A
96	S92A	D56A, N100A	
114	M32L, S92A	D56A, N100A	S298A, E333A, K334A
115	M32L, S92A	D56A, N100A	S298A, E333A, K334A, E356D, M358L
116	M32L, S92A	D56A, N100A	S298A, K334A, K322A
138	M32L, S92A	D56A, N100A	S298A, E333A, K334A, K326A
477	M32L, S92A	D56A, N100A	S298A, E333A, K334A, K326A, N434W
375	-	-	K334L
588	-	-	S298A, E333A, K334A, K326A
511	M32L, S92A	D56A, N100Y, S100aR	S298A, E333A, K334A, K326A

TABLE 4

2H7 version	V _L SEQ ID NO.	V _H SEQ ID NO.	Full L chain SEQ ID NO.	Full H chain SEQ ID NO.
16	136	137	138	139
114	144	145	140	141
138	144	145	140	142
511	144	146	140	143

Residue numbering is according to Kabat et al., Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991), with insertions shown as a, b, c, d, and e, and gaps shown as dashes in the sequence figures. In the CD20 binding antibodies that comprise Fc region, the C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during purification of the Ab or by recombinant engineering the nucleic acid encoding the antibody polypeptide. Accordingly, a CD20 binding antibody composition useful in this invention can comprise antibody

with K447, with all K447 removed, or a mixture of antibody with and without the K447 residue.

The N-glycosylation site in IgG is at Asn297 in the CH2 domain. CD20-binding and BR3-binding antibodies useful in the treatment methods of the present invention include compositions of any of the preceding antibodies having a Fc region, wherein about 80-100% (and preferably about 90-99%) of the antibody in the composition comprises a mature core carbohydrate structure which lacks fucose, attached to the Fc region of the glycoprotein.

CD20 binding antibodies encompass bispecific CD20 binding antibodies wherein one arm of the antibody has a H and L chain of a CD20 binding antibody such as a H and L chain of the humanized 2H7 antibody of the invention, and the other arm has V region binding specificity for a second antigen. In specific embodiments, the second antigen is selected from the group consisting of CD3, CD64, CD32A, CD16, NKG2D or other NK activating ligands.

ASSAY METHODS

Serum BAFF levels can be measured by a variety of techniques. The most convenient techniques for assaying serum BAFF levels include western blot, dot blot, ELISA, immunoprecipitation or any other immunoassays or techniques using anti-BAFF antibodies or molecules that specifically bind BAFF. For example, a sandwich ELISA for measurement of the soluble form of BAFF can be performed as described below or in Example 1. See also Zhang, J., et al., (2001) *J. Immunol.* 166:6-10. Briefly, 96 well plates can be coated with a purified murine anti-BAFF monoclonal antibody (clone 3D4, mIgG1) at 2 µg/ml in phosphate buffered saline (PBS) at 4°C overnight and blocked with 1% bovine serum albumin (BSA)/PBS. All specimens can be diluted 1:10 in 3% BSA/PBS and incubated in the ELISA plate at 37°C for four hours. After washing, the plate can be incubated first with 0.2 µg/ml biotin conjugated polyclonal anti-BAFF antibody and then with 1:30,000 diluted HRP conjugated streptavidin (Southern Biotechnology, Birmingham, AL). To avoid any confounding effect of rheumatoid factor activity, an mIgG1 isotype can be used as a background control for the capture antibody with each specimen. The reaction can be developed with trimethylbenzidine substrate (Sigma, St Louis, MO) and read in an E-Max plate reader (Molecular Devices, Sunnyvale, CA). In this assay, the absorbance values in

the mIgG1 control wells can be subtracted from the corresponding anti-BAFF capture wells and were typically <10% of total absorbance. A standard curve using serial dilutions of recombinant BAFF can be incorporated into each assay.

All publications (including patents and patent applications) cited herein are hereby incorporated in their entirety by reference. Also incorporated herein in their entirety are United States Provisional Patent Application No. 60/739,266, filed November 23, 2005, and the United States Provisional Patent Application entitled METHODS AND COMPOSITIONS RELATED TO B CELL ASSAYS, filed November 10, 2006 (Inventor: Flavius Martin).

Commercially available reagents referred to in the Examples were generally used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following Examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA. Unless otherwise noted, the present invention uses standard procedures of recombinant DNA technology, such as those described hereinabove and in the following textbooks: Sambrook *et al.*, *supra*; Ausubel *et al.*, Current Protocols in Molecular Biology (Green Publishing Associates and Wiley Interscience, N.Y., 1989); Innis *et al.*, PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc.: N.Y., 1990); Harlow *et al.*, Antibodies: A Laboratory Manual (Cold Spring Harbor Press: Cold Spring Harbor, 1988); Gait, Oligonucleotide Synthesis (IRL Press: Oxford, 1984); Freshney, Animal Cell Culture, 1987; Coligan *et al.*, Current Protocols in Immunology, 1991.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

The foregoing written description is considered to be sufficient to enable one skilled in the art to practice the invention. The following Examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

EXAMPLES

Example 1 - Serum BAFF is upregulated upon B cell depletion in mice.

Mice were injected with 200ug of control (mouse IgG2a), anti-BR3 antibody or anti-CD20 antibody (N = 5 mice/group). Seven days after injection, the mice were tested for B cell depletion and BAFF levels. Typically, BAFF serum levels were determined as follows: human BCMA-Fc (Genentech, Inc.) was diluted to 0.5 µg/mL in PBS and coated onto 384 well ELISA plates (Immuno Plate with MaxiSorp surface, Nunc, Neptune, NJ) by incubating for 12-72 hr at 2-8°C. After blocking with PBS / 0.5% BSA, mouse serum samples diluted in sample buffer (PBS / 0.5% BSA / 0.05% Tween-20 / 0.25% CHAPS / 0.2% bovine gamma globulin / 5 mM EDTA / 0.35 M NaCl) were added to the plate. The plate was incubated for 2 hr at room temperature with gentle agitation on an orbital plate shaker. The plates were then washed in PBS + 0.05% Tween-20 wash buffer at room temperature. A standard curve of mouse BAFF (Genentech, Inc.) diluted in the same buffer was also added (range: 1000 – 15.6 pg/mL). Plate-bound BAFF was detected with a rat anti-mouse BAFF monoclonal antibody (R&D Systems, Minneapolis, MN), and bound anti-BAFF mAb was detected using a goat anti-rat IgG Fc-HRP antibody (Jackson ImmunoResearch, West Grove, PA). Color was developed using tetramethyl benzidine (TMB) (Kirkegaard & Perry Laboratories, Gaithersburg, MD), and the reaction was stopped with 1 M phosphoric acid. Sample BAFF concentrations were interpolated from a 4-parameter fit of the BAFF standard curve. The minimum quantifiable concentration, given a 1/4 minimum dilution of the serum samples, was 62.5 pg/mL.

Treatments with either anti-BR3 antibody (Genentech, Inc.) or anti-CD20 antibody (Genentech, Inc.) resulted in >95% blood B cell depletion and >75% spleen and lymph node B cell depletion. At the same time, the levels of serum BAFF increased 10-20 fold after anti-BR3 antibody treatment and 4-10 fold after anti-CD20 treatment. See Figure 1.

Based on these results, it was hypothesized that there might be a correlation between the levels of serum BAFF and the extent of B cell depletion in tissues. This hypothesis is supported by data in the following four figures. Without being bound by theory, it is likely that levels of BAFF in the serum can be dependent on the levels of

its receptors present. In this way, an increase in B cell depletion or BAFF receptor blockade would result in an increase the serum BAFF concentration.

Example 2 - Serum BAFF upregulation correlates with the extent of anti-CD20 tissue B cell depletion in mice.

Five mice/group were treated with control (mIgG2a), 1.25 ug, 12.5ug or 125 ug anti-CD20 antibody (mouse 2H7). B cell depletion in the blood and spleen were measured by flow cytometry three days later. The levels of serum BAFF are plotted against the % B cell depletion. The control mice were considered to have 0% B cell depletion. Figure 2 shows that a large number of B cells were depleted from the blood of 12.5 ug and 125 ug treated mice. On the contrary, only the higher dose depleted extensive numbers of B cells in the spleen. There was a good dose dependent correlation between the increased serum BAFF levels and increased tissue B cell depletion (e.g., spleen). See Figure 2.

Example 3 - Serum BAFF is a predictor of tissue B cell repletion in B cell depleted mice.

Groups of mice were treated with anti-BR3 antibody or anti-CD20 antibody (200ug/mouse). B cell depletion was measured using flow cytometry (B220 or CD19 positive cells) with blood and spleen samples at different time points. Samples from control mice treated with mIgG2a were used to as control samples to determine % B cell depletion. After anti-BR3 treatment, there was some blood B cells depletion at day 1 with slightly more blood B cell depletion at day seven. In the spleen, on the other hand, there was only minimal tissue B cell depletion at day one and extensive tissue B cell depletion at day seven. At the same time, serum levels of BAFF were proportionally increasing between day 1 and day 7. Therefore, serum levels of BAFF and levels of B cells in the tissue (e.g., spleen and other lymphoid organs) were inversely related after treatment with the B cell depleting agent. Similarly, anti-CD20 treated mice had high levels of serum BAFF at day 7 post-treatment.

After maximum tissue B cell depletion post-treatment, serum BAFF levels decreased as the B cell levels recovered in the tissue. Only later did B cell levels recover in the blood. This indicates that the serum BAFF levels are early indicators

for evaluating B cell repletion in tissues while the B cells are still depleted in the blood.

Example 4 - Anti-BR3 peripheral B cell depletion and soluble BAFF level in cyno blood.

Similar to mice, treatment of non-human primates (cynomolgous monkeys) with anti-BR3 antibody causes B cell depletion in tissues with increased BAFF levels in the sera.

Figure 4A shows the % CD20 blood B cell depletion and serum BAFF levels in monkeys treated with 20mg/kg single dose anti-BR3 antibody over a 6 month post-treatment evaluation period. % CD20 blood B cell depletion was calculated by comparing the test samples to samples from the monkeys before treatment with anti-BR3 antibody. The monkeys experienced a maximum blood B cell depletion phase coinciding with elevated serum BAFF levels (delta+) followed subsequently by a drop in serum BAFF levels (delta-) and coinciding with B cell repletion. Two monkeys, labeled 1 and 2 in Figure 4A, are singled out during depletion and are studied in more detail as described in Figure 4B. Figure 4B shows a kinetics depiction of B cell depletion and serum BAFF in monkey 1 and 2. The arrows show that maximum serum BAFF levels coincide with maximum B cell depletion followed by a drop in serum BAFF levels and less B cell depletion (see arrow direction). This suggests that serum BAFF drop to baseline (delta-) is an earlier event than blood B cell recovery.

Example 5 - Peripheral CD20 B cell depletion and soluble BAFF levels in cyno blood after treatment with anti-BR3 antibody – individual kinetics in two representative cyno.

The data from the two cyno monkeys studied in Example 4 are represented as full kinetic curves in Figure 5. Both monkeys show that serum BAFF levels increase (delta+) concomitant with blood B cell depletion. As seen in cyno monkey #01 (Figure 5A), serum BAFF levels drops at ~day 22 (delta-) and the B cell recovery phase begins and is fully on by ~day 40. In the cyno monkey #09 (Figure 5B), serum BAFF levels are up while the blood B cells levels are down. Cyno monkey #09 showed little to no blood B cell recovery (see beyond day 50). This study again shows the inverse relationship between serum BAFF levels and B cell levels in the

blood of cynos and, it is believed that the lag between B cell depletion and repletion in the blood versus tissue observed in mice translates to primates. Therefore, serum BAFF levels present an excellent early indicator of tissue B cell compartment size (spleen, lymph nodes, etc).

CLAIMS

What is claimed:

1. A method for monitoring B cell levels in a subject comprising the steps of determining the serum BAFF levels in a test sample of the subject, determining the serum BAFF levels in a control sample, and calculating the B cell levels in the subject relative to the control, which calculation comprises the step of comparing the serum BAFF level in the test sample to the serum BAFF level in the control sample.

2. The method according to claim 1, wherein the control sample is from the subject before treatment with a therapeutic agent and the test sample is from the subject after treatment with the therapeutic agent.

3. The method according to claim 1, wherein the test sample is from the subject who is suffering from a disease and the control sample is from a subject that is not suffering from the disease.

4. The method for treating a subject suffering from a disease comprising the steps of (1) administering a therapeutically effective amount of a therapeutic agent to the subject, (2) determining the serum BAFF levels in a test sample of the subject, (3) comparing the B cell level in the test sample relative to a control sample and (3) administering a therapeutically effective amount of the same or different therapeutic agent at a time point dependent on the serum BAFF level in the subject.

5. A method for treating a subject suffering from a disease comprising the steps of (1) administering a therapeutically effective amount of a therapeutic agent to the subject, (2) determining the serum BAFF levels in a test sample of the subject, and (3) administering a therapeutically effective amount of the same or different therapeutic agent at a time point dependent on the serum BAFF level in the test sample.

6. A method of maintenance therapy for a subject previously treated with a B cell depletion agent for a disease comprising the step of determining the serum BAFF levels in the subject and treating the subject with a B cell depletion agent at a time point after maximum B cell depletion and while serum BAFF levels are decreasing.
7. The method according to claim 4 or 5, wherein the time point is at the time of or after the maximum B cell depletion phase.
8. The method according to claim 4 or 5, wherein the time point is during the B cell recovery phase.
9. The method according to claim 8, wherein the B cell recovery phase is characterized by decreasing serum BAFF levels.
10. The method according to claim 6 or claim 7, wherein the maximum B cell depletion phase is characterized by maximum levels of BAFF in the sera of a subject.
11. The method according to any one of claims 4-5, wherein the therapeutic agent is a B cell depletion agent.
12. The method according to any one of claims 4-5, wherein the therapeutic agent is not a BAFF antagonist that binds to BAFF.
13. The method according to claim 4 or 5, wherein the therapeutic agent does bind BAFF and block BAFF from binding to BCMA, TACI or BR3.
14. The method according to claim 4 or 5, wherein the therapeutic agent is a B cell promoting agent.
15. The method according to claim 11, wherein the therapeutic agent is a B cell depletion agent that binds to a B cell surface antigen selected from the group consisting of CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD40, CD52, D53, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD79b, CD80,

CD81, CD82, CD83, CDw84, CD85, CD86, CD180 (RP105), FcRH2 (IRTA4), CD79A, C79B, CR2, CCR6, CD72, P2X5, HLA-DOB, CXCR5 (BLR1), FCER2, BR3 (aka BAFF-R), TACI, BTLA, NAG14 (aka LRRC4), SLGC16270 (ala LOC283663), FcRH1 (IRTA5), FcRH5 (IRTA2), ATWD578 (aka MGC15619), FcRH3 (IRTA3), FcRH4 (IRTA1), FcRH6 (aka LOC343413) and BCMA (aka TNFRSF17), HLA-DO, HLA-Dr10 and MHC ClassII.

16. The method according to claim 15, wherein the B cell depletion agent is an antibody.

17. The method according to any one of claims 4-16, wherein the disease is an immunological disorder.

18. The method according to claim 4 or 5, wherein the disease is an immunodeficiency disease.

19. The method according to any one of claims 4-13, wherein the disease is an autoimmune disease elected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), 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, glomerulonephritis, Neuromyelitis Optica (NMO) and IgG neuropathy.

20. The method according to any one of claims 4-13, wherein the disease is a cancer selected from the group consisting of B cell lymphoma, B cell leukemia and multiple myeloma.

21. The method according to any one of claims 4-12, wherein the B cells express CD19.

22. The method according to any one of claims 4-12, wherein the B cells express CD20.
23. The method according to any one of claims 4-12, wherein the subject is a mammal.
24. The method according to claim 22, wherein the subject is a human.
25. The method according to claim 11, wherein the B cell depletion agent is selected from the group consisting of an anti-CD20 antibody, an anti-BR3 antibody, an anti-CD22 antibody and an anti-CD52 antibody.
26. The method according to claim 24, wherein the anti-CD20 antibody is rituximab or 2H7.
27. The method according to claim 14, wherein the B cell promoting agent is a cytokine.
28. The method according to any one of claims 4-5, wherein the different therapeutic agent is selected from the group consisting of a T cell depleting agent, an immunosuppressive agent, a DMARD and a vaccine.
29. The method according to any one of claims 4-6, wherein the time point is before or during tissue B cell recovery that is prior to peripheral blood B cell recovery.
30. An kit comprising a BAFF binding reagent and a package insert comprising instructions for determining serum BAFF levels using the BAFF binding reagent and for relating serum BAFF levels to B cell levels in the patient after treatment with a B cell depleting or promoting agent.

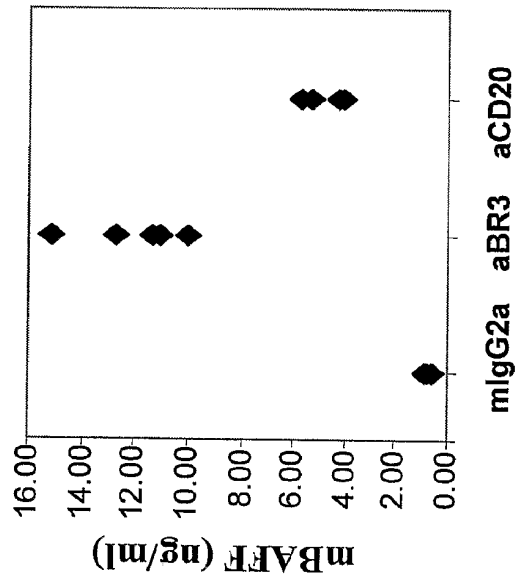


FIG.1

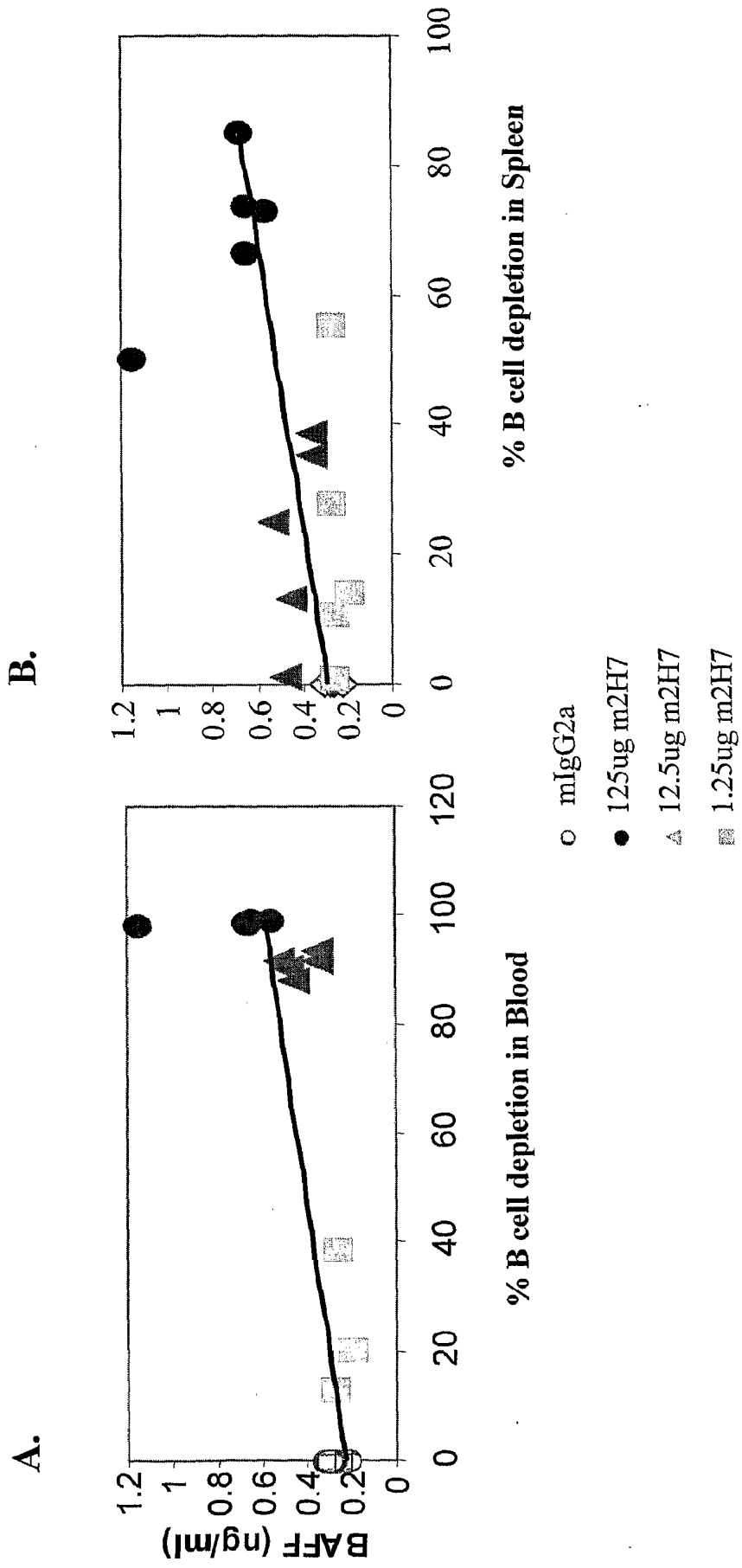


FIG.2

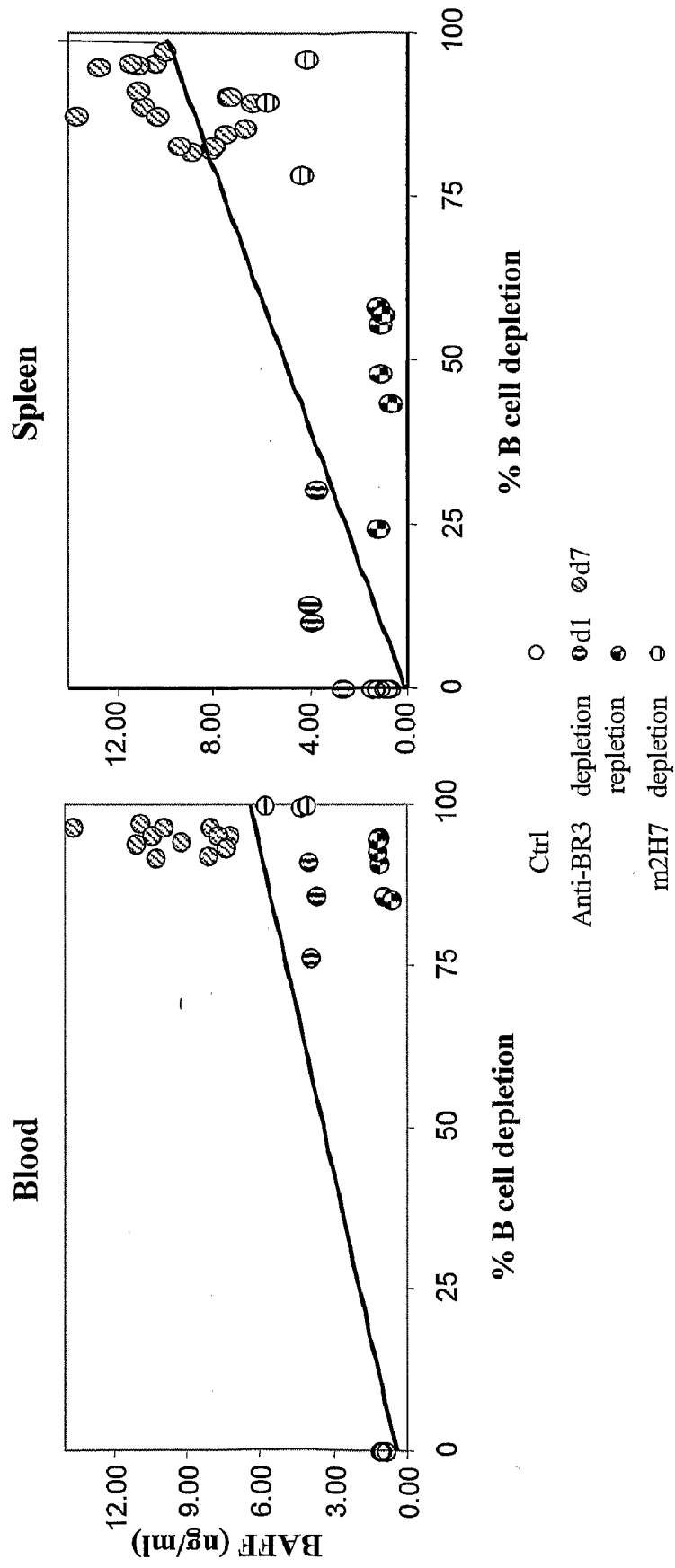


FIG.3

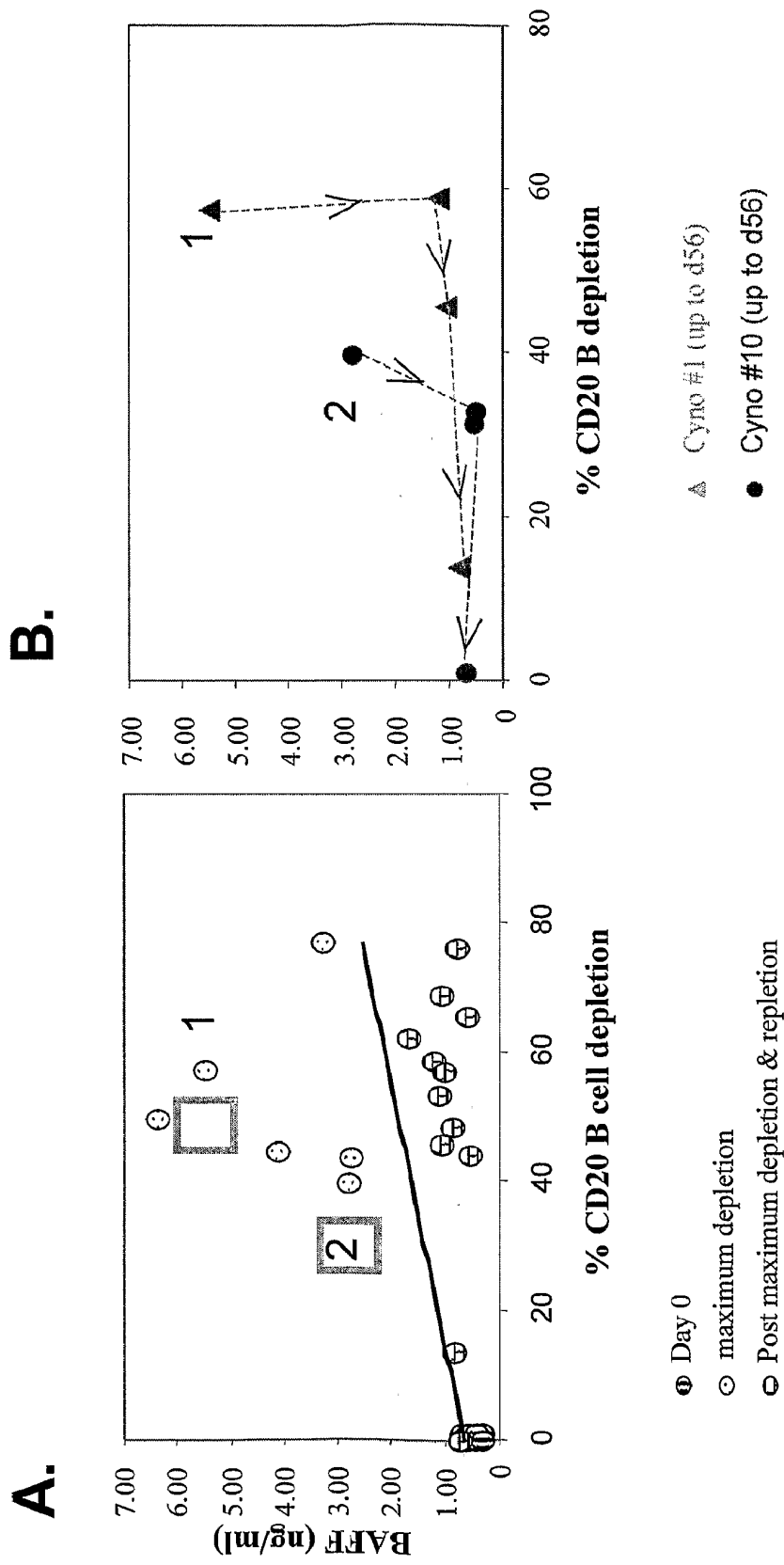


FIG.4

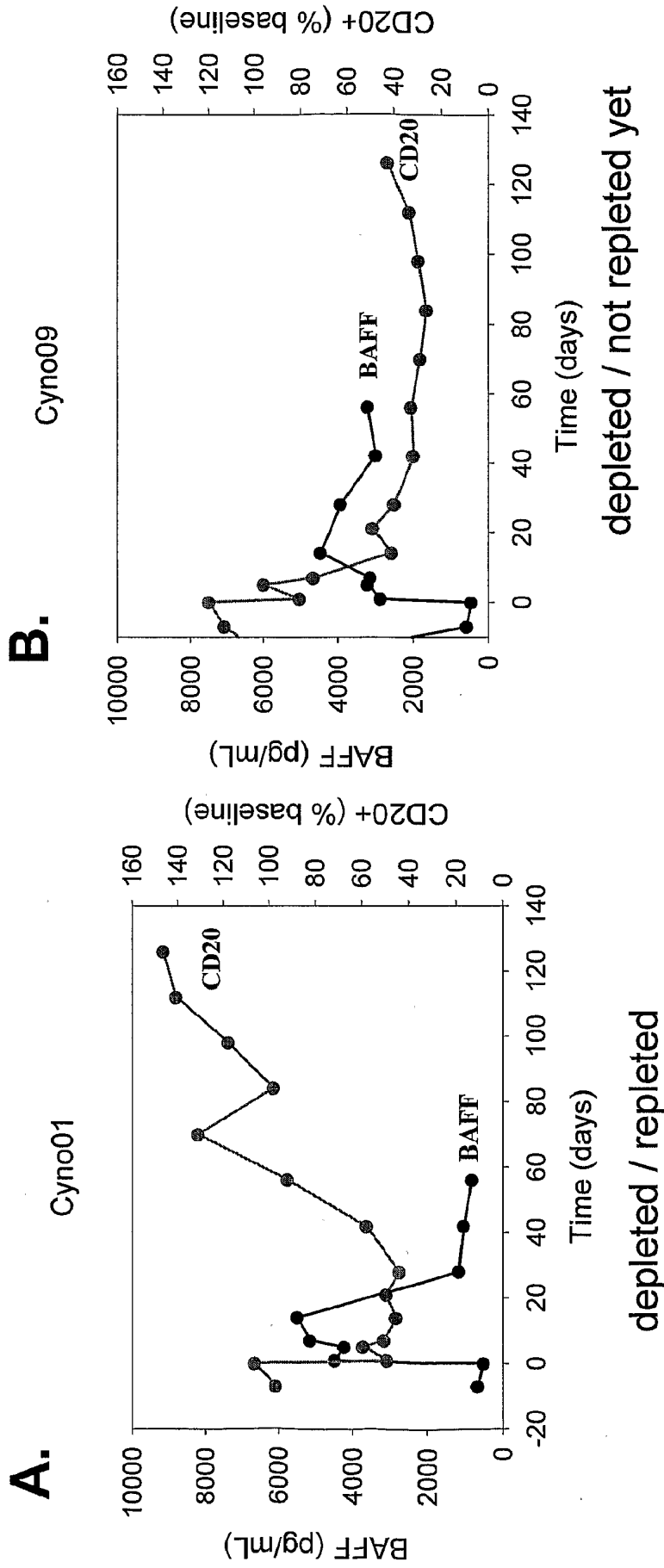


FIG.5

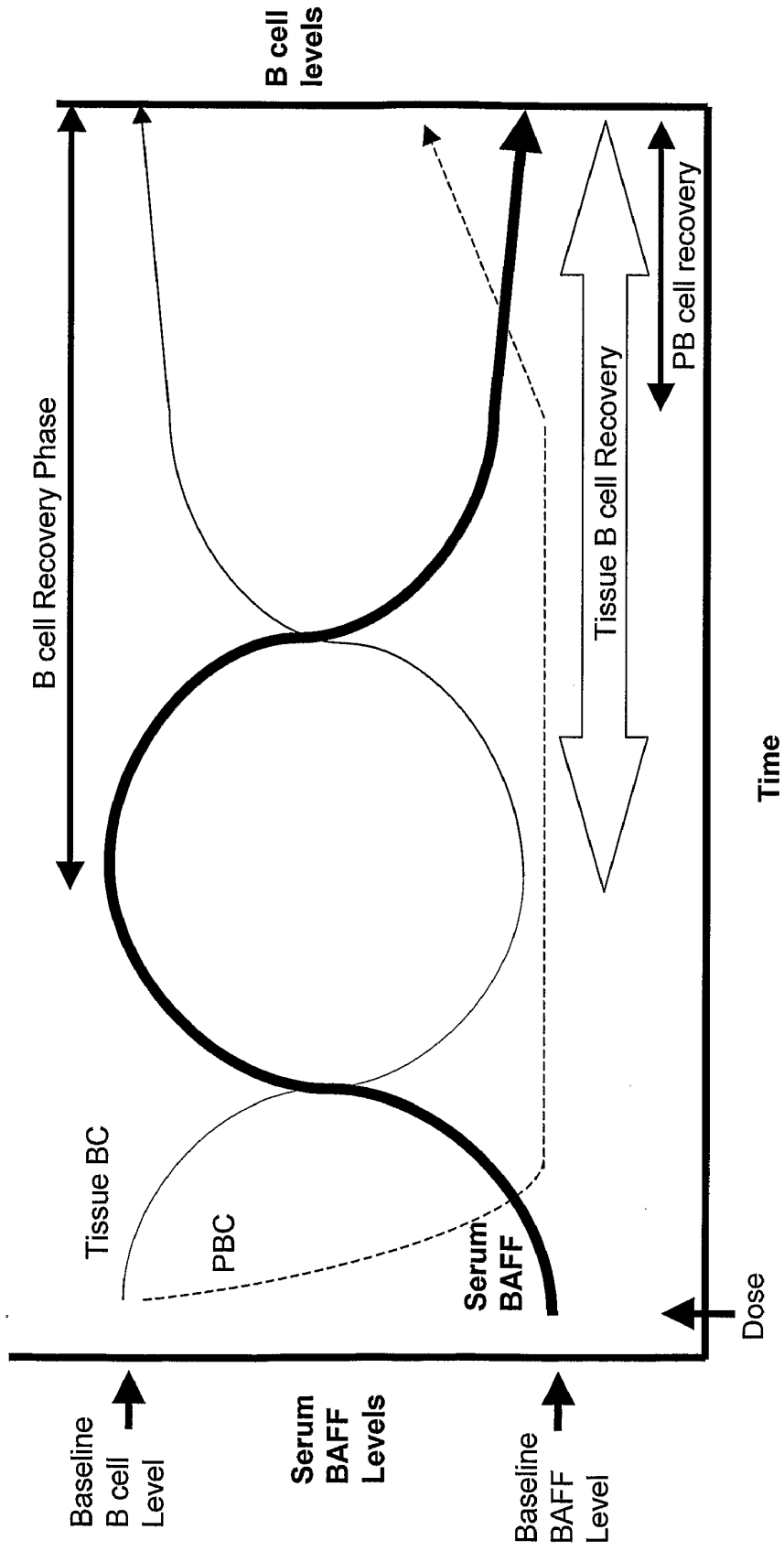


FIG.6

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Tyr Ile Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

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

Leu Val Thr Val Ser Ser
 115

<210> 14
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 14

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Glu Ser Ala Tyr
 20 25 30

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

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

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

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

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

Leu Val Thr Val Ser Ser
 115

<210> 15

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 15

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

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

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

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

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

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

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

Leu Val Thr Val Ser Ser
 115

<210> 16
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 16

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ala Thr Gly Ile Gly Tyr
 20 25 30

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

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

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

Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85

90

95

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

Leu Val Thr Val Ser Ser
115

<210> 17
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 17

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
65 70 75 80

Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

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

Leu Val Thr Val Ser Ser
115

<210> 18
<211> 118
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 18

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Trp Thr Glu His Gly His
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
 85 90 95

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

Leu Val Thr Val Ser Ser
 115

<210> 19

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 19

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 20
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 20

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Pro Arg Arg Gly Tyr
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85 90 95
 Tyr Cys Ala Gln Val Arg Arg Ala Leu Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

Leu Val Thr Val Ser Ser
 115

<210> 21
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 21

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 22
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 22

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 23

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 23

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

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

Tyr Val Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 24
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 24

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 26

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 27

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 27

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Leu Arg Gly Ser
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 28
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 28

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

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

Tyr Ile Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

```

                85                90                95

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

Leu Val Thr Val Ser Ser
                115

<210> 29
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 29

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
65                70                75                80

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

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

Leu Val Thr Val Ser Ser
                115

<210> 30
<211> 118
<212> PRT

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<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 30

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ile Ala Thr Gly His
 20 25 30

Tyr Ile Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 31

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 31

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 32
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 32

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Leu Gly Pro Gly Arg
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85 90 95
 Tyr Cys Ala Gln Val Arg Arg Ala Leu Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

Leu Val Thr Val Ser Ser
 115

<210> 33
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 33

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 34
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 34

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 35

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 35

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 36
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 36

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ala Gly Tyr
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85 90 95
 Tyr Cys Ala Gln Val Arg Arg Ala Leu Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

Leu Val Thr Val Ser Ser
 115

<210> 37
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 37

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 38
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 38

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
65 70 75 80

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

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

Leu Val Thr Val Ser Ser
115

<210> 39

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 39

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Trp Thr Gly Arg
20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 40
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 40

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85

90

95

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

Leu Val Thr Val Ser Ser
 115

<210> 41
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 41

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Pro Tyr
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 42
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 42

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

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

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
65 70 75 80

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

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

Leu Val Thr Val Ser Ser
115

<210> 43

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 43

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Thr Asp Gly Thr Tyr
20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 44
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 44

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

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

Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85

90

95

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

Leu Val Thr Val Ser Ser
 115

<210> 45
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 45

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Asp Thr Gly His
 20 25 30

Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 46
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 46

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Ser Leu Asn Gly Tyr
 20 25 30

Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 47

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 47

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

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

Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 48
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 48

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Pro Gly Thr Gly Ser
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

			85						90						95
Tyr	Cys	Ala	Gln	Val	Arg	Arg	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser										
			115												
<210>	49														
<211>	118														
<212>	PRT														
<213>	Artificial Sequence														
<220>															
<223>	Synthetic construct														
<400>	49														
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5						10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Pro	Leu	Thr	Gly	Ser
			20					25					30		
Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Gly	Phe	Ile	Arg	Asp	Lys	Ala	Asn	Gly	Tyr	Thr	Thr	Glu	Tyr	Asn	Pro
	50					55					60				
Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	Ser	Lys	Asn	Thr
65					70					75				80	
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr
			85						90					95	
Tyr	Cys	Ala	Gln	Val	Arg	Arg	Ala	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser										
			115												
<210>	50														
<211>	118														
<212>	PRT														

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 50

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ile Gly Ser
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 51

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 51

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ala His
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 52
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 52

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Ser Tyr Thr Glu Asn Gly Tyr
 20 25 30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

85 90 95

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

Leu Val Thr Val Ser Ser
115

<210> 53
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 53

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Glu Gly Gly Phe
20 25 30

Tyr Val Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
65 70 75 80

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

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

Leu Val Thr Val Ser Ser
115

<210> 54
<211> 118
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 54

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Glu Asp Ser Tyr
 20 25 30

Tyr Val Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

<210> 55

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 55

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Gly Gly Thr Phe
 20 25 30

Tyr Val Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

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

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

Leu Val Thr Val Ser Ser
 115

- <210> 56
- <211> 220
- <212> PRT
- <213> Artificial Sequence
- <220>
- <223> Synthetic construct
- <400> 56

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

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

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

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

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

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr
 65 70 75 80

Phe Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
 85 90 95

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- <210> 58
- <211> 214
- <212> PRT
- <213> Artificial Sequence
- <220>
- <223> Synthetic construct
- <400> 58

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

<211> 232
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 59

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Ser Ser Val Arg Gly Cys Ala Gly Ala Met
 100 105 110

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

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 130 135 140

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

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 180 185 190

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

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

Pro Lys Ser Cys Asp Lys Thr His
 225 230

<210> 60
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 60

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Gly Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 61

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

<220>
 <223> Synthetic construct

<400> 61

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Thr Gly Ser
 20 25 30

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

Ala Trp Ile Tyr Pro Asp Gly Gly Tyr Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Ser Lys Pro Ala Gly Pro Phe Gly Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 62
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 62

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Thr Gly Tyr

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

<210> 63
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 63

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

<211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 65

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Thr
 20 25 30

Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

Ala Arg Arg Lys Val Val Ser Ser His Val Thr Asn Lys Tyr Val Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 66
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 66

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Asn Gly Ser

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

<210> 67
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<220>
 <221> misc_feature
 <222> (30)..(33)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (54)..(55)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (59)..(59)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (99)..(104)
 <223> Xaa can be any naturally occurring amino acid

<400> 67

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Xaa Xaa Xaa
 20 25 30

Xaa Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Trp Ile Ser Pro Xaa Xaa Gly Asn Thr Xaa Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Ala Ala Met Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 68

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<220>

<221> misc_feature

<222> (30)..(33)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (50)..(50)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (54)..(55)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (104)..(105)

<223> Xaa can be any naturally occurring amino acid

<400> 68

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Xaa Xaa Xaa
 20 25 30

Xaa Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Xaa Ile Ser Pro Xaa Xaa Gly Asp Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Ala Leu Cys Ala Pro Xaa Xaa Ala Met Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 69

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 69

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala

20 25 30

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Arg Ile Thr Pro Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 70
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 70

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 71
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 71

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Ser Thr Ser Pro Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 72
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 72

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Asn Leu Gly Val Cys Ala Gly Ala Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 73
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 73

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 74
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 74

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asp Arg Ala Arg Val Cys Ala Gly Ala Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 75
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 75

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

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

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

Tyr Gly Ala Ser Asn Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ala Ser Pro Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 76
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 76

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Arg Arg
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Ser Ser Val Arg Gly Cys Ala Gly Ala Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 77
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 77

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Arg Ile Ser Pro Pro

<400> 79

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Gly His Gly Ser Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 80

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 80

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Asn Thr Pro Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 81
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 81

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Thr His Gly Ser Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115 120 125

<210> 82
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 82

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ile Ala Arg Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Leu Pro Ser Ala Gly Ser Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 83
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 83

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 85
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 85

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Arg Met Ser Pro Pro
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 86
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 86

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn His Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 87

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 87

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

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

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 88
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 88

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ile Ser Asn His
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Val Thr Pro Ser Tyr Gly Ile Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 89
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 89

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 90
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 90

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Asn
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Trp Val Thr Pro Gly Val Gly Ser Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 91
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 91

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 93

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly Ile Ser Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 94

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic construct

<400> 94

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ile Arg Asn Asn
20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Trp Val Leu Pro Ser Asn Gly Val Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 95
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 95

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

100

105

<210> 96
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 96

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Asn Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 97
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 97

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 99
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 99

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115 120 125

<210> 100
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 100

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
 210

<210> 101
 <211> 232
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 101

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

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

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser

130 135 140

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

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 180 185 190

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

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

Pro Lys Ser Cys Asp Lys Thr His
 225 230

<210> 102
 <211> 285
 <212> PRT
 <213> Homo sapiens

<400> 102

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

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 Leu Leu
 275 280 285

- <210> 103
- <211> 184
- <212> PRT
- <213> Homo sapiens
- <400> 103

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

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
 85 90 95

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
 145 150 155 160

Val Pro Val Pro Ala Thr Glu Leu Gly Ser Thr Glu Leu Val Thr Thr
 165 170 175

Lys Thr Ala Gly Pro Glu Gln Gln
 180

<210> 104
 <211> 61
 <212> PRT
 <213> Homo sapiens
 <400> 104

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

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

<210> 105
 <211> 64
 <212> PRT
 <213> Mus sp.

<400> 105

Met Gly Ala Arg Arg Leu Arg Val Arg Ser Gln Arg Ser Arg Asp Ser
 1 5 10 15

Ser Val Pro Thr Gln Cys Asn Gln Thr Glu Cys Phe Asp Pro Leu Val
 20 25 30

Arg Asn Cys Val Ser Cys Glu Leu Phe His Thr Pro Asp Thr Gly His
 35 40 45

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

<210> 106
 <211> 314
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 106

Met Ser Ala Leu Leu Ile Leu Ala Leu Val Gly Ala Ala Val Ala Ser
 1 5 10 15

Thr Gly Ala Arg Arg Leu Arg Val Arg Ser Gln Arg Ser Arg Asp Ser
 20 25 30

Ser Val Pro Thr Gln Cys Asn Gln Thr Glu Cys Phe Asp Pro Leu Val
 35 40 45

Arg Asn Cys Val Ser Cys Glu Leu Phe His Thr Pro Asp Thr Gly His
 50 55 60

Thr Ser Ser Leu Glu Pro Gly Thr Ala Leu Gln Pro Gln Glu Gly Gln
 65 70 75 80

Val Thr Gly Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro
 85 90 95

Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
 100 105 110

Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
 115 120 125

Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
 130 135 140

Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu
 145 150 155 160

Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met
 165 170 175

His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
 180 185 190

Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
 195 200 205

Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln
 210 215 220

Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe
 225 230 235 240

Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu
 245 250 255

Asn Tyr Lys Asn Thr Gln Pro Ile Met Asn Thr Asn Gly Ser Tyr Phe
 260 265 270

Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn
 275 280 285

Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
 290 295 300

Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 305 310

- <210> 107
- <211> 125
- <212> PRT
- <213> Artificial Sequence
- <220>
- <223> Synthetic construct
- <400> 107

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ala Ser Ser
 20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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

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

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

Ala Arg Arg Val Cys Tyr Asn Arg Leu Gly Val Cys Ala Gly Gly Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115 120 125

<210> 108
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 108

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

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

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

Phe Ala Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 109
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 109

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asp Ile Ser Ser Ser

20 25 30

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

Phe Ser Ala Ser Phe Leu Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 110
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 110

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

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

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

Phe Ala Ala Ser Tyr Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 111
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 111

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

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

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

Phe Ala Ala Ser Tyr Leu Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 112
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 112

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

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

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

Phe Ala Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

- <210> 113
- <211> 107
- <212> PRT
- <213> Artificial Sequence

- <220>
- <223> Synthetic construct

<400> 113

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

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

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

Phe Ala Ala Ser Tyr Leu Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gln Val Ala Pro Pro

85

90

95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 114
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 114

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

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

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

Phe Ala Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 115
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 115

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

90

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

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

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

Phe Ala Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 119
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic construct

<400> 119

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

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

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

Phe Ser Ala Ser Tyr Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

<400> 121

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

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

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

Phe Ala Ala Ser Tyr Leu Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 122

<211> 8

<212> PRT

<213> Mus sp.

<400> 122

Gln Val Arg Arg Ala Leu Asp Tyr
 1 5

<210> 123

<211> 20

<212> PRT

<213> Mus sp.

<400> 123

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

Ser Val Lys Gly
 20

<210> 124
<211> 10
<212> PRT
<213> Mus sp.

<400> 124

Gly Phe Thr Val Thr Ala Tyr Tyr Met Ser
1 5 10

<210> 125
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 125

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

<210> 126
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 126

Gly Phe Thr Ile Ser Ser Asn Ser Ile His
1 5 10

<210> 127
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 127

Ala Trp Ile Thr Pro Ser Asp Gly Asn Thr Asp
1 5 10

<210> 128
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 128

Gly Phe Thr Ile Ser Ser Ser Ser Ile His
1 5 10

<210> 129
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 129

Ala Trp Val Leu Pro Ser Val Gly Phe Thr Asp
1 5 10

<210> 130
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 130

Arg Ala Ser Glu Asp Ile Ser Thr Ala Val Ala
1 5 10

<210> 131
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 131

Tyr Ala Ala Ser Phe Leu Tyr Ser
1 5

<210> 132
<211> 9

<212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic peptide

<400> 132

Gln Gln Ser Gln Ile Ser Pro Pro Thr
 1 5

<210> 133
 <211> 17
 <212> PRT
 <213> Mus sp.

<400> 133

Lys Ser Ser Gln Ser Leu Leu Tyr Ser Ser Asn Gln Asn Asn Tyr Leu
 1 5 10 15

Ala

<210> 134
 <211> 7
 <212> PRT
 <213> Mus sp.

<400> 134

Trp Ala Ser Thr Arg Glu Ser
 1 5

<210> 135
 <211> 9
 <212> PRT
 <213> Mus sp.

<400> 135

Gln Gln Tyr Tyr Thr Tyr Pro Tyr Thr
 1 5

<210> 136
 <211> 107
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 136

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
 20 25 30

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

Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
 50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 137

<211> 122

<212> PRT

<213> Artificial sequence

<220>

<223> sequence is synthesized

<400> 137

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

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

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 138
 <211> 213
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 138

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
 20 25 30

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

Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
 50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
 85 90 95

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

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr

115 120 125

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

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

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

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

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

Asn Arg Gly Glu Cys
 210

<210> 139
 <211> 451
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 139

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

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

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 130 135 140

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

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

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

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

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 260 265 270

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
 355 360 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385 390 395 400

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

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

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

Ser Pro Gly
 450

<210> 140
 <211> 213
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 140

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Leu

20					25					30					
His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Pro	Leu	Ile	Tyr
		35					40					45			
Ala	Pro	Ser	Asn	Leu	Ala	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser
	50					55					60				
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu
65					70					75					80
Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Trp	Ala	Phe	Asn	Pro	Pro	Thr
				85					90					95	
Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	Pro
			100						105					110	
Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr
		115						120					125		
Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys
		130						135					140		
Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu
145						150					155				160
Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser
				165						170					175
Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala
			180						185					190	
Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe
			195					200						205	
Asn	Arg	Gly	Glu	Cys											
			210												
<210>	141														
<211>	451														
<212>	PRT														
<213>	Artificial sequence														

<220>

<223> sequence is synthesized

<400> 141

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

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

Gly Ala Ile Tyr Pro Gly Asn Gly Ala Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 130 135 140

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

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

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

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

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 260 265 270

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 325 330 335

Ile Ala Ala Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
 355 360 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385 390 395 400

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

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

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

Ser Pro Gly
 450

<210> 142
 <211> 451
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 142

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

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

Gly Ala Ile Tyr Pro Gly Asn Gly Ala Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr

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

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

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

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

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

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

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Ala Pro
 325 330 335

Ile Ala Ala Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
 355 360 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385 390 395 400

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

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

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

Ser Pro Gly
 450

<210> 144
 <211> 107
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 144

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

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

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Leu Ile Tyr

35 40 45

Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
 50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
 65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ala Phe Asn Pro Pro Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 145
 <211> 122
 <212> PRT
 <213> Artificial sequence

<220>
 <223> sequence is synthesized

<400> 145

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

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

Gly Ala Ile Tyr Pro Gly Asn Gly Ala Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 146

<211> 122

<212> PRT

<213> Artificial sequence

<220>

<223> sequence is synthesized

<400> 146

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

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

Gly Ala Ile Tyr Pro Gly Asn Gly Ala Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

专利名称(译)	与b细胞测定有关的方法和组合物		
公开(公告)号	EP1952150A4	公开(公告)日	2009-06-24
申请号	EP2006838235	申请日	2006-11-21
[标]申请(专利权)人(译)	健泰科生物技术公司		
申请(专利权)人(译)	基因泰克, INC.		
当前申请(专利权)人(译)	基因泰克, INC.		
[标]发明人	FLAVIUS MARTIN		
发明人	FLAVIUS, MARTIN		
IPC分类号	G01N33/53 G01N33/50 G01N33/68		
CPC分类号	A61P1/04 A61P13/12 A61P17/06 A61P21/04 A61P25/00 A61P29/00 G01N33/5052 G01N33/6863 G01N2333/525 G01N2333/70578		
优先权	60/739266 2005-11-23 US 60/857925 2006-11-10 US		
其他公开文献	EP1952150B1 EP1952150A2		
外部链接	Espacenet		

摘要(译)

本发明涉及通过测量受试者中的血清BAFF水平来治疗受试者中的疾病和监测B细胞水平以及与其相关的组合物和组合物的新方法。

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys