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(54) **Title:** HUMAN HINGE CORE MIMETIBODIES, COMPOSITIONS, METHODS AND USES

(57) **Abstract:** The present invention relates to at least one novel human hinge core mimetibody or specified portion or variant, including isolated nucleic acids that encode at least one hinge core mimetibody or specified portion or variant, hinge core mimetibody or specified portion or variants, vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.

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HUMAN HINGE CORE MIMETIBODIES, COMPOSITIONS, METHODS AND USES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to hinge core mimetibodies, specified portions and variants specific for bologically active proteins, fragment or ligands, hinge core mimetibody encoding and complementary nucleic acids, host cells, and methods of making and using thereof, including therapeutic formulations, administration and devices.

RELATED ART

Recombinant proteins are an emerging class of therapeutic agents. Such recombinant therapeutics have engendered advances in protein formulation and chemical modification. Such modifications can potentially enhance the therapeutic utility of therapeutic proteins, such as by increaseing half lives (e.g., by blocking their exposure to proteolytic enzymes), enhancing biological activity, or reducing unwanted side effects. One such modification is the use of immunoglobulin fragments fused to receptor proteins, such as enteracept. Therapeutic proteins have also been constructed using the Fc domain to attempt to provide a longer half-life or to incorporate functions such as Fc receptor binding, protein A binding, and complement fixation.

Accordingly, there is a need to provide improved and/or modified versions of therapeutic proteins, which overcome one more of these and other problems known in the art.

SUMMARY OF THE INVENTION

The present invention provides isolated human hinge core mimetibodies, including modified immunoglobulins, cleavage products and other specified portions and variants thereof, as well as hinge core mimetibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and/or enabled herein, in combination with what is known in the art.

The present invention also provides at least one hinge core mimetibody or specified portion or variant as described herein and/or as known in the art. The hinge core mimetibody can optionally comprise at least one CH3 region directly linked with at least one CH2 region directly linked with at least one portion of a truncated hinge region or fragment thereof (H)

directly linked with at an optional linker sequence (L), directly linked to at least one therapeutic peptide (P), optionally further directly linked with at least a portion of at least one variable antibody sequence (V). In a preferred embodiment a pair of a IgG CH3-CH2-partial hinge(H) linker (L)-therapeutic peptide (P) with an optional N-terminal variable sequence, the pair optionally linked by association or covalent linkage, such as, but not limited to, at least one Cys-Cys disulfide bond or at least one CH4 or other immunglobulin sequence. In one embodiment, a hinge core mimetibody comprises formula (I):

((V(m)-P(n)-L(o)-H(p)-CH2(q)-CH3(r))(s),

where V is at least one portion of an N-terminus of an immunoglobulin variable region, P is at least one bioactive peptide, L is at least one linker polypeptide H is at least one portion of at least one immunoglobulin hinge region, CH2 is at least a portion of an immunoglobulin CH2 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, m, n, o, p, q, r and s are independently an integer between 0, 1 or 2 and 10, mimicing different types of immunoglobulin molecules, e.g., but not limited to IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgD, IgE, and the like, or any subclass thereof, or any combination thereof.

Thus, a hinge core mimetibody of the present invention mimics at least a portion of an antibody or immnuoglobulin structure or function with its inherent properties and functions, while providing a therapeutic peptide and its inherent or acquired in vitro, in vivo or in situ properties or activities. The various portions of the antibody and therapeutic peptide portions of at least one hinge core mimetibody of the present invention can vary as described herein in combination with what is known in the art.

At least one hinge core mimetibody or specified portion or variant of the invention mimics the binding of the P portion of the mimetibody to at least one ligand, or has at least one biological activity of, at least one protein, subunit, fragment, portion or any combination thereof.

The present invention also provides at least one isolated hinge core mimetibody or specified portion or variant as described herein and/or as known in the art, wherein the hinge core mimetibody or specified portion or variant has at least one activity, such as, but not limited to known biological activities of at least one bioactive peptide or polypeptide corresponding to the P portion of Formula I. A hinge core mimetibody can thus be screened for a corresponding activity according to known methods, such as at least one neutralizing activity towards a protein or fragment thereof.

In one aspect, the present invention provides at least one isolated hinge core mimetibody, comprising at least one P(n) region comprising at least a bilogically active portion

of at least one of SEQ ID NOS:1-979, or optionally with one or more substitutions, deletions or insertions as described herein and/or as known in the art.

In another aspect, the present invention provides at least one isolated hinge core mimetibody, wherein the hinge core mimetibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of at least one ligand or binding region which ligand binds to at least a portion of at least one of SEQ ID NOS: 1-979, or optionally with one or more substitutions, deletions or insertions as described herein or as known in the art.

The at least one hinge core mimetibody can optionally further comprise at least one characteristic selected from (i) bind at least one protein with an affinity of at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M; and/or (ii) substantially neutralize at least one activity of at least one protein or portion thereof.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, having significant identity or hybridizing to, a polynucleotide encoding specific mimetibodies or specified portions or variants thereof, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising at least one of said isolated hinge core mimetibody nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such hinge core mimetibody nucleic acids, vectors and/or host cells.

Also provided is an isolated nucleic acid encoding at least one isolated hinge core mimetibody; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one hinge core mimetibody, comprising translating the hinge core mimetibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the hinge core mimetibody is expressed in detectable or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated hinge core mimetibody or specified portion or variant encoding nucleic acid and/or hinge core mimetibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. The composition can optionally further comprise at least one further compound, protein or composition.

Also provided is a composition comprising at least one isolated hinge core mimetibody and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

The present invention further provides at least one anti-idiotype antibody to at least one hinge core mimetibody of the present invention. The anti-idiotype antibody includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complimetarity determing region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into a hinge core mimetibody of the present invention. A hinge core mimetibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like.

The present invention further provides an anti-idiotype antibody or fragment that specifically binds at least one hinge core mimetibody of the present invention.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding at least one hinge core mimetibody anti-idiotype antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said hinge core mimetibody anti-idiotype antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotype antiobody nucleic acids, vectors and/or host cells.

The present invention also provides at least one method for expressing at least one hinge core mimetibody or specified portion or variant, or hinge core mimetibody anti-idiotype antibody, in a host cell, comprising culturing a host cell as described herein and/or as known in the art under conditions wherein at least one hinge core mimetibody or specified portion or variant, or anti-idiotype antibody is expressed in detectable and/or recoverable amounts.

The present invention further provides at least one hinge core mimetibody, specified portion or variant in a method or composition, when administered in a therapeutically effective amount, for modulation, for treating or reducing the symptoms of at least one of a bone and joint disorder, cardiovascular disoder, a dental or oral disorder, a dermatologic disorder, an ear, nose or throat disorder, an endocrine or metabolic disorder, a gastrointestinal disorder, a gynecologic disorder, a hepatic or biliary disorder, a an obstetric disorder, a hematologic disorder, an immunologic or allergic disorder, an infectious disease, a musculoskeletal disorder, a oncologic disorder, a neurologic disorder, a nutritrional disorder, an opthalmologic disorder, a pediatric disorder, a poisoning disorder, a psychiatric disorder, a renal disorder, a pulmonary disorder, or any other known disorder. (See., e.g., The Merck Manual, 17th ed. , Merck Research Laboratories, Merck and Co., Whitehouse Station, NJ (1999), entirely incoporated herein by reference), as needed in many different conditions, such as but not limited to, prior to, subsequent to, or during a related disease or treatment condition, as known in the art.

The present invention further provides at least one hinge core mimetibody, specified portion or variant in a method or composition, when administered in a therapeutically effective amount, for modulation, for treating or reducing the symptoms of, at least one immune, cardiovascular, infectious, malignant, and/or neurologic disease in a cell, tissue, organ, animal or patient and/or, as needed in many different conditions, such as but not limited to, prior to, subsequent to, or during a related disease or treatment condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one hinge core mimetibody or specified portion or variant, according to the present invention.

The present invention also provides at least one composition comprising (a) an isolated hinge core mimetibody encoding nucleic acid and/or hinge core mimetibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known carriers or diluents. The composition can optionally further comprise at least one further compound, protein or composition.

The present invention further provides at least one hinge core mimetibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one protein related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one hinge core mimetibody, according to the present invention.

The present invention further provides at least one hinge core mimetibody method or composition, for diagnosing at least one protein related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one hinge core mimetibody, according to the present invention.

Also provided is a method for diagnosing or treating a disease condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one isolated hinge core mimetibody of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.001-50 mg/kilogram of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a

nutritional drug, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is a medical device, comprising at least one isolated hinge core mimetibody of the invention, wherein the device is suitable to contacting or administerting the at least one hinge core mimetibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated hinge core mimetibody of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated hinge core mimetibody of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the hinge core mimetibody. Further provided in the present invention is at least one hinge core mimetibody produced by the above method.

The present invention further provides any invention described herein.

DESCRIPTION OF THE INVENTION

The present invention provides isolated, recombinant and/or synthetic mimetibodies or specified portions or variants, as well as compositions and encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one hinge core mimetibody. Such mimetibodies or specified portions or variants of the present invention comprise specific hinge core mimetibody sequences, domains, fragments and specified variants thereof. The present invention also provides methods of making and using said nucleic acids and mimetibodies or specified portions or variants, including therapeutic compositions, methods and devices.

The present invention also provides at least one isolated hinge core mimetibody or specified portion or variant as described herein and/or as known in the art. The hinge core mimetibody can optionally comprise at least one CH3 region directly linked with at least one CH2 region directly linked with at least one hinge region or fragment thereof (H) directly linked with at least one optional linker sequence (L), directly linked to at least one therapeutic peptide (P), optionally further directly linked with at least a portion of at least one variable (V) antibody sequence.

In a preferred embodiment a hinge core mimetibody comprises formula (I):

((V(m)-P(n)-L(o)-H(p)-CH2(q)-CH3(r))(s),

where V is at least one portion of an N-terminus of an immunoglobulin variable region, P is at least one bioactive peptide, L is polypeptide that provides structural flexablity by allowing the mimietibody to have alternative orientations and binding properties, H is at least a portion of an immunoglobulin variable hinge region, CH2 is at least a portion of an immunoglobulin CH2 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, and m, n, o, p, q, r, and s can be independently an integer between 0, 1 or 2 and 10, mimicing different types of immunoglobulin molecules, e.g., but not limited to IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgD, IgE, and the like, or combination thereof. The monomer where m=1 can be linked to other monomers by association or covalent linkage, such as, but not limited to, a Cys-Cys disulfide bond or other immnuoglobulin sequence. Thus, a hinge core mimetibody of the present invention mimics an antibody structure with its inherent properties and functions, while providing a therapeutic peptide and its inherent or acquired in vitro, in vivo or in situ properties or activities. The various portions of the antibody and therapeutic peptide portions of at least one hinge core mimetibody of the present invention can vary as described herein in combinatoin with what is known in the art.

As used herein, a "hinge core mimetibody," "hinge core mimetibody portion," or "hinge core mimetibody fragment" and/or "hinge core mimetibody variant" and the like mimics, has or simulates at least one ligand binding or at least one biological activity of at least one protein, such as but not limited to at least one biologically active portion of at least one of SEQ ID NOS:1-979, *in vitro, in* situ and/or preferably in *vivo*. For example, a suitable hinge core mimetibody, specified portion or variant of the present invention can bind at least one protein ligand and includes at least one protein ligand, receptor, soluble receptor, and the like. A suitable hinge core mimetibody, specified portion, or variant can also modulate, increase, modify, activate, at least one protein receptor signaling or other measurable or detectable activity.

Mimetibodies useful in the methods and compositions of the present invention are characterized by suitable affinity binding to protein ligands or receptors and optionally and preferably having low toxicity. In particular, a hinge core mimetibody, where the individual components, such as the portion of variable region, constant region (without a CH1 portion) and framework, or any portion thereof (e.g., a portion of the J, D or V rgions of the variable heavy or light chain;, at least one portion of at least one hinge region, the constant heavy chain or light chain, and the like) individually and/or collectively optionally and preferably possess low immunogenicity, is useful in the present invention. The mimetibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, may contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAMA, HACA or HAHA responses in less than about 75%, or preferably less than about 50, 45, 40, 35, 30, 35, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, and/or 1 % of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (see, e.g., Elliott *et al.*, *Lancet 344*:1125-1127 (1994)).

Utility

The isolated nucleic acids of the present invention can be used for production of at least one hinge core mimetibody, fragment or specified variant thereof, which can be used to effect in an cell, tissue, organ or animal (including mammals and humans), to modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one protein related condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or

disease, an anemia; an immune/autoimmune; and/or an cancerous/infecteous, as well as other known or specified protein related conditions.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one hinge core mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.0001 to 500 mg/kg per single or multiple administration, or to achieve a serum concentration of 0.0001-5000 μg/ml serum concentration per single or multiple adminstration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2003); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, Antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2003); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2003).

Mimetibodies of the Present Invention

The hinge core mimetibody can optionally comprise at least one CH3 region directly linked with at least one CH2 region directly linked with at least portion of at lesat one hinge region fragment (H), such as comprising at least one core hinge region, directly linked with an optional linker sequence (L), directly linked to at least one therapeutic peptide (P), optionally further directly linked with at least a portion of at least one variable antibody sequence (V). In a preferred embodiment of a pair of a CH3-CH2-H-L-V, the pair can be linked by association or covalent linkage. Thus, a hinge core mimetibody of the present invention mimics an antibody structure with its inherent properties and functions, while providing a therapeutic peptide and its inherent or acquired in vitro, in vivo or in situ properties or activities. The various portions of the antibody and therapeutic peptide portions of at least one hinge core

mimetibody of the present invention can vary as described herein in combinatoin with what is known in the art.

Mimetibodies of the present invention thus provide at least one suitable property as compared to known proteins, such as, but not limited to, at least one of increased half-life, increased activity, more specific activity, increased avidity, increased or descrease off rate, a selected or more suitable subset of activities, less immungenicity, increased quality or duration of at least one desired therapeutic effect, less side effects, and the like.

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. For example, papain or pepsin cleavage can generate hinge core mimetibody Fab or $F(ab')_2$ fragments, respectively. Other proteases with the requisite substrate specificity can also be used to generate Fab or $F(ab')_2$ fragments or portions thereof. Mimetibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a chimeric gene encoding a $F(ab')_2$ heavy chain portion can be designed to include DNA sequences encoding the CH1 domain and/or hinge region of the heavy chain. The various portions of mimetibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, a nucleic acid encoding the variable and constant regions of a human antibody chain can be expressed to produce a contiguous protein for use in mimetibodies of the present invention. See, e.g., Ladner *et al.,* U.S. Patent No. 4,946,778 and Bird, R.E. *et al., Science, 242:* 423-426 (1988), regarding single chain antibodies.

As used herein, the term "human mimetibody" refers to an antibody in which substantially every part of the protein (e.g., therapeutic peptide, framework, C_L, C_H domains (e.g., C_H2, C_H3), hinge, (V_L, V_H)) is expected to be substantially non-immunogenic, with only minor sequence changes or variations. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans relative to non-modified human antibodies, or mimetibodies of the prsent invention. Thus, a human antibody and corresponding hinge core mimetibody of the present invention is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody and hinge core mimetibody can be produced by a non-human animal or cell that is capable of expressing human immunoglobulins (e.g., heavy chain and/or light chain) genes, and for a hinge core mimetibody.

Human mimetibodies that are specific for at least one protein ligand or receptor thereof can be designed against an appropriate ligand, such as isolated and/or protein receptor or ligand, or a portion thereof (including synthetic molecules, such as synthetic peptides).

Preparation of such mimetibodies are performed using known techniques to identify and characterize ligand binding regions or sequences of at least one protein or portion thereof.

In a preferred embodiment, at least one hinge core mimetibody or specified portion or variant of the present invention is produced by at least one cell line, mixed cell line, immortalized cell or clonal population of immortalized and/or cultured cells. Immortalized protein producing cells can be produced using suitable methods. Preferably, the at least one hinge core mimetibody or specified portion or variant is generated by providing nucleic acid or vectors comprising DNA derived or having a substantially similar sequence to, at least one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement, and which further comprises a mimetibody structure as described herein, e.g., but not limited to Formula (I), wherein known portions of :C- and N-termiinal variable regions can be used for V, hinge regions for H, CH2 for CH2 and CH3 for CH3, as known in the art.

The term "functionally rearranged," as used herein refers to a segment of nucleic acid from an immunoglobulin locus that has undergone V(D)J recombination, thereby producing an immunoglobulin gene that encodes an immunoglobulin chain (e.g., heavy chain, light chain), or any portion thereof. A functionally rearranged immunoglobulin gene can be directly or indirectly identified using suitable methods, such as, for example, nucleotide sequencing, hybridization (e.g., Southern blotting, Northern blotting) using probes that can anneal to coding joints between gene segments or enzymatic amplification of immunoglobulin genes (e.g., polymerase chain reaction) with primers that can anneal to coding joints between gene segments. Whether a cell produces an hinge core mimetibody or portion or variant comprising a particular variable region or a variable region comprising a particular sequence (e.g., at least one P sequence can also be determined using suitable methods.

Mimetibodies, specified portions and variants of the present invention can also be prepared using at least one hinge core mimetibody or specified portion or variant encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce such mimetibodies or specified portions or variants in their milk. Such animals can be provided using known methods as applied for antibody encoding sequences. See, e.g., but not limited to, US patent nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

Mimetibodies, specified portions and variants of the present invention can additionally be prepared using at least one hinge core mimetibody or specified portion or variant encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to

tobacco and maize) that produce such mimetibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, e.g., using an inducible promoter. See, e.g., Cramer et al., Curr. Top. Microbol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian proteins at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain mimetibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., Plant Mol. Biol. 38:101-109 (1998) and references cited therein. Thus, mimetibodies, specified portions and variants of the present invention can also be produced using transgenic plants, according to know methods. See also, e.g., Fischer et al., Biotechnol. Appl. Biochem. 30:99-108 (Oct., 1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem. Soc. Trans. 22:940-944 (1994); and references cited therein. The above references are entirely incorporated herein by reference.

The mimetibodies of the invention can bind human protein ligands with a wide range of affinities (K_D). In a preferred embodiment, at least one human hinge core mimetibody of the present invention can optionally bind at least one protein ligand with high affinity. For example, at least one hinge core mimetibody of the present invention can bind at least one protein ligand with a K_D equal to or less than about 10^{-9} M or, more preferably, with a K_D equal to or less than about 0.1-9.9 (or any range or value therein) X 10^{-10} M, 10^{-11}, 10^{-12}, 10^{-13} or any range or value therein.

The affinity or avidity of a hinge core mimetibody for at least one protein ligand can be determined experimentally using any suitable method, e.g., as used for determing antibody-antigen binding affinity or avidity. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular hinge core mimetibody-ligand interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other ligand-binding parameters (e.g., K_D, K_a, K_d) are preferably made with standardized solutions of hinge core mimetibody and ligand, and a standardized buffer, such as the buffer described herein.

Nucleic Acid Molecules

Using the information provided herein, such as the nucleotide sequences encoding at least 90-100% of the contiguous amino acids of at least one of SEQ ID NOS:1-979 as well as at least one portion of an antibody, wherein the above sequences are inserted as the P sequence of Formula (I) to provide a hinge core mimetibody of the present invention, further comprising specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one hinge core mimetibody or specified portion or variant can be obtained using methods described herein or as known in the art.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combination thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

Isolated nucleic acid molecules of the present invention can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, nucleic acid molecules comprising the coding sequence for a hinge core mimetibody or specified portion or variant; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one hinge core mimetibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate nucleic acid variants that code for specific hinge core mimetibody or specified portion or variants of the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention.

As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding a hinge core mimetibody or specified portion or variant can include, but are not limited to, those encoding the amino acid sequence of a hinge core mimetibody fragment, by itself; the coding sequence for the entire hinge core mimetibody or a portion thereof; the coding sequence for a hinge core mimetibody, fragment or portion, as well as additional sequences, such as the coding sequence of at least one signal leader or fusion peptide, intron, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and

polyadenylation signals (for example - ribosome binding and stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding a hinge core mimetibody or specified portion or variant can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused hinge core mimetibody or specified portion or variant comprising a hinge core mimetibody fragment or portion.

Polynucleotides Which Selectively Hybridize to a Polynucleotide as Described Herein

The present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein, or others disclosed herein, including specified variants or portions thereof. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides.

Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 40-99% sequence identity and can be employed to identify orthologous or paralogous sequences.

Optionally, polynucleotides of this invention will encode at least a portion of a hinge core mimetibody or specified portion or variant encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding a hinge core mimetibody or specified portion or variant of the present invention. See, e.g., Ausubel, supra; Colligan, supra, each entirely incorporated herein by reference.

Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well-known in the art.

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the proteins of the present invention. The nucleic acid of the present invention -

excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. See, e.g., Ausubel, *supra*; or Sambrook, *supra*.

Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under suitable stringency conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, is well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*).

Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., supra). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter sequences.

Recombinant Expression Cassettes

The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence of the present invention, for example a cDNA or a genomic sequence encoding a hinge core mimetibody or specified portion or variant of the present invention, can be used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids of the present invention.

In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in intron) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can be altered *in vivo* or *in vitro* by mutation. deletion and/or substitution, as known in the art. A polynucleotide of the present invention can be expressed in either sense or anti-sense orientation as desired. It will be appreciated that control of gene expression in either sense or anti-sense orientation can have a direct impact on the observable characteristics. Another method of suppression is sense suppression. Introduction of nucleic acid configured in the sense orientation has been shown to be an effective means by which to block the transcription of target genes.

Vectors And Host Cells

The present invention also relates to vectors that include isolated nucleic acid molecules of the present invention, host cells that are genetically engineered with the recombinant vectors, and the production of at least one hinge core mimetibody or specified portion or variant by recombinant techniques, as is well known in the art. See, e.g., Sambrook, et al., supra; Ausubel, et al., supra, each entirely incorporated herein by reference.

The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced into a cell using suitable known methods, such as electroporation and the like, other known methods include the use of the vector as a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it can be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites optionally for at least one of transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

Expression vectors will preferably but optionally include at least one selectable marker. Such markers include, e.g., but not limited to, methotrexate (MTX), dihydrofolate reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos. 5,122,464; 5,770,359; 5,827,739) resistance for eukaryotic cell culture, and

tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other known methods. Such methods are described in the art, such as Sambrook, supra, Chapters 1-4 and 16-18; Ausubel, supra, Chapters 1, 9, 13, 15, 16.

At least one hinge core mimetibody or specified portion or variant of the present invention can be expressed in a modified form, such as a fusion protein, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of a hinge core mimetibody or specified portion or variant to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to a hinge core mimetibody or specified portion or variant of the present invention to facilitate purification. Such regions can be removed prior to final preparation of a hinge core mimetibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a protein of the present invention.

Illustrative of cell cultures useful for the production of the mimetibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated proteins have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, hepG2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are readily available from, for example, American Type Culture Collection, Manassas, Va. Preferred host cells include cells of lymphoid origin such as myeloma and lymphoma cells. Particularly preferred host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or a SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., supra; Sambrook, et al., supra. Other cells useful for production of nucleic acids or proteins of the present invention are known and/or available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenlyation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenlyation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can also be included. An example of a splicing sequence is the VP1 intron from SV40 (Sprague, et al., J. Virol. 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

Purification of an hinge core mimetibody or specified portion or variant Thereof

A hinge core mimetibody or specified portion or variant can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2003), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

Mimetibodies or specified portions or variants of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the hinge core mimetibody or specified portion or variant of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Sections 17.37-

17.42; Ausubel, supra, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein Science, supra, Chapters 12-14, all entirely incorporated herein by reference.

MIMETIBODIES, SPECIFIED FRAGMENTS AND/OR VARIANTS

The isolated mimetibodies of the present invention comprise a hinge core mimetibody or specified portion or variant encoded by any one of the polynucleotides of the present invention as discussed more fully herein, or any isolated or prepared hinge core mimetibody or specified portion or variant thereof.

Preferably, the hinge core mimetibody or ligand-binding portion or variant binds at least one protein ligand or receptor, and, thereby provides at least one biological activity of the corresponding protein or a fragment thereof. Different therapeutically or diagnostically significant proteins are well known in the art and suitable assays or biological activities of such proteins are also well known in the art. The following is a general discussion of the variety of proteins, peptides and biological molecules that may be used in the in accordance with the teachings herein. These descriptions do not serve to limit the scope of the invention, but rather illustrate the breadth of the invention.

Thus, an embodiment of the present invention may target one or more growth factors, or, conversely, derive the target-binding moiety from one or more growth factors. Briefly, growth factors are hormones or cytokine proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Many growth factors are quite versatile, stimulating cellular division in numerous different cell types; while others are specific to a particular cell-type. The following Table 1 presents several factors, but is not intended to be comprehensive or complete, yet introduces some of the more commonly known factors and their principal activities.

Table 1: Growth Factors

Factor	Principal Source	Primary Activity	Comments
Platelet Derived Growth Factor (PDGF)	Platelets, endothelial cells, placenta.	Promotes proliferation of connective tissue, glial and smooth muscle cells. PDGF receptor has intrinsic tyrosine kinase activity.	Dimer required for receptor binding. Two different protein chains, A and B, form 3 distinct dimer forms.
Epidermal Growth Factor (EGF)	Submaxillary gland, Brunners gland.	promotes proliferation of mesenchymal, glial and epithelial cells.	EGF receptor has tyrosine kinase activity, activated in response to EGF binding.

Factor	Principal Source	Primary Activity	Comments
Fibroblast Growth Factor (FGF)	Wide range of cells; protein is associated with the ECM; nineteen family members. Receptors widely distributed in bone, implicated in several bone-related diseases.	Promotes proliferation of many cells including skeletal and nervous system; inhibits some stem cells; induces mesodermal differentiation. Non-proliferative effects include regulation of pituitary and ovarian cell function.	Four distinct receptors, all with tyrosine kinase activity. FGF implicated in mouse mammary tumors and Kaposi's sarcoma.
NGF		Promotes neurite outgrowth and neural cell survival.	Several related proteins first identified as proto-oncogenes; trkA (*trackA*), trkB, trkC.
Erythropoietin (Epo)	Kidney.	Promotes proliferation and differentiation of erythrocytes.	Also considered a 'blood protein,' and a colony stimulating factor.
Transforming Growth Factor a (TGF-a)	Common in transformed cells, found in macrophages and keratinocytes.	Potent keratinocyte growth factor.	Related to EGF.
Transforming Growth Factor v (TGF-b)	Tumor cells, activated TH_1 cells (T-helper) and natural killer (NK) cells.	Anti-inflammatory (suppresses cytokine production and class II MHC expression), proliferative effects on many mesenchymal and epithelial cell types, may inhibit macrophage and lymphocyte proliferation.	Large family of proteins including activin, inhibin and bone morpho-genetic protein. Several classes and subclasses of cell-surface receptors.
Insulin-Like Growth Factor-I (IGF-I)	Primarily liver, produced in response to GH and then induces subsequent cellular activities, particularly on bone growth.	Promotes proliferation of many cell types, autocrine and paracrine activities in addition to the initially observed endocrine activities on bone.	Related to IGF-II and proinsulin, also called Somatomedin C. IGF-I receptor, like the insulin receptor, has intrinsic tyrosine kinase activity. IGF-I can bind to the insulin receptor.
Insulin-Like Growth Factor-II (IGF-II)	Expressed almost exclusively in embryonic and neonatal tissues.	Promotes proliferation of many cell types primarily of fetal origin. Related to IGF-I and proinsulin.	IGF-II receptor is identical to the mannose-6-phosphate receptor that is responsible for the integration of lysosomal enzymes.

Additional growth factors that may be produced in accordance with the present invention include Activin (Vale et al., 321 Nature 776 (1986); Ling et al., 321 Nature 779

(1986)), Inhibin (U.S. Patent Nos. 4,737,578; 4,740,587), and Bone Morphongenic Proteins (BMPs) (U.S. Patent No. 5,846,931; Wozney, Cellular & Molecular Biology of Bone 131-167 (1993)).

In addition to the growth factors discussed above, the present invention may target or use other cytokines. Secreted primarily from leukocytes, cytokines stimulate both the humoral and cellular immune responses, as well as the activation of phagocytic cells. Cytokines that are secreted from lymphocytes are termed lymphokines, whereas those secreted by monocytes or macrophages are termed monokines. A large family of cytokines are produced by various cells of the body. Many of the lymphokines are also known as interleukins (ILs), because they are not only secreted by leukocytes, but are also able to affect the cellular responses of leukocytes. More specifically, interleukins are growth factors targeted to cells of hematopoietic origin. The list of identified interleukins grows continuously. *See, e.g.,* U.S. Patent No. 6,174,995; U.S. Patent No. 6,143,289; Sallusto et al., 18 Annu. Rev. Immunol. 593 (2000) Kunkel et al., 59 J. Leukocyto Biol. 81 (1996).

Additional growth factor/cytokines encompassed in the present invention include pituitary hormones such as human growth hormone (HGH), follicle stimulating hormones (FSH, FSHα, and FSHβ), Human Chorionic Gonadotrophins (HCG, HCGα, HCGβ), uFSH (urofollitropin), Gonatropin releasing hormone (GRH), Growth Hormone (GH), leuteinizing hormones (LH, LHα, LHβ), somatostatin, prolactin, thyrotropin (TSH, TSHα, TSHβ), thyrotropin releasing hormone (TRH), parathyroid hormones, estrogens, progesterones, testosterones, or structural or functional analog thereof. All of these proteins and peptides are known in the art.

The cytokine family also includes tumor necrosis factors, colony stimulating factors, and interferons. *See, e.g.,* Cosman, 7 Blood Cell (1996); Gruss et al., 85 Blood 3378 (1995); Beutler et al., 7 Annu. Rev. Immunol. 625 (1989); Aggarwal et al., 260 J. Biol. Chem. 2345 (1985); Pennica et al., 312 Nature 724 (1984); R & D Systems, Cytokine Mini-Reviews, *at* http://www.rndsystems.com. Several cytokines are introduced, briefly, in Table 2 below.

Table 2: Cytokines

Cytokine	Principal Source	Primary Activity
Interleukins IL1-a and -b	Primarily macrophages but also neutrophils, endothelial cells, smooth muscle cells, glial cells, astrocytes, B- and T-cells, fibroblasts, and keratinocytes	Costimulation of APCs and T cells; stimulates IL-2 receptor production and expression of interferon-γ; may induce proliferation in non-lymphoid cells.

Cytokine	Principal Source	Primary Activity
IL-2	CD4+ T-helper cells, activated TH_1 cells, NK cells	Major interleukin responsible for clonal T-cell proliferation. IL-2 also exerts effects on B-cells, macrophages, and natural killer (NK) cells. IL-2 receptor is not expressed on the surface of resting T-cells, but expressed constitutively on NK cells, that will secrete TNF-α, IFN-γ and GM-CSF in response to IL-2, which in turn activate macrophages.
IL-3	Primarily T-cells	Also known as multi-CSF, as it stimulates stem cells to produce all forms of hematopoietic cells.
IL-4	TH_2 and mast cells	B cell proliferation, eosinophil and mast cell growth and function, IgE and class II MHC expression on B cells, inhibition of monokine production
IL-5	TH_2 and mast cells	eosinophil growth and function
IL-6	Macrophages, fibroblasts, endothelial cells and activated T-helper cells. Does not induce cytokine expression.	IL-6 acts in synergy with IL-1 and TNF-α in many immune responses, including T-cell activation; primary inducer of the acute-phase response in liver; enhances the differentiation of B-cells and their consequent production of immunoglobulin; enhances Glucocorticoid synthesis.
IL-7	thymic and marrow stromal cells	T and B lymphopoiesis
IL-8	Monocytes, neutrophils, macrophages, and NK cells	Chemoattractant (chemokine) for neutrophils, basophils and T-cells; activates neutrophils to degranulate.
IL-9	T cells	hematopoietic and thymopoietic effects
IL-10	activated TH_2 cells, $CD8^+$ T and B cells, macrophages	inhibits cytokine production, promotes B cell proliferation and antibody production, suppresses cellular immunity, mast cell growth
IL-11	stromal cells	synergisitc hematopoietic and thrombopoietic effects
IL-12	B cells, macrophages	proliferation of NK cells, INF-g production, promotes cell-mediated immune functions
IL-13	TH_2 cells	IL-4-like activities
IL-18	macrophages/Kupffer cells, keratinocytes, glucocorticoid-secreting adrenal cortex cells, and osteoblasts	Interferon-gamma-inducing factor with potent pro-inflammatory activity
IL-21	Activated T cells	IL21 has a role in proliferation and maturation of natural killer (NK) cell populations from bone marrow, in the proliferation of mature B-cell populations co-stimulated with anti-CD40, and in the proliferation of T cells co-stimulated with anti-CD3.

Cytokine	Principal Source	Primary Activity
IL-23	Activated dendritic cells	A complex of p19 and the p40 subunit of IL-12. IL-23 binds to IL-12R beta 1 but not IL-12R beta 2; activates Stat4 in PHA blast T cells; induces strong proliferation of mouse memory T cells; stimulates IFN-gamma production and proliferation in PHA blast T cells, as well as in CD45RO (memory) T cells.
TumorNecrosis Factor TNF-α	Primarily activated macrophages.	Once called cachectin; induces the expression of other autocrine growth factors, increases cellular responsiveness to growth factors; induces signaling pathways that lead to proliferation; induces expression of a number of nuclear proto-oncogenes as well as of several interleukins.
(TNF-β)	T-lymphocytes, particularly cytotoxic T-lymphocytes (CTL cells); induced by IL-2 and antigen-T-Cell receptor interactions.	Also called lymphotoxin; kills a number of different cell types, induces terminal differentiation in others; inhibits lipoprotein lipase present on the surface of vascular endothelial cells.
Interferons INF-a and -b	macrophages, neutrophils and some somatic cells	Known as type I interferons; antiviral effect; induction of class I MHC on all somatic cells; activation of NK cells and macrophages.
Interferon INF-γ	Primarily CD8+ T-cells, activated TH_1 and NK cells	Type II interferon; induces of class I MHC on all somatic cells, induces class II MHC on APCs and somatic cells, activates macrophages, neutrophils, NK cells, promotes cell-mediated immunity, enhances ability of cells to present antigens to T-cells; antiviral effects.
Monocyte Chemoattractant Protein-1 (MCP1)	Peripheral blood monocytes/macrophages	Attracts monocytes to sites of vascular endothelial cell injury, implicated in atherosclerosis.
Colony Stimulating Factors (CSFs)		Stimulate the proliferation of specific pluripotent stem cells of the bone marrow in adults.
Granulocyte-CSF (G-CSF)		Specific for proliferative effects on cells of the granulocyte lineage; proliferative effects on both classes of lymphoid cells.
Macrophage-CSF (M-CSF)		Specific for cells of the macrophage lineage.
Granulocyte-MacrophageCSF (GM-CSF)		Proliferative effects on cells of both the macrophage and granulocyte lineages.

Other cytokines of interest that may be produced by the invention described herein include adhesion molecules (R & D Systems, Adhesion Molecule I (1996), *at*

http://www.rndsystems.com); angiogenin (U.S. Patent No. 4,721,672; Moener et al., 226 Eur. J. Biochem. 483 (1994)); annexin V (Cookson et al., 20 Genomics 463 (1994); Grundmann et al., 85 Proc. Natl. Acad. Sci. USA 3708 (1988); U.S. Patent No. 5,767,247); caspases (U.S. Patent No. 6,214,858; Thornberry et al., 281 Science 1312 (1998)); chemokines (U.S. Patent Nos. 6,174,995; 6,143,289; Sallusto et al., 18 Annu. Rev. Immunol 593 (2000) Kunkel et al., 59 J. Leukocyte Biol. 81 (1996)); endothelin (U.S. Patent Nos. 6,242,485; 5,294,569; 5,231,166); eotaxin (U.S. Patent No. 6,271,347; Ponath et al., 97(3) J. Clin. Invest. 604-612 (1996)); Flt-3 (U.S. Patent No. 6,190,655); heregulins (U.S. Patent Nos. 6,284,535; 6,143,740; 6,136,558; 5,859,206; 5,840,525); Leptin (Leroy et al., 271(5) J. Biol. Chem. 2365 (1996); Maffei et al., 92 Proc. Natl. Acad. Sci. USA 6957 (1995); Zhang Y. et al. (1994) Nature 372: 425-432); Macrophage Stimulating Protein (MSP) (U.S. Patent Nos. 6,248,560; 6,030,949; 5,315,000); Neurotrophic Factors (U.S. Patent Nos. 6,005,081; 5,288,622); Pleiotrophin/Midkine (PTN/MK) (Pedraza et al., 117 J. Biochem. 845 (1995); Tamura et al., 3 Endocrine 21 (1995); U.S. Patent No. 5,210,026; Kadomatsu et al., 151 Biochem. Biophys. Res. Commun. 1312 (1988)); STAT proteins (U.S. Patent Nos. 6,030808; 6,030,780; Darnell et al., 277 Science 1630-1635 (1997)); Tumor Necrosis Factor Family (Cosman, 7 Blood Cell (1996); Gruss et al., 85 Blood 3378 (1995); Beutler et al., 7 Annu. Rev. Immunol. 625 (1989); Aggarwal et al., 260 J. Biol. Chem. 2345 (1985); Pennica et al., 312 Nature 724 (1984)).

Also of interest regarding cytokines are proteins or chemical moieties that interact with cytokines, such as Matrix Metalloproteinases (MMPs) (U.S. Patent No. 6,307,089; Nagase, Matrix Metalloproteinases in Zinc Metalloproteinases in Health and Disease (1996)), and Nitric Oxide Synthases (NOS) (Fukuto, 34 Adv. Pharm 1 (1995); U.S. Patent No. 5,268,465).

The present invention may also be used to affect blood proteins, a generic name for a vast group of proteins generally circulating in blood plasma, and important for regulating coagulation and clot dissolution. *See, e.g.,* Haematologic Technologies, Inc., HTI CATALOG, *at* www.haemtech.com. Table 3 introduces, in a non-limiting fashion, some of the blood proteins contemplated by the present invention.

Table 3: Blood Proteins

Protein	Principle Activity	Reference

Protein	Principle Activity	Reference
Factor V	In coagulation, this glycoprotein pro-cofactor, is converted to active cofactor, factor Va, via the serine protease α-thrombin, and less efficiently by its serine protease cofactor Xa. The prothrombinase complex rapidly converts zymogen prothrombin to the active serine protease, α-thrombin. Down regulation of prothrombinase complex occurs via inactivation of Va by activated protein C.	Mann et al., 57 ANN. REV. BIOCHEM. 915 (1988); *see also* Nesheim et al., 254 J. BIOL. CHEM. 508 (1979); Tracy et al., 60 BLOOD 59 (1982); Nesheim et al., 80 METHODS ENZYMOL. 249 (1981); Jenny et al., 84 PROC. NATL. ACAD. SCI. USA 4846 (1987).
Factor VII	Single chain glycoprotein zymogen in its native form. Proteolytic activation yields enzyme factor VIIa, which binds to integral membrane protein tissue factor, forming an enzyme complex that proteolytically converts factor X to Xa. Also known as extrinsic factor Xase complex. Conversion of VII to VIIa catalyzed by a number of proteases including thrombin, factors IXa, Xa, XIa, and XIIa. Rapid activation also occurs when VII combines with tissue factor in the presence of Ca, likely initiated by a small amount of pre-existing VIIa. Not readily inhibited by antithrombin III/heparin alone, but is inhibited when tissue factor added.	*See generally*, Broze et al., 80 METHODS ENZYMOL. 228 (1981); Bajaj et al., 256 J. BIOL. CHEM. 253 (1981); Williams et al., 264 J. BIOL. CHEM. 7536 (1989); Kisiel et al., 22 THROMBOSIS RES. 375 (1981); Seligsohn et al., 64 J. CLIN. INVEST. 1056 (1979); Lawson et al., 268 J. BIOL. CHEM. 767 (1993).
Factor IX	Zymogen factor IX , a single chain vitamin K-dependent glycoprotein, made in liver. Binds to negatively charged phospholipid surfaces. Activated by factor XIα or the factor VIIa/tissue factor/phospholipid complex. Cleavage at one site yields the intermediate IXα, subsequently converted to fully active form IXaβ by cleavage at another site. Factor IXaβ is the catalytic component of the "intrinsic factor Xase complex" (factor VIIIa/IXa/Ca^{2+}/phospholipid) that proteolytically activates factor X to factor Xa.	Thompson, 67 BLOOD, 565 (1986); Hedner et al., HEMOSTASIS AND THROMBOSIS 39-47 (R.W. Colman, J. Hirsh, V.J. Marder, E.W. Salzman ed., 2nd ed. J.P. Lippincott Co., Philadelphia) 1987; Fujikawa et al., 45 METHODS IN ENZYMOLOGY 74 (1974).

Protein	Principle Activity	Reference
Factor X	Vitamin K-dependent protein zymogen, made in liver, circulates in plasma as a two chain molecule linked by a disulfide bond. Factor Xa (activated X) serves as the enzyme component of prothrombinase complex, responsible for rapid conversion of prothrombin to thrombin.	*See* Davie et al., 48 ADV. ENZYMOL 277 (1979); Jackson, 49 ANN. REV. BIOCHEM. 765 (1980); *see also* Fujikawa et al., 11 BIOCHEM. 4882 (1972); Discipio et al., 16 BIOCHEM. 698 (1977); Discipio et al., 18 BIOCHEM. 899 (1979); Jackson et al., 7 BIOCHEM. 4506 (1968); McMullen et al., 22 BIOCHEM. 2875 (1983).
Factor XI	Liver-made glycoprotein homodimer circulates, in a non-covalent complex with high molecular weight kininogen, as a zymogen, requiring proteolytic activation to acquire serine protease activity. Conversion of factor XI to factor XIa is catalyzed by factor XIIa. XIa unique among the serine proteases, since it contains two active sites per molecule. Works in the intrinsic coagulation pathway by catalyzing conversion of factor IX to factor IXa. Complex form, factor XIa/HMWK, activates factor XII to factor XIIa and prekallikrein to kallikrein. Major inhibitor of XIa is a_1-antitrypsin and to lesser extent, antithrombin-III. Lack of factor XI procoagulant activity causes bleeding disorder: plasma thromboplastin antecedent deficiency.	Thompson et al., 60 J. CLIN. INVEST. 1376 (1977); Kurachi et al., 16 BIOCHEM. 5831 (1977); Bouma et al., 252 J. BIOL. CHEM. 6432 (1977); Wuepper, 31 FED. PROC. 624 (1972); Saito et al., 50 BLOOD 377 (1977); Fujikawa et al., 25 BIOCHEM. 2417 (1986); Kurachi et al., 19 BIOCHEM. 1330 (1980); Scott et al., 69 J. CLIN. INVEST. 844 (1982).
Factor XII (Hageman Factor)	Glycoprotein zymogen. Reciprocal activation of XII to active serine protease factor XIIa by kallikrein is central to start of intrinsic coagulation pathway. Surface bound α-XIIa activates factor XI to XIa. Secondary cleavage of α-XIIa by kallikrein yields β-XIIa, and catalyzes solution phase activation of kallikrein, factor VII and the classical complement cascade.	Schmaier et al., 18-38, and Davie, 242-267 HEMOSTASIS & THROMBOSIS (Colman et al., eds., J.B. Lippincott Co., Philadelphia, 1987).

Protein	Principle Activity	Reference
Factor XIII	Zymogenic form of glutaminyl-peptide γ-glutamyl transferase factor XIIIa (fibrinoligase, plasma transglutaminase, fibrin stabilizing factor). Made in the liver, found extracellularly in plasma and intracellularly in platelets, megakaryocytes, monocytes, placenta, uterus, liver and prostrate tissues. Circulates as a tetramer of 2 pairs of nonidentical subunits (A_2B_2). Full expression of activity is achieved only after the Ca^{2+}- and fibrin(ogen)-dependent dissociation of B subunit dimer from A_2' dimer. Last of the zymogens to become activated in the coagulation cascade, the only enzyme in this system that is not a serine protease. XIIIa stabilizes the fibrin clot by crosslinking the α and γ-chains of fibrin. Serves in cell proliferation in wound healing, tissue remodeling, atherosclerosis, and tumor growth.	*See* McDonaugh, 340-357 HEMOSTASIS & THROMBOSIS (Colman et al., eds., J.B. Lippincott Co., Philadelphia, 1987); Folk et al., 113 METHODS ENZYMOL. 364 (1985); Greenberg et al., 69 BLOOD 867 (1987). Other proteins known to be substrates for Factor XIIIa, that may be hemostatically important, include fibronectin (Iwanaga et al., 312 ANN. NY ACAD. SCI. 56 (1978)), a_2-antiplasmin (Sakata et al., 65 J. CLIN. INVEST. 290 (1980)), collagen (Mosher et al., 64 J. CLIN. INVEST. 781 (1979)), factor V (Francis et al., 261 J. BIOL. CHEM. 9787 (1986)), von Willebrand Factor (Mosher et al., 64 J. CLIN. INVEST. 781 (1979)) and thrombospondin (Bale et al., 260 J. BIOL. CHEM. 7502 (1985); Bohn, 20 MOL. CELL BIOCHEM. 67 (1978)).

Protein	Principle Activity	Reference
Fibrinogen	Plasma fibrinogen, a large glycoprotein, disulfide linked dimer made of 3 pairs of non-identical chains (Aa, Bb and g), made in liver. Aa has N-terminal peptide (fibrinopeptide A (FPA), factor XIIIa crosslinking sites, and 2 phosphorylation sites. Bb has fibrinopeptide B (FPB), 1 of 3 N-linked carbohydrate moieties, and an N-terminal pyroglutamic acid. The g chain contains the other N-linked glycos. site, and factor XIIIa cross-linking sites. Two elongated subunits $((AaBbg)_2)$ align in an antiparallel way forming a trinodular arrangement of the 6 chains. Nodes formed by disulfide rings between the 3 parallel chains. Central node (n-disulfide knot, E domain) formed by N-termini of all 6 chains held together by 11 disulfide bonds, contains the 2 IIa-sensitive sites. Release of FPA by cleavage generates Fbn I, exposing a polymerization site on Aa chain. These sites bind to regions on the D domain of Fbn to form proto-fibrils. Subsequent IIa cleavage of FPB from the Bb chain exposes additional polymerization sites, promoting lateral growth of Fbn network. Each of the 2 domains between the central node and the C-terminal nodes (domains D and E) has parallel a-helical regions of the Aa, Bb and g chains having protease- (plasmin-) sensitive sites. Another major plasmin sensitive site is in hydrophilic preturbance of a-chain from C-terminal node. Controlled plasmin degradation converts Fbg into fragments D and E.	FURLAN, *Fibrinogen*, IN HUMAN PROTEIN DATA, (Haeberli, ed., VCH Publishers, N.Y.,1995); Doolittle, in HAEMOSTASIS & THROMBOSIS, 491-513 (3rd ed., Bloom et al., eds., Churchill Livingstone, 1994); HANTGAN, et al., in HAEMOSTASIS & THROMBOSIS 269-89 (2d ed., Forbes et al., eds., Churchill Livingstone, 1991).

Protein	Principle Activity	Reference
Fibronectin	High molecular weight, adhesive, glycoprotein found in plasma and extracellular matrix in slightly different forms. Two peptide chains interconnected by 2 disulfide bonds, has 3 different types of repeating homologous sequence units. Mediates cell attachment by interacting with cell surface receptors and extracellular matrix components. Contains an Arg-Gly-Asp-Ser (RGDS) cell attachment-promoting sequence, recognized by specific cell receptors, such as those on platelets. Fibrin-fibronectin complexes stabilized by factor XIIIa-catalyzed covalent cross-linking of fibronectin to the fibrin a chain.	Skorstengaard et al., 161 Eur. J. BIOCHEM. 441 (1986); Kornblihtt et al., 4 EMBO J. 1755 (1985); Odermatt et al., 82 PNAS 6571 (1985); Hynes, R.O., ANN. REV. CELL BIOL., 1, 67 (1985); Mosher 35 ANN. REV. MED. 561 (1984); Rouslahti et al., 44 Cell 517 (1986); Hynes 48 CELL 549 (1987); Mosher 250 BIOL. CHEM. 6614 (1975).
b_2-Glycoprotein I	Also called b_2I and Apolipoprotein H. Highly glycosylated single chain protein made in liver. Five repeating mutually homologous domains consisting of approximately 60 amino acids disulfide bonded to form Short Consensus Repeats (SCR) or Sushi domains. Associated with lipoproteins, binds anionic surfaces like anionic vesicles, platelets, DNA, mitochondria, and heparin. Binding can inhibit contact activation pathway in blood coagulation. Binding to activated platelets inhibits platelet associated prothrombinase and adenylate cyclase activities. Complexes between b_2I and cardiolipin have been implicated in the anti-phospholipid related immune disorders LAC and SLE.	*See, e.g.*, Lozier et al., 81 PNAS 2640-44 (1984); Kato & Enjyoi 30 BIOCHEM. 11687-94 (1997); Wurm, 16 INT'L J. BIOCHEM. 511-15 (1984); Bendixen et al., 31 BIOCHEM. 3611-17 (1992); Steinkasserer et al., 277 BIOCHEM. J. 387-91 (1991); Nimpf et al., 884 BIOCHEM. BIOPHYS. ACTA 142-49 (1986); Kroll et.al. 434 BIOCHEM. BIOPHYS. Acta 490-501 (1986); Polz et al., 11 INT'L J. BIOCHEM. 265-73 (1976); McNeil et al., 87 PNAS 4120-24 (1990); Galli et al;. I LANCET 1544-47 (1990); Matsuuna et al., II LANCET 177-78 (1990); Pengo et al., 73 THROMBOSIS & HAEMOSTASIS 29-34 (1995).
Osteonectin	Acidic, noncollagenous glycoprotein (Mr=29,000) originally isolated from fetal and adult bovine bone matrix . May regulate bone metabolism by binding hydroxyapatite to collagen. Identical to human placental SPARC. An alpha granule component of human platelets secreted during activation. A small portion of secreted osteonectin expressed on the platelet cell surface in an activation-dependent manner	Villarreal et al., 28 BIOCHEM. 6483 (1989); Tracy et al., 29 INT'L J. BIOCHEM. 653 (1988); Romberg et al., 25 BIOCHEM. 1176 (1986); Sage & Bornstein 266 J. BIOL. CHEM. 14831 (1991); Kelm & Mann 4 J. BONE MIN. RES. 5245 (1989); Kelm et al., 80 BLOOD 3112 (1992).

Protein	Principle Activity	Reference
Plasminogen	Single chain glycoprotein zymogen with 24 disulfide bridges, no free sulfhydryls, and 5 regions of internal sequence homology, "kringles", each five triple-looped, three disulfide bridged, and homologous to kringle domains in t-PA, u-PA and prothrombin. Interaction of plasminogen with fibrin and α2-antiplasmin is mediated by lysine binding sites. Conversion of plasminogen to plasmin occurs by variety of mechanisms, including urinary type and tissue type plasminogen activators, streptokinase, staphylokinase, kallikrein, factors IXa and XIIa, but all result in hydrolysis at Arg560-Val561, yielding two chains that remain covalently associated by a disulfide bond.	*See* Robbins, 45 METHODS IN ENZYMOLOGY 257 (1976); COLLEN, 243-258 BLOOD COAG. (Zwaal et al., eds., New York, Elsevier, 1986); *see also* Castellino et al., 80 METHODS IN ENZYMOLOGY 365 (1981); Wohl et al., 27 THROMB. RES. 523 (1982); Barlow et al., 23 BIOCHEM. 2384 (1984); SOTTRUP-JENSEN ET AL., 3 PROGRESS IN CHEM. FIBRINOLYSIS & THROMBOLYSIS 197-228 (Davidson et al., eds., Raven Press, New York 1975).
tissue Plasminogen Activator	t-PA, a serine endopeptidase synthesized by endothelial cells, is the major physiologic activator of plasminogen in clots, catalyzing conversion of plasminogen to plasmin by hydrolising a specific arginine-alanine bond. Requires fibrin for this activity, unlike the kidney-produced version, urokinase-PA.	*See* Plasminogen.
Plasmin	*See* Plasminogen. Plasmin, a serine protease, cleaves fibrin, and activates and/or degrades compounds of coagulation, kinin generation, and complement systems. Inhibited by a number of plasma protease inhibitors *in vitro*. Regulation of plasmin *in vivo* occurs mainly through interaction with a_2-antiplasmin, and to a lesser extent, a_2-macroglobulin.	*See* Plasminogen.

Protein	Principle Activity	Reference
Platelet Factor-4	Low molecular weight, heparin-binding protein secreted from agonist-activated platelets as a homotetramer in complex with a high molecular weight, proteoglycan, carrier protein. Lysine-rich, COOH-terminal region interacts with cell surface expressed heparin-like glycosaminoglycans on endothelial cells, PF-4 neutralizes anticoagulant activity of heparin exerts procoagulant effect, and stimulates release of histamine from basophils. Chemotactic activity toward neutrophils and monocytes. Binding sites on the platelet surface have been identified and may be important for platelet aggregation.	Rucinski et al., 53 BLOOD 47 (1979); Kaplan et al., 53 BLOOD 604 (1979); George 76 BLOOD 859 (1990); Busch et al., 19 THROMB. RES. 129 (1980); Rao et al., 61 BLOOD 1208 (1983); Brindley, et al., 72 J CLIN. INVEST. 1218 (1983); Deuel et al., 74 PNAS 2256 (1981); Osterman et al., 107 BIOCHEM. BIOPHYS. RES. COMMUN. 130 (1982); Capitanio et al., 839 BIOCHEM. BIOPHYS. ACTA 161 (1985).
Protein C	Vitamin K-dependent zymogen, protein C, made in liver as a single chain polypeptide then converted to a disulfide linked heterodimer. Cleaving the heavy chain of human protein C converts the zymogen into the serine protease, activated protein C. Cleavage catalyzed by a complex of α-thrombin and thrombomodulin. Unlike other vitamin K dependent coagulation factors, activated protein C is an anticoagulant that catalyzes the proteolytic inactivation of factors Va and VIIIa, and contributes to the fibrinolytic response by complex formation with plasminogen activator inhibitors.	*See* Esmon, 10 PROGRESS IN THROMB. & HEMOSTS. 25 (1984); Stenflo, 10 SEMIN. IN THROMB. & HEMOSTAS. 109 (1984); Griffen et al., 60 BLOOD 261 (1982); Kisiel et al., 80 METHODS ENZYMOL. 320 (1981); Discipio et al., 18 BIOCHEM. 899 (1979).
Protein S	Single chain vitamin K-dependent protein functions in coagulation and complement cascades. Does not possess the catalytic triad. Complexes to C4b binding protein (C4BP) and to negatively charged phospholipids, concentrating C4BP at cell surfaces following injury. Unbound S serves as anticoagulant cofactor protein with activated Protein C. A single cleavage by thrombin abolishes protein S cofactor activity by removing gla domain.	Walker 10 SEMIN. THROMB. HEMOSTAS. 131 (1984); Dahlback et al., 10 SEMIN. THROMB. HEMOSTAS., 139 (1984); Walker 261 J. BIOL. CHEM. 10941 (1986).

Protein	Principle Activity	Reference
Protein Z	Vitamin K-dependent, single-chain protein made in the liver. Direct requirement for the binding of thrombin to endothelial phospholipids. Domain structure similar to that of other vitamin K-dependant zymogens like factors VII, IX, X, and protein C. N-terminal region contains carboxyglutamic acid domain enabling phospholipid membrane binding. C-terminal region lacks "typical" serine protease activation site. Cofactor for inhibition of coagulation factor Xa by serpin called protein Z-dependant protease inhibitor. Patients diagnosed with protein Z deficiency have abnormal bleeding diathesis during and after surgical events.	Sejima et al., 171 BIOCHEM. BIOPHYSICS RES. COMM. 661 (1990); Hogg et al., 266 J. BIOL. CHEM. 10953 (1991); Hogg et al., 17 BIOCHEM. BIOPHYSICS RES. COMM. 801 (1991); Han et al., 38 BIOCHEM. 11073 (1999); Kemkes-Matthes et al., 79 THROMB. RES. 49 (1995).
Prothrombin	Vitamin K-dependent, single-chain protein made in the liver. Binds to negatively charged phospholipid membranes. Contains two "kringle" structures. Mature protein circulates in plasma as a zymogen and, during coagulation, is proteolytically activated to the potent serine protease α-thrombin.	Mann et al., 45 METHODS IN ENZYMOLOGY 156 (1976); Magnusson et al., PROTEASES IN BIOLOGICAL CONTROL 123-149 (Reich et al., eds. Cold Spring Harbor Labs., New York 1975); Discipio et al., 18 BIOCHEM. 899 (1979).
α-Thrombin	See Prothrombin. During coagulation, thrombin cleaves fibrinogen to form fibrin, the terminal proteolytic step in coagulation, forming the fibrin clot. Thrombin also responsible for feedback activation of procofactors V and VIII. Activates factor XIII and platelets, functions as vasoconstrictor protein. Procoagulant activity arrested by heparin cofactor II or the antithrombin III/heparin complex, or complex formation with thrombomodulin. Formation of thrombin/thrombomodulin complex results in inability of thrombin to cleave fibrinogen and activate factors V and VIII, but increases the efficiency of thrombin for activation of the anticoagulant, protein C.	45 METHODS ENZYMOL. 156 (1976).

Protein	Principle Activity	Reference
b-Thrombo-globulin	Low molecular weight, heparin-binding, platelet-derived tetramer protein, consisting of four identical peptide chains. Lower affinity for heparin than PF-4. Chemotactic activity for human fibroblasts, other functions unknown.	*See, e.g.*, George 76 BLOOD 859 (1990); Holt & Niewiarowski 632 BIOCHIM. BIOPHYS. ACTA 284 (1980); Niewiarowski et al., 55 BLOOD 453 (1980); Varma et al., 701 BIOCHIM. BIOPHYS. ACTA 7 (1982); Senior et al., 96 J. CELL. BIOL. 382 (1983).
Thrombopoietin	Human TPO (Thrombopoietin, Mpl-ligand, MGDF) stimulates the proliferation and maturation of megakaryocytes and promotes increased circulating levels of platelets *in vivo*. Binds to c-Mpl receptor.	Horikawa et al., 90(10) BLOOD 4031-38 (1997); de Sauvage et al., 369 NATURE 533-58 (1995).
Thrombo-spondin	High-molecular weight, heparin-binding glycoprotein constituent of platelets, consisting of three, identical, disulfide-linked polypeptide chains. Binds to surface of resting and activated platelets, may effect platelet adherence and aggregation. An integral component of basement membrane in different tissues. Interacts with a variety of extracellular macromolecules including heparin, collagen, fibrinogen and fibronectin, plasminogen, plasminogen activator, and osteonectin. May modulate cell-matrix interactions.	Dawes et al., 29 THROMB. RES. 569 (1983); Switalska et al., 106 J. LAB. CLIN. MED. 690 (1985); Lawler et al. 260 J. BIOL. CHEM. 3762 (1985); Wolff et al., 261 J. BIOL. CHEM. 6840 (1986); Asch et al., 79 J. CLIN. CHEM. 1054 (1987); Jaffe et al., 295 NATURE 246 (1982); Wright et al., 33 J. HISTOCHEM. CYTOCHEM. 295 (1985); Dixit et al., 259 J. BIOL. CHEM. 10100 (1984); Mumby et al., 98 J. CELL. BIOL. 646 (1984); Lahav et al, 145 EUR. J. BIOCHEM. 151 (1984); Silverstein et al, 260 J. BIOL. CHEM. 10346 (1985); Clezardin et al. 175 EUR. J. BIOCHEM. 275 (1988); Sage & Bornstein (1991).
Von Willebrand Factor	Multimeric plasma glycoprotein made of identical subunits held together by disulfide bonds. During normal hemostasis, larger multimers of vWF cause platelet plug formation by forming a bridge between platelet glycoprotein IB and exposed collagen in the subendothelium. Also binds and transports factor VIII (antihemophilic factor) in plasma.	Hoyer 58 BLOOD 1 (1981); Ruggeri & Zimmerman 65 J. CLIN. INVEST. 1318 (1980); Hoyer & Shainoff 55 BLOOD 1056 (1980); Meyer et al., 95 J. LAB. CLIN. INVEST. 590 (1980); Santoro 21 THROMB. RES. 689 (1981); Santoro, & Cowan 2 COLLAGEN RELAT. RES. 31 (1982); Morton et al., 32 THROMB. RES. 545 (1983); Tuddenham et al., 52 BRIT. J. HAEMATOL. 259 (1982).

Additional blood proteins contemplated herein include the following human serum proteins, which may also be placed in another category of protein (such as hormone or antigen): Actin, Actinin, Amyloid Serum P, Apolipoprotein E, B2-Microglobulin, C-Reactive Protein (CRP), Cholesterylester transfer protein (CETP), Complement C3B, Ceruplasmin, Creatine Kinase, Cystatin, Cytokeratin 8, Cytokeratin 14, Cytokeratin 18, Cytokeratin 19, Cytokeratin 20, Desmin, Desmocollin 3, FAS (CD95), Fatty Acid Binding Protein, Ferritin,

Filamin, Glial Filament Acidic Protein, Glycogen Phosphorylase Isoenzyme BB (GPBB), Haptoglobulin, Human Myoglobin, Myelin Basic Protein, Neurofilament, Placental Lactogen, Human SHBG, Human Thyroid Peroxidase, Receptor Associated Protein, Human Cardiac Troponin C, Human Cardiac Troponin I, Human Cardiac Troponin T, Human Skeletal Troponin I, Human Skeletal Troponin T, Vimentin, Vinculin, Transferrin Receptor, Prealbumin, Albumin, Alpha-1-Acid Glycoprotein, Alpha-1-Antichymotrypsin, Alpha-1-Antitrypsin, Alpha-Fetoprotein, Alpha-1-Microglobulin, Beta-2-microglobulin, C-Reactive Protein, Haptoglobulin, Myoglobulin, Prealbumin, PSA, Prostatic Acid Phosphatase, Retinol Binding Protein, Thyroglobulin, Thyroid Microsomal Antigen, Thyroxine Binding Globulin, Transferrin , Troponin I, Troponin T, Prostatic Acid Phosphatase, Retinol Binding Globulin (RBP). All of these proteins, and sources thereof, are known in the art. Many of these proteins are available commercially from, for example, Research Diagnostics, Inc. (Flanders, N.J.).

The target in the present invention may also incorporate or target neurotransmitters, or functional portions thereof. Neurotransmitters are chemicals made by neurons and used by them to transmit signals to the other neurons or non-neuronal cells (e.g., skeletal muscle; myocardium, pineal glandular cells) that they innervate. Neurotransmitters produce their effects by being released into synapses when their neuron of origin fires (i.e., becomes depolarized) and then attaching to receptors in the membrane of the post-synaptic cells. This causes changes in the fluxes of particular ions across that membrane, making cells more likely to become depolarized, if the neurotransmitter happens to be excitatory, or less likely if it is inhibitory. Neurotransmitters can also produce their effects by modulating the production of other signal-transducing molecules ("second messengers") in the post-synaptic cells. *See generally* COOPER, BLOOM & ROTH, THE BIOCHEMICAL BASIS OF NEUROPHARMACOLOGY (7th Ed. Oxford Univ. Press, NYC, 1996); http://web.indstate.edu/thcme/mwking/nerves. Neurotransmitters contemplated in the present invention include, but are not limited to, Acetylcholine, Serotonin, γ-aminobutyrate (GABA), Glutamate, Aspartate, Glycine, Histamine, Epinephrine, Norepinephrine, Dopamine, Adenosine, ATP, Nitric oxide, and any of the peptide neurotransmitters such as those derived from pre-opiomelanocortin (POMC), as well as antagonists and agonists of any of the foregoing.

Numerous other proteins or peptides may serve as either targets, or as a source of target-binding moieties as described herein. Table 4 presents a non-limiting list and description of some pharmacologically active peptides that may serve as, or serve as a source of a functional derivative of, the target of the present invention.

Table 4: Pharmacologically active peptides

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
c-Mpl (linear)	TPO-mimetic	Cwirla et al., 276 SCIENCE 1696-9 (1997); U.S. Pat. No. 5,869,451, issued Feb. 9,1999; U.S. Pat. No. 5,932,946, issued Aug. 3,1999.
c-Mpl (C-terminally cross-linked dimer)	TPO-mimetic	Cwirla et al., 276 SCIENCE 1696-9 (1997).
(disulfide-linked dimer)	stimulation of hematopoesis ("G-CSF-mimetic")	Paukovits et al., 364 HOPPE-SEYLERS Z. PHYSIOL. CHEM. 30311 (1984); Laerumgal., 16 EXP. HEMAT. 274-80 (1988).
(alkylene-linked dimer)	G-CSF-mimetic	Batnagar et al., 39 J. MED. CHEM. 38149 (1996); Cuthbertson et al., 40 J. MED. CHEM. 2876-82 (1997); King et al., 19 EXP. HEMATOL. 481 (1991); King et al., 86(Suppl. 1) BLOOD 309 (1995).
IL-1 receptor (linear)	inflammatory and autoimmune diseases ("IL-1 antagonist" or "IL-1 ra-mimetic")	U.S. Pat. No. 5,608,035; U.S. Pat. No. 5,786,331; U.S Pat. No. 5,880,096; Yanofsky et al., 93 PNAS 7381-6 (1996); Akeson et al., 271 J. BIOL. CHEM. 30517-23 (1996); Wiekzorek et al., 49 POL. J. PHARMACOL. 107-17 (1997); Yanofsky, 93 PNAS 7381-7386 (1996).
Facteur thymique (linear)	stimulation of lymphocytes (FTS-mimetic)	Inagaki-Ohara et al., 171 CELLULAR IMMUNOL. 30-40 (1996); Yoshida, 6 J. IMMUNOPHARMACOL 141-6 (1984).
CTLA4 MAb (intrapeptide di-sulfide bonded)	CTLA4-mimetic	Fukumoto et al., 16 NATURE BIOTECH. 267-70 (1998).
TNF-a receptor (exo-cyclic)	TNF-a antagonist	Takasaki et al., 15 NATURE BIOTECH. 1266-70 (1997); WO 98/53842, published December 3, 1998.
TNF-a receptor (linear)	TNF-a antagonist	Chirinos-Rojas, J. IMM., 5621-26.
C3b (intrapeptide di-sulfide bonded)	inhibition of complement activation; autoimmune diseases (C3b antagonist)	Sahu et al., 157 IMMUNOL. 884-91 (1996); Morikis et al., 7 PROTEIN SCI. 619-27 (1998).
vinculin (linear)	cell adhesion processes, cell growth, differentiation wound healing, tumor metastasis ("vinculin binding")	Adey et al., 324 BIOCHEM. J. 523-8 (1997).
C4 binding protein (C413P) (linear)	anti-thrombotic	Linse et al. 272 BIOL. CHEM. 14658-65 (1997).

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
urokinase receptor (linear)	processes associated with urokinase interaction with its receptor (e.g. angiogenesis, tumor cell invasion and metastasis; (URK antagonist)	Goodson et al., 91 PNAS 7129-33 (1994); International patent application WO 97/35969, published October 2, 1997.
Mdm2, Hdm2 (linear)	Inhibition of inactivation of p53 mediated by Mdm2 or hdm2; anti-tumor ("Mdm/hdm antagonist")	Picksley et al., 9 ONCOGENE 2523-9 (1994); Bottger et al. 269 J. MOL. BIOL. 744-56 (1997); Bottger et al., 13 ONCOGENE 13: 2141-7 (1996).
$p21^{WAF1}$ (linear)	anti-tumor by mimicking the activity of $p21^{WAF1}$	Ball et al., 7 CURR. BIOL. 71-80 (1997).
farnesyl transferase (linear)	anti-cancer by preventing activation of ras oncogene	Gibbs et al., 77 CELL 175-178 (1994).
Ras effector domain (linear)	anti-cancer by inhibiting biological function of the ras oncogene	Moodie et at., 10 TRENDS GENEL 44-48 (1994); Rodriguez et al., 370 NATURE 527-532 (1994).
SH2/SH3 domains (linear)	anti-cancer by inhibiting tumor growth with activated tyrosine kinases	Pawson et al, 3 CURR. BIOL. 434-432 (1993); Yu et al., 76 CELL 933-945 (1994).
$p16^{INK4}$ (linear)	anti-cancer by mimicking activity of p16; e.g., inhibiting cyclin D-Cdk complex ("p,16-mimetic")	Fahraeus et al., 6 CURR. BIOL. 84-91 (1996).
Src, Lyn (linear)	inhibition of Mast cell activation, IgE-related conditions, type I hypersensitivity ("Mast cell antagonist").	Stauffer et al., 36 BIOCHEM. 9388-94 (1997).
Mast cell protease (linear)	treatment of inflammatory disorders mediated by release of tryptase-6 ("Mast cell protease inhibitors")	International patent application WO 98/33812, published August 6, 1998.
SH3 domains (linear)	treatment of SH3-mediated disease states ("SH3 antagonist")	Rickles et al., 13 EMBO J. 5598-5604 (1994); Sparks et al., 269 J. BIOL. CHEM. 238536 (1994); Sparks et al., 93 PNAS 1540-44 (1996).
HBV core antigen (HBcAg) (linear)	treatment of HBV viral antigen (HBcAg) infections ("anti-HBV")	Dyson & Muray, PNAS 2194-98 (1995).
selectins (linear)	neutrophil adhesion inflammatory diseases ("selectin antagonist")	Martens et al., 270 J. BIOL. CHEM. 21129-36 (1995); European Pat. App. EP 0 714 912, published June 5, 1996.

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
calmodulin (linear, cyclized)	calmodulin antagonist	Pierce et al., 1 MOLEC. DIVEMILY 25965 (1995); Dedman et al., 267 J. BIOL. CHEM. 23025-30 (1993); Adey & Kay, 169 GENE 133-34 (1996).
integrins (linear, cyclized)	tumor-homing; treatment for conditions related to integrin-mediated cellular events, including platelet aggregation, thrombosis, wound healing, osteoporosis, tissue repair, angiogenesis (e.g., for treatment of cancer) and tumor invasion ("integrin-binding")	International patent applications WO 95/14714, published June 1, 1995; WO 97/08203, published March 6,1997; WO 98/10795, published March 19,1998; WO 99/24462, published May 20, 1999; Kraft et al., 274 J. BIOL. CHEM. 1979-85 (1999).
fibronectin and extracellular matrix components of T-cells and macrophages (cyclic, linear)	treatment of inflammatory and autoimmune conditions	International patent application WO 98/09985, published March 12, 1998.
somatostatin and cortistatin (linear)	treatment or prevention of hormone-producing tumors, acromegaly, giantism, dementia, gastric ulcer, tumor growth, inhibition of hormone secretion, modulation of sleep or neural activity	European patent application EP 0 911 393, published Apr. 28, 1999.
bacterial lipopoly-saccharide (linear)	antibiotic; septic shock; disorders modulatable by CAP37	U.S. Pat. No. 5,877,151, issued March 2, 1999.
parclaxin, mellitin (linear or cyclic)	antipathogenic	International patent application WO 97/31019, published 28 August 1997.
VIP (linear, cyclic)	impotence, neuro-degenerative disorders	International patent application WO 97/40070, published October 30, 1997.
CTLs (linear)	cancer	European patent application EP 0 770 624, published May 2,1997.
THF-gamma2 (linear)		Burnstein, 27 BIOCHEM. 4066-71 (1988).
Amylin (linear)		Cooper, 84 PNAS 8628-32 (1987).
Adreno-medullin (linear)		Kitamura, 192 BBRC 553-60 (1993).
VEGF (cyclic, linear)	anti-angiogenic; cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis ("VEGF antagonist")	Fairbrother, 37 BIOCHEM. 17754-64 (1998).

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
MMP (cyclic)	inflammation and autoimmune disorders; tumor growth ("MMP inhibitor")	Koivunen, 17 NATURE BIOTECH. 768-74 (1999).
HGH fragment (linear)		U.S. Pat. No. 5,869,452, issued Feb. 9, 1999.
Echistatin	inhibition of platelet aggregation	Gan, 263 J. BIOL. 19827-32 (1988).
SLE autoantibody (linear)	SLE	International patent application WO 96/30057, published Oct. 3, 1996.
GD1 alpha	suppression of tumor metastasis	Ishikawa et al., 1 FEBS LETT. 20-4 (1998).
anti-phospholipid β-2 glycoprotein-1 (β2GPI) antibodies	endothelial cell activation, anti-phospholipid syndrome (APS), thromboembolic phenomena, thrombocytopenia, and recurrent fetal loss	Blank Mal., 96 PNAS 5164-8 (1999).
T-Cell Receptor β chain (linear)	diabetes	International patent application WO 96/101214, published Apr. 18, 1996.
Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
EPO receptor (intrapeptide disulfide-bonded)	EPO mimetic	Wrighton et al. (1996), Science 273: 458-63; U.S. Pat. No. 5,773,569, issued June 30, 1998 to Wrighton et al.
EPO receptor (C-terminally cross-linked dimer)	EPO mimetic	Livnah et al. (1996), Science 273: 464-71; Wrighton et al. (1997), Nature Biotechnology 15:1261-5; int'l patent application WO 96/40772, published Dec. 19,1996
EPO receptor (linear)	EPO mimetic	Naranda et al., 96 PNAS 7569-74 (1999)
c-Mpl (linear)	TPO-mimetic	Cwirla et al.(1997) Science 276:1696-9; U.S. Pat. No. 5,869,451, issued Feb. 9,1999; U.S. Pat. No. 5,932,946, issued Aug. 3,1999
c-Mpl (C-terminally cross-linked dimer)	TPO-mimetic	Cwirla et al. (1997) Science 276:1696-9
(disulfide-linked dimer)	stimulation of hematopoesis ("G-CSF-mimetic")	Paukovits et al. (1984), Hoppe-Seylers Z. Physiol. Chem. 365: 30311; Laerum gal. (1988), Exp. Hemat. 16:274-80
(alkylene-linked dimer)	G-CSF-mimetic	Batnagar 91-al. (1996), linked dimer J. Med. Chem. 39:38149; Cuthbertson et al. (1997), J. Med. Chem. 40: 2876-82; King et al. (1991), Exp. Hematol. 19:481; King et al. (1995), Blood 86 (Suppl. 1): 309

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
IL-1 receptor (linear)	inflammatory and autoimmune diseases ("IL-1 antagonist" or "IL-1 ra-mimetic")	U.S. Pat. No. 5,608,035; U.S. Pat. No. 5,786,331; U.S-Pat. No. 5,880,096; Yanofsky 91-al. (1996) PNAS 93:7381-6; Akeson et al. (1996), J. Biol. Chem. 271: 30517-23; Wiekzorek et al. (1997), Pol. J. Pharmacol. 49:107-17; Yanofsky (1996), PNAs, 93:7381-7386.
Facteur thyrnique (linear)	stimulation of lymphocytes (FTS-mimetic)	Inagaki-Ohara et al. (1996), Cellular Immunol. 171: 30-40; Yoshida (1984), J. Immunopharmacol, 6:141-6.
CTLA4 MAb (intrapeptide di-sulfide bonded)	CTLA4-mimetic	Fukumoto et al. (1998), Nature Biotech. 16:267-70
TNF-a receptor (exo-cyclic)	TNF-a antagonist	Takasaki et al. (1997), Nature Biotech. 15:1266-70; WO 98/53842, published December 3, 1998.
TNF-a receptor (linear)	TNF-a antagonist	Chirinos-Rojas J. Imm., 5621-26.
C3b (intrapeptide di-sulfide bonded)	inhibition of complement activation; autoimmune diseases (C3b antagonist)	Sahu et al. (1996), Immunol. 157:884-91; Morikis et al. (1998), Protein Sci. 7:619-27.
vinculin (linear)	cell adhesion processes, cell growth, differentiation wound healing, tumor metastasis ("vinculin binding")	Adey et al. (1997), Biochem. J. 324:523-8
C4 binding protein (C413P) (linear)	anti-thrombotic	Linse et al. 272 Biol. Chem. 14658-65 (1997)
urokinase receptor (linear)	processes associated with urokinase interaction with its receptor (e.g. angiogenesis, tumor cell invasion and metastasis; (URK antagonist)	Goodson et al. (1994), 91 PNAS 7129-33; International application WO 97/35969, published October 2, 1997
Mdm2, Hdm2 (linear)	Inhibition of inactivation of p53 mediated by Mdm2 or hdm2; anti-tumor ("Mdm/hdm antagonist")	Picksley et al. (1994), Oncogene 9: 2523-9; Bottger et al. (1997) J. Mol. Biol. 269: 744-56; Bottger et al. (1996), Oncogene 13: 2141-7
$p21^{WAF1}$ (linear)	anti-tumor by mimicking the activity of $p21^{WAF1}$	Ball et al.(1997), Curr. Biol. 7: 71-80.
farnesyl transferase (linear)	anti-cancer by preventing activation of ras oncogene	Gibbs et al. (1994), Cell 77:175-178
Ras effector domain (linear)	anti-cancer by inhibiting biological function of the ras oncogene	Moodie et at. (1994), Trends Genel 10:44-48 Rodriguez et al. (1994), Nature 370:527-532 .
SH2/SH3 domains (linear)	anti-cancer by inhibiting tumor growth with activated tyrosine kinases	Pawson et al (1993), Curr. Biol. 3:434-432, Yu et al. (1994), Cell 76:933-945.

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
$p16^{INK4}$ (linear)	anti-cancer by mimicking activity of p16; e.g., inhibiting cyclin D-Cdk complex ("p,16-mimetic")	Fahraeus et al. (1996), Curr. Biol. 6:84-91
Src, Lyn (linear)	inhibition of Mast cell activation, IgE-related conditions, type I hypersensitivity ("Mast cell antagonist").	Stauffer et al. (1997), Biochem. 36: 9388-94.
Mast cell protease (linear)	treatment of inflammatory disorders mediated by release of tryptase-6 ("Mast cell protease inhibitors")	International application WO 98/33812, published August 6, 1998
SH3 domains (linear)	treatment of SH3-mediated disease states ("SH3 antagonist")	Rickles et al. (1994), EMBO J. 13:5598-5604;Sparks aLal. (1994), J. Biol. Chem. 269: 238536; Sparks et al. (1996), PNAS 93:1540-44.
HBV core antigen (HBcAg) (linear)	treatment of HBV viral antigen (HBcAg) infections ("anti-HBV")	Dyson & Muray (1995), Proc. NatI. Acad. Sci. 92:2194-98.
selectins (linear)	neutrophil adhesion inflammatory diseases ("selectin antagonist")	Martens et al. (1995), J. Biol. Chem. 270: 21129-36; European pat. app.EP 0 714 912, published June 5, 1996
calmodulin (linear, cyclized)	calmodulin antagonist	Pierce et al. (1995), Molec. Divemily 1: 25965; Dedman et al. (1993), J. Biol. Chem. 268: 23025-30; Adey & Kay (1996), Gene 169:133-34.
integrins (linear, cyclized)	tumor-homing; treatment for conditions related to integrin-mediated cellular events, including platelet aggregation, thrombosis, wound healing, osteoporosis, tissue repair, angiogenesis (e.g., for treatment of cancer) and tumor invasion ("integrin-binding")	International applications WO 95/14714, published June 1, 1995; WO 97/08203, published March 6,1997; WO 98/10795, published March 19,1998; WO 99/24462, published May 20, 1999; Kraft et al. (1999), J. Biol. Chem. 274:1979-85.
fibronectin and extracellular matrix components of T-cells and macrophages (cyclic, linear)	treatment of inflammatory and autoimmune conditions	WO 98/09985, published March 12, 1998.

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
somatostatin and cortistatin (linear)	treatment or prevention of hormone-producing tumors, acromegaly, giantism, dementia, gastric ulcer, tumor growth, inhibition of hormone secretion, modulation of sleep or neural activity	European patent application 0 911 393, published Apr. 28, 1999.
bacterial lipopoly-saccharide (linear)	antibiotic; septic shock; disorders modulatable by CAP37	U.S. Pat. No. 5,877,151, issued March 2,1999.
parclaxin, mellitin (linear or cyclic)	antipathogenic	WO 97/31019, published 28 August 1997.
VIP (linear, cyclic)	impotence, neuro-degenerative disorders	WO 97/40070, published October 30, 1997.
CTLs (linear)	cancer	EP 0 770 624, published May 2,1997.
THF-gamma2 (linear)		Burnstein (1988), Biochem., 27:4066-71
Amylin (linear)		Cooper (1987), PNAS 84:8628-32.
Adreno-medullin (linear)		Kitamura (1993), BBRC, 192:553-60
VEGF (cyclic, linear)	anti-angiogenic; cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis ("VEGF antagonist")	Fairbrother (1998), Biochem., 37:17754-64.
MMP (cyclic)	inflammation and autoimmune disorders; tumor growth ("MMP inhibitor")	Koivunen 17 Nature Biotech., 768-74 (1999).
HGH fragment (linear)		U.S. Pat. No. 5,869,452.
Echistatin	inhibition of platelet aggregation	Gan (1988), J. Biol. 263:19827-32.
SLE autoantibody (linear)	SLE	WO 96/30057, published Oct. 3, 1996.
GD1 alpha	suppression of tumor metastasis	Ishikawa et al., 1 FEBS Lett. 20-4 (1998).
anti-phospholipid β-2 glycoprotein-1 (β2GPI) antibodies	endothelial cell activation, anti-phospholipid syndrome (APS), thromboembolic phenomena, thrombocytopenia, and recurrent fetal loss	Blank Mal. (1999), PNAS 96: 5164-8.
T-Cell Receptor β chain (linear)	diabetes	WO 96/101214, published Apr. 18, 1996.

Peptides

Any number of peptides may be used in conjunction with the present invention. Of particular interest are peptides that mimic the activity of EPO, TPO, growth hormone, G-CSF, GM-CSF, IL-1ra, leptin, CTLA4, TRAIL, TGF-α, and TGF-β. Peptide antagonists are also of interest, particularly those antagonistic to the activity of TNF, leptin, any of the interleukins (IL-1 – IL-23, etc.), and proteins involved in complement activation (e.g., C3b). Targeting peptides are also of interest, including tumor-homing peptides, membrane-transporting peptides, and the like. All of these classes of peptides may be discovered by methods described in the references cited in this specification and other references.

A particularly preferred group of peptides are those that bind to cytokine receptors. Cytokines have recently been classified according to their receptor code. See Inglot (1997), Archivum Immunologiae e Therapiae Experimentalis 45: 353-7, which is hereby incorporated entirely by reference.

Non-limiting examples of suitable peptides for this invention appear in Tables 5 through 21 below. These peptides may be prepared by methods disclosed and/or known in the art. Single letter amino acid abbreviations are used in most cases. The X in these sequences (and throughout this specification, unless specified otherwise in a particular instance) means that any of the 20 naturally occurring amino acid residues or know derivatives thereof may be present, or any know modified amino acid thereof. Any of these peptides may be linked in tandem (i.e., sequentially), with or without linkers, and a few tandemlinked examples are provided in the table. Linkers are listed as "Δ" and may be any of the linkers described herein. Tandem repeats and linkers are shown separated by dashes for clarity. Any peptide containing a cysteinyl residue may optionally be cross-linked with another Cys-containing peptide, either or both of which may be linked to a vehicle. A few crosslinked examples are provided in the table. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well; see, for example, EPO-mimetic peptides in Table 5. A few examples of intrapeptide disulfide-bonded peptides are specified in the table. Any of these peptides may be derivatized as described herein, and a few derivatized examples are provided in the table. For derivatives in which the carboxyl terminus may be capped with an amino group, the capping amino group is shown as $-NH_2$. For derivatives in which amino acid residues are substituted by moieties other than amino acid residues, the substitutions are denoted by a δ, which signifies any of the moieties known in the art,

e.g., as described in Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9 and Cuthbertson et al. (1997), J. Med. Chem. 40:2876-82, which are entirely incorporated by reference. The J substituent and the Z substituents (Z_5, Z_6, ... Z_{40}) are as defined in U.S. Pat. Nos. 5,608,035, 5,786,331, and 5,880,096, which are entirely incorporated herein by reference. For the EPO-mimetic sequences (Table 5), the substituents X_2 through X_{11} and the integer "n" are as defined in WO 96/40772, which is entirely incorporated by reference. The substituents "Ψ" "Θ," and "+" are as defined in Sparks et al. (1996), Proc. Natl. Acad. Sci. 93: 1540-4, which is entirely incorporated by reference. X4, X5, X6, and X7 are as defined in U.S. Pat. No. 5,773,569, which is hereby entirely incorporated by reference, except that: for integrin-binding peptides, X1, X2, X3, X4, X5, X6, X7, and X8 (Table 10), are as defined in PCT applications WO 95/14714, published June 1, 1995 and WO 97/08203, published March 6,1997, which are also entirely incorporated by reference; and for VIP-mimetic peptides (Table 13), X_1, X_1', X_1'', X_2, X_3, X_4, X_5, X_6, and Z; and the integers m and n are as defined in WO 97/40070, published October 30,1997, which is also entirely incorporated herein by reference. Xaa and Yaa below are as defined in WO 98/09985, published March 12,1998, which is entirely incorporated herein by reference. AA_1, AA_2, AB_1, AB_2, and AC are as defined in International application WO 98/53842, published December 3, 1998, which is entirely incorporated by reference. X^1, X^2, X^3, and X^4 in Table 18 only are as, defined in European application EP 0 911 393, published April 28,1999, entirely incorporated herein by reference. Residues appearing in boldface are D-amino acids, but can be optionally L-amino acids. All peptides are linked through peptide bonds unless otherwise noted. Abbreviations are listed at the end of this specification. In the "SEQ ID NO." column, "NR" means that no sequence listing is required for the given sequence.

Table 5-EPO-mimetic peptide sequences

Sequence/structure:	SEQ ID NO:
YXCXXGPXTWXCXP	1
YXCXXGPXTWXCXP-YXCXXGPXTWXCXP	2
YXCXXGPXTWXCXP-A-YXCXXGPXTWXCXP	3

YXCXXGPXTWXCXP-Δ–ε–amine)

4

\

K

/

YXCXXGPXTWXCXP-Δ– (α-amine)

4

GGTYSCHFGPLTWVCKPQGG

5

GGDYHCRMGPLTWVCKPLGG

6

GGVYACRMGPITWVCSPLGG

7

VGNYMCHFGPITWVCRPGGG

8

GGLYLCRFGPVTWDCGYKGG

9

GGTYSCHFGPLTWVCKPQGG-

10

GGTYSCHFGPLTWVCKPQGG -Δ-GGTYSCHFGPLTWVCKPQGG

11

GGTYSCHFGPLTWVCKPQGGSSK

12

GGTYSCHFGPLTWVCKPQGGSSK

13

GGTYSCHFGPLTWVCKPQGGSSK

14

GGTYSCHFGPLTWVCKPQGGSSK-Δ-GGTYSCHFGPLTWVCKPQGGSSK

GGTYSCHFGPLTWVCKPQGGSS -Δ–ε–amine)

\

K

/

GGTYSCHFGPLTWVCKPQGGSS-Δ– (α-amine)

15

GGTYSCHFGPLTWVCKPQGGSSK(-Δ-biotin)

16

$CX_4X_5GPX_6TWX_7C$

17

GGTYSCHGPLTWVCKPQGG

18

VGNYMAHMGPITWVCRPGG

19

GGPHHVYACRMGPLTWIC

20

GGTYSCHFGPLTWVCKPQ

21

GGLYACHMGPMTWVCQPLRG

22

TIAQYICYMGPETWECRPSPKA

23

YSCHFGPLTWVCK

24

YCHFGPLTWVC

25

$X_3X_4X_5GPX_6TWX_7X_8$

26

$YX_2X_3X_4X_5GPX_6TWX_7X_8$

27

$X_1YX_2X_3X_4X_5GPX_6X_7X_8X_9X_{10}X_{11}$

28

$X_1YX_2CX_4X_5GPX_6TWX_7CX_9X_{10}X_{11}$

29

GGLYLCRFGPVTWDCGYKGG

30

GGTYSCHFGPLTWVCKPQGG

31

GGDYHCRMGPLTWVCKPLGG

32

VGNYMCHFGPITWVCRPGGG

33

GGVYACRMGPITWVCSPLGG

34

VGNYMAHMGPITWVCRPGG

35

GGTYSCHFGPLTWVCKPQ

36

GGLYACHMGPMTWVCQPLRG

37

TIAQYICYMGPETWECRPSPKA

38

YSCHFGPLTWVCK

39

YCHFGPLTWVC

40

SCHFGPLTWVCK

41

$(AX_2)_nX_3X_4X_5GPX_6TWX_7X_8$

42

Table 6-IL-1 antagonist peptide sequences

SEQUENCE/STRUCTURE	SEQ ID NO:
$Z_{11}Z_7Z_8ZQZ_5YZ_6Z_9Z_{10}$	43
$XXQZ_5YZ_6XX$	44
$Z_7XQZ_5YZ_6XX$	45
$Z_7Z_8QZ_5YZ_6Z_9Z_{10}$	46
$Z_{11}Z_7Z_8QZ_5YZ_6Z_9Z_{10}$	47

$Z_{12}Z_{13}Z_{14}Z_{15}Z_{16}Z_{17}Z_{18}Z_{19}Z_{20}Z_{21}Z_{22}Z_{11}Z_7Z_8QZ_5YZ_6Z_9Z_{10}L$

48

$Z_{23}NZ_{24}Z_{39}Z_{25}Z_{26}Z_{27}Z_{28}Z_{29}Z_{30}Z_{40}$

49

TANVSSFEWTPYYWQPYALPL

50

SWTDYGYWQPYALPISGL

51

ETPFTWEESNAYYWQPYALPL

52

ENTYSPNWADSMYWQPYALPL

53

SVGEDHNFWTSEYWQPYALPL

54

DGYDRWRQSGERYWQPYALPL

55

FEWTPGYWQPY

56

FEWTPGYWQHY

57

FEWTPGWYQJY

58

AcFEWTPGWYQJY

59

FEVffPGWpYQJY

60

FAWTPGYWQJY

61

FEWAPGYWQJY

62

FEWVPGYWQJY

63

FEWTPGYWQJY

64

AcFEWTPGYWQJY

65

FEWTPaWYQJY

66

FEWTPSarWYQJY

67

FEWTPGYYQPY

68

FEWTPGWWQPY

69

FEWTPNYWQPY

70

FEVff PvYWQJY

71

FEWTPecGYWQJY

72

FEWTPAibYWQJY

73

FEVffSarGYWQJY

74

FEWTPGYWQPY

75

FEWTPGYWQHY

76

FEWTPGWYQJY

77

AcFEWTPGWYQJY

78

FEWTPGW-pY-QJY

79

FAWTPGYWQJY

80

FEWAPGYWQJY

81

FEWVPGYWQJY

82

FEWTPGYWQJY

83

AcFEWTPGYWQJY

84

FEWTPAWYQJY

85

FEWTPSarWYQJY

86

FEWTPGYYQPY

87

FEWTPGWWQPY

88

FEWTPNYWQPY

89

FEWTPVYWQJY

90

FEWTPecGYWQJY

91

FEWTPAibYWQJY

92

FEWTSarGYWQJY

93

FEWTPGYWQPYALPL

94

NapEWTPGYYQJY

95

YEWTPGYYQJY

96

FEWVPGYYQJY

97

FEWTPSYYQJY

99

FEWTPNYYQJY

99

TKPR

100

RKSSK

101

RKQDK

102

NRKQDK

103

RKQDKR

104

ENRKQDKRF

105

VTKFYF

106

VTKFY

107

VTDFY

108

SHLYWQPYSVQ

109

TLVYWQPYSLQT

110

RGDYWQPYSVQS

111

VHVYWQPYSVQT

112

RLVYWQPYSVQT

113

SRVWFQPYSLQS

114

NMVYWQPYSIQT

115

SVVFWQPYSVQT

116

TFVYWQPYALPL

117

TLVYWQPYSIQR

118

RLVYWQPYSVQR

119

SPVFWQPYSIQI

120

WIEWWQPYSVQS

121

SLIYWQPYSLQM

122

TRLYWQPYSVQR

123

RCDYWQPYSVQT

124

MRVFWQPYSVQN

125

KIVYWQPYSVQT

126

RHLYWQPYSVQR

127

ALVWWQPYSEQI

128

SRVWFQPYSLQS

129

WEQPYALPLE

130

QLVWWQPYSVQR

131

DLRYWQPYSVQV

132

ELVWWQPYSLQL

133

DLVWWQPYSVQW

134

NGNYWQPYSFQV

135

ELVYWQPYSIQR

136

ELMY)AIQPYSVQE

137

NLLYWQPYSMQD

138

GYEWYQPYSVQR

139

SRVWYQPYSVQR

140

LSEQYQPYSVQR

141

GGGWWQPYSVQR

142

VGRWYQPYSVQR

143

VHVYWQPYSVQR

144

QARWYQPYSVQR

145

VHVYWQPYSVQT

146

RSVYWQPYSVQR

147

TRVWFQPYSVQR

148

GRIWFQPYSVQR

149

GRVWFQPYSVQR

150

ARTWYQPYSVQR

151

ARVWWQPYSVQM

152

RLMFYQPYSVQR

153

ESMWYQPYSVQR

154

HFGWWQPYSVHM

155

ARFWWQPYSVQR

156

RLVYWQPYAPIY

157

RLVYWQPYSYQT

158

RLVYWQPYSLPI

159

RLVYWQPYSVQA

160

SRVWYQPYAKGL

161

SRVWYQPYAQGL

162

SRVWYQPYAMPL

163

SRVWYQPYSVQA

164

SRVWYQPYSLGL

165

SRVWYQPYAREL

166

SRVWYQPYSRQP

167

SRVWYQPYFVQP

168

EYEWYQPYALPL

169

IPEYWQPYALPL

170

SRIWWQPYALPL

171

DPLFWQPYALPL

172

SRQWVQPYALPL

173

IRSWWQPYALPL

174

RGYWQPYALPL

175

RLLWVQPYALPL

176

EYRWFQPYALPL

177

DAYWVQPYALPL

178

WSGYFQPYALPL

179

NIEFWQPYALPL

180

TRDWVQPYALPL

181

DSSWYQPYALPL

182

IGNWYQPYALPL

183

NLRWDQPYALPL

184

LPEFWQPYALPL

185

DSYWWQPYALPL

186

RSQYYQPYALPL

187

ARFWLQPYALPL

188

NSYFWQPYALPL

189

RFMYWQPYSVQR

190

AHLFWQPYSVQR

191

WWQPYALPL

192

YYQPYALPL

193

YFQPYALGL

194

YWYQPYALPL

195

RWWQPYATPL

196

GWYQPYALGF

197

YWYQPYALGL

198

IWYQPYAMPL

199

SNMQPYQRLS

200

TFVYWQPYAVGLPAAETACN

201

TFVYWQPYSVQMTITGKVTM

202

TFVYWQPYSSHXXVPXGFPL

203

TFVYWQPYYGNPQWAIHVRH

204

TFVYWQPYVLLELPEGAVRA

205

TFVYWQPYVDYVWPIPIAQV

206

GWYQPYVDGWR

207

RWEQPYVKDGWS

208

EWYQPYALGWAR

209

GWWQPYARGL

210

LFEQPYAKALGL

211

GWEQPYARGLAG

212

AWVQPYATPLDE

213

MWYQPYSSQPAE

214

GWTQPYSQQGEV

215

DWFQPYSIQSDE

216

PWIQPYARGFG

217

RPLYWQPYSVQV

218

TLIYWQPYSVQI

219

RFDYWQPYSDQT

220

WHQFVQPYALPL

221

EWDSVYWQPYSVQTLLR

223

WEQNVYWQPYSVQSFAD

224

SDVVYWQPYSVQSLEM

225

YYDGVYWQPYSVQVMPA

226

SDIWYQPYALPL

227

QRIWWQPYALPL

228

SRIWWQPYALPL

229

RSLYWQPYALPL

230

TIIWEQPYALPL

231

WETWYQPYALPL

232

SYDWEQPYALPL

233

SRIWCQPYALPL

234

EIMFWQPYALPL

235

DYVWQQPYALPL

236

MDLLVQWYQPYALPL

237

GSKVILWYQPYALPL

238

RQGANIWYQPYALPL

239

GGGDEPWYQPYALPL

240

SQLERTWYQPYALPL

241

ETWVREWYQPYALPL

242

KKGSTQWYQPYALPL

243

LQARMNWYQPYALPL

244

EPRSQKWYQPYALPL

245

VKQKWRWYQPYALPL

246

LRRHDVWYQPYALPL

247

RSTASIWYQPYALPL

248

ESKEDQWYQPYALPL

249

EGLTMKWYQPYALPL

250

EGSREGWYQPYALPL

251

VIEWWQPYALPL

252

VWYWEQPYALPL

253

ASEWWQPYALPL

254

FYEWWQPYALPL

255

EGWWVQPYALPL

256

WGEWLQPYALPL

257

DYVWEQPYALPL

258

AHTWWQPYALPL

259

FIEWFQPYALPL

260

WLAWEQPYALPL

261

VMEWWQPYALPL

262

ERMWQPYALPL

263

NXXWXXPYALPL

264

WGNWYQPYALPL

265

TLYWEQPYALPL

266

VWRWEQPYALPL

267

LLWTQPYALPL

268

SRIWXX PYALPL

269

SDIWYQPYALPL

270

WGYYXX PYALPL

271

TSGWYQPYALPL

272

VHPYXXPYALPL

273

EHSYFQPYALPL

274

XXIWYQPYALPL

275

AQLHSQPYALPL

276

WANWFQPYALPL

277

SRLYSQPYALPL

278

GVTFSQPYALPL

279

SIVWSQPYALPL

280

SRDLVQPYALPL

281

HWGHVYWQPYSVQDDLG

282

SWHSVYWQPYSVQSVPE

283

WRDSVYWQPYSVQPESA

284

TWDAVYWQPYSVQKWLD

285

TPPWVYWQPYSVQSLDP

286

YWSSVYWQPYSVQSVHS

287

YWYQPYALGL

288

YWYQPYALPL

289

EWIQPYATGL

290

NWEQPYAKPL

291

AFYQPYALPL

292

FLYQPYALPL

293

VCKQPYLEWC

294

ETPFTWEESNAYYWQPYALPL

295

QGWLTWQDSVDMYWQPYALPL

296

FSEAGYTWPENTYWQPYALPL

297

TESPGGLDWAKIYWQPYALPL

298

DGYDRWRQSGERYWQPYALPL

299

TANVSSFEWTPGYWQPYALPL

300

SVGEDHNFWTSE YWQPYALPL

301

MNDQTSEVSTFPYWQPYALPL

302

SWSEAFEQPRNLYWQPYALPL

303

QYAEPSALNDWGYWQPYALPL

304

NGDWATADWSNYYWQPYALPL

305

THDEHIYWQPYALPL

306

MLEKTYTTWTPG YWQPYALPL

307

WSDPLTRDADLYWQPYALPL

308

SDAFTTQDSQAMYWQPYALPL

309

GDDAAWRTDSLTYWQPYALPL

310

AIIRQLYRWSEMYWQPYALPL

311

ENTYSPNWADSMYWQPYALPL

312

MNDQTSEVSTFPYWQPYALPL

313

SVGEDHNFWTSEYWQPYALPL

314

QTPFTWEESNAYYWQPYALPL

315

ENPFTWQESNAYYWQPYALPL

316

VTPFTWEDSNVF YWQPYALPL

317

QIPFTWEQSNAYYWQPYALPL

318

QAPLTWQESAAYYWQPYALPL

319

EPTFTWEESKAT YWQPYALPL

320

TTTLTWEESNAYYWQPYALPL

321

ESPLTWEESSALYWQPYALPL

322

ETPLTWEESNAYYWQPYALPL

323

EATFTWAESNAYYWQPYALPL

324

EALFTWKESTAYYWQPYALPL

325

STP-TWEESNAYYWQPYALPL

326

ETPFTWEESNAYYWQPYALPL

327

KAPFTWEESQAYYWQPYALPL

328

STSFTWEESNAYYWQPYALPL

329

DSTFTWEESNAYYWQPYALPL

330

YIPFTWEESNAYYWQPYALPL

331

QTAFTWEESNAYYWQPYALPL

332

ETLFTWEESNAT YWQPYALPL

333

VSSFTWEESNAYYWQPYALPL

334

QPYALPL

335

Py-1-NapPYQJYALPL

336

TANVSSFEWTPG YWQPYALPL

337

FEWTPGYWQPYALPL

338

FEWTPGYWQJYALPL

339

FEWTPGYYQJYALPL

340

ETPFTWEESNAYYWQPYALPL

341

FTWEESNAYYWQJYALPL

342

ADVLYWQPYAPVTLWV

343

GDVAEYWQPYALPLTSL

344

SWTDYGYWQPYALPISGL

345

FEWTPGYWQPYALPL

346

FEWTPGYWQJYALPL

347

FEWTPGWYQPYALPL

348

FEWTPGWYQJYALPL

349

FEWTPGYYQPYALPL

350

FEWTPGYYQJYALPL

351

TANVSSFEWTPGYWQPYALPL

352

SWTDYGYWQPYALPISGL

353

ETPFTWEESNAWAIQPYALPL

354

ENTYSPNWADSMYWQPYALPL

355

SVGEDHNFWTSEYWQPYALPL

356

DGYDRWRQSGERYWQPYALPL

357

FEWTPGYWQPYALPL

358

FEWTPGYWQPY

359

FEWTPGYWQJY

360

EWTPGYWQPY

361

FEWTPGWYQJY

362

AEWTPGYWQJY

363

FAWTPGYWQJY

364

FEATPGYWQJY

365

FEWAPGYWQJY

366

FEWTAGYWQJY

367

FEWTPAYWQJY

368

FEWTPGAWQJY

369

FEWTPGYAQJY

370

FEWTPGYWQJA

371

FEWTGGYWQJY

372

FEWTPGYWQJY

373

FEWTJGYWQJY

374

FEVff PecGYWQJY

375

FEWTPAibYWQJY

376

FEWTPSarWYQJY

377

FEWTSarGYWQJY

378

FEWTPNYWQJY

379

FEWTPVYWQJY

380

FEWTVPYWQJY

381

AcFEWTPGVVYQJY

382

AcFEVffPGYWQJY

383

INap-EVff PGYYQJY

384

YEWTPGYYQJY

385

FEWVPGYYQJY

386

FEVff PGYYQJY

387

FEVff PsYYQJY

388

FEWTPnYYQJY

389

SHLY-Nap-QPYSVQM

390

TLVY-Nap-LDPYSLQT

391

RGDY-Nap-QPYSVQS

392

NMVY-Nap-QPYSIQT

393

VYWQPYSVQ

394

VY-Nap-QPYSVQ

395

TFVYWQJYALPL

396

FEWTPGYYQJ-Bpa

397

XaaFEWTPGYYQJ-Bpa

398

FEWTPGY-Bpa-QJY

399

AeFEWTPGY-Bpa-QJY

400

FEWTPG-Bpa-YQJY

401

AcFEWTPG-Bpa-YQJY

402

AcFE-Bpa-TPGYYQJY

403

AcFE-Bpa-TPGYYQJY

404

Bpa-EWTPGYYQJY

405

AcBpa-EWTPGYYQJY

406

VYWQPYSVQ

407

RLVYWQPYSVQR

408

RLVY-Nap-QPYSVQR

409

RLDYWQPYSVQR

410

RLVWFQPYSVQR

411

RLVYWQPYSIQR

412

DNSSWYDSFLL

413

DNTAWYESFLA

414

DNTAWYENFLL

415

PAREDNTAWYDSFLIWC

416

TSEYDNTTWYEKFLASQ

417

SQIPDNTAWYQSFLLHG

418

SPFIDNTAWYENFLLTY

419

EQIYDNTAWYDHFLLSY

420

TPFIDNTAWYENFLLTY

421

TYTYDNTAWYERFLMSY

422

TMTQDNTAWYENFLLSY

423

TIDNTAWYANLVQTYPQ

424

TIDNTAWYERFLAQYPD

425

HIDNTAWYENFLLTYTP

426

SQDNTAWYENFLLSYKA

427

QIDNTAWYERFLLQYNA

428

NQDNTAWYESFLLQYNT

429

TIDNTAWYENFLLNHNL

430

HYDNTAWYERFLQQGWH

431

ETPFTWEESNAYYWQPYALPL

432

YIPFTWEESNAYYWQPYALPL

433

DGYDRWRQSGERYWQPYALPL

434

pY-INap-pY-QJYALPL

435

TANVSSFEWTPGYWQPYALPL

436

FEWTPGYWQJYALPL

437

FEWTPGYWQPYALPLSD

438

FEWTPGYYQJYALPL

439

FEWTPGYWQJY

440

AcFEVVTPGYWQJY

441

AcFEWTPGWYQJY

442

AcFEWTPGYYQJY

443

AcFEWTPaYWQJY

444

AcFEWTPaWYQJY

445

AcFEWTPaYYQJY

446

FEWTPGYYQJYALPL

447

FEWTPGYWQJYALPL

448

FEWTPGWYQJYALPL

449

TANVSSFEWTPGYWQPYALPL

450

AcFEWTPGYWQJY

451

AcFEWTPGWYQJY

452

AcFEWTPGYYQJY

453

AcFEWTPAYWQJY

454

AcFEWTPAWYQJY

455

AcFEWTPAYYQJY

456

Table 7-TPO-mimetic peptide sequences

Sequence/structure	SEQ-ID-NO:
EGPTLRQWLAARA	457
IEGPTLRQWLAAKA	458
IEGPTLREWLAARA	459
IEGPTLRQWLAARA-A-IEGPTLRQWLAARA	460
IEGPTLRQWLAAKA-A-IEGPTLRQWLAAKA	461
IEGPTLRQCLAARA-A-IEGPTLRQCLAARA	462
IEGPTLRQWLAARA-A-K(BrAc)-A-IEGPTLRQWLAARA	463
IEGPTLRQWLAARA-A-K(PEG)-A-IEGPTLRQWLAARA	464
IEGPTLRQCLAARA-A-IEGPTLRQWLAARA	465
IEGPTLRQCLAARA-Δ-IEGPTLRQCLAARA	466
IEGPTLRQWLAARA-A-IEGPTLRQULA/AtIA	467
VRDQIXXXL	468
TLREWL	469
GRVRDQVAGW	470
GRVKDQIAQL	471
GVRDQVSWAL	472
ESVREQVMKY	473
SVRSQISASL	474
GVRETVYRHM	475
GVREVIVMHML	476
GRVRDQIWAAL	477
AGVRDQILIWL	478
GRVRDQIMLSL	479
GRVRDQI$(X)_3$L	480

Sequence/structure	SEQ-ID-NO:
CTLRQWLQGC	481
CTLQEFLEGC	482
CTRTEWLHGC	483
CTLREWLHGGFC	484
CTLREWVFAGLC	485
CTLRQWLILLGMC	486
CTLAEFLASGVEQC	487
CSLQEFLSHGGYVC	488
CTLREFLDPTTAVC	489
CTLKEWLVSHEVWC	490
$CTLREWL(X)_{2-6}C$	491-495
REGPTLRQWM	496
EGPTLRQWLA	497
ERGPFWAKAC	498
REGPRCVMWM	499
CGTEGPTLSTWLDC	500
CEQDGPTLLEWLKC	501
CELVGPSLMSWLTC	502
CLTGPFVTQWLYEC	503
CRAGPTLLEWLTLC	504
CADGPTLREWISFC	505
$C(X)_{1-2}EGPTLREWL(X)_{1-2}C$	506-510
GGCTLREWLHGGFCGG	511
GGCADGPTLREWISFCGG	512
GNADGPTLRQWLEGRRPKN	513
LAIEGPTLRQWLHGNGRDT	514
HGRVGPTLREWKTQVATKK	515
TIKGPTLRQWLKSREHTS	516
ISDGPTLKEWLSVTRGAS	517
SIEGPTLREWLTSRTPHS	518

Table 8-G-CSF-mimetic peptide sequences

Sequence/structure	SEQ ID NO:
EEDCK	519
EEDαK	520
pGluEDαK	521
PicSDαK	522
EEDCK-Δ-EEDCK	523
EEDXK-Δ-EEDXK	524

Table 9-TNF-antagonist peptide sequences

Sequence/structure	SEQ ID NO:
YCFTASENHCY	525
YCFTNSENHCY	526
YCFTRSENHCY	527
FCASENHCY	528
YCASENHCY	529
FCNSENHCY	530
FCNSENRCY	

531

FCNSVENRCY

532

YCSQSVSNDCF

533

FCVSNDRCY

534

YCRKELGQVCY

535

YCKEPGQCY

536

YCRKEMGCY

537

FCRKEMGCY

538

YCWSQNLCY

539

YCELSQYLCY

540

YCWSQNYCY

541

YCWSQYLCY

542

DFLPHYKNTSLGHRP

543

Table 10-Integrin-binding peptide sequences

Sequence/structure	SEQ ID NO:
$RX_1ETX2WX_3$	544
$RX_1ETX_2WX_3$	545

RGDGX

546

CRGDGXC

547

$CX_1X_2RLDX_3X_4C$

548

CARRLDAPC

549

CPSRLDSPC

550

$X_1X_2X_3RGDX_4X_5X_6$

551

$CX_2CRGDCX_5C$

552

CDCRGDCFC

553

CDCRGDCLC

554

CLCRGDCIC

555

$X_1X_2DDX_4X_5X_7X_8$

556

$X_1X_2X_3DDX_4X_5X_6X_7X_8$

557

CWDDGWL

558

CWDDLWWLC

559

CWDDGLMC

560

CWDDGWMC

561

CSWDDGWLC

562

CPDDLWWLC

563

NGR

NR

GSL

NR

RGD

NR

CGRECPRLCQSSC

564

CNGRCVSGCAGRC

565

CLSGSLSC

566

RGD

NR

NGR

NR

GSL

NR

NGRAHA

567

CNGRC

568

CDCRGDCFC

569

CGSLVRC

570

DLXXL

571

RTDLDSLRTYTL

572

RTDLDSLRTY

573

RTDLDSLRT

574

RTDLDSLR

575

GDLDLLKLRLTL

576

GDLHSLRQLLSR

577

RDDLHMLRLQLW

578

SSDLHALKKRYG

579

RGDLKQLSELTW

580

RGDLAALSAPPV

581

Table 11-Selectin antagonist peptide sequences

Sequence/structure	SEQ ID NO:
DITWDQLWDLMK	582
DITWDELWKIMN	583
DYTWFELWDMMQ	584
QITWAQLWNMMK	585
DMTWHDLWTLMS	586
DYSWHDLWEMMS	587
EITWDQLWEVMN	

588

HVSWEQLWDIMN

589

HITWDQLWRIMT

590

RNMSWLELWEHMK

591

AEWTWDQLWHVMNPAESQ

592

HRAEWLALWEQMSP

593

KKEDWLALWRIMSV

594

ITWDQLWDLMK

595

DITWDQLWDLMK

596

DITWDQLWDLMK

597

DITWDQLWDLMK

598

CQNRYTDLVAIQNKNE

599

AENWADNEPNNKRNNED

600

RKNNKTWTWVGTKKALTNE

601

KKALTNEAENWAD

602

CQXRYTDLVAIQNKXE

603

RKXNXXWTWVGTXKXLTEE

604

AENWADGEPNNKXNXED

605

CXXXYTXLVAIQNKXE

606

RKXXXXWXWVGTXKXLTXE

607

AXNWXXXEPNNXXXED

608

XKXKTXEAXNWXX

609

Table 12-Antipathogenic peptide sequences

Sequence/structure	SEQ ID NO:
GFFALIPKIISSPLFKTLLSAVGSALSSSGGQQ	610
GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE	611
GFFALIPKIISSPLFKTLLSAV	612
GFFALIPKIISSPLFKTLLSAV	613
KGFFALIPKIISSPLFKTLLSAV	614
KKGFFALIPKIISSPLFKTLLSAV	615
KKGFFALIPKIISSPLFKTLLSAV	616
GFFALIPKIIS	617
GIGAVLKVLTTGLPALISWIKRKRQQ	618
GIGAVLKVLTTGLPALISWIKRKRQQ	619

GIGAVLKVLTTGLPALISWIKRKRQQ

620

GIGAVLKVLTTGLPALISWIKR

621

AVLKVLTTGLPALISWIKR

622

KLLLLLKLLLLK

623

KLLLKLLLKLLK

624

KLLLKLKLKLLK

625

KKLLKLKLKLKK

626

KLLLKLLLKLLK

627

KLLLKLKLKLLK

628

KLLLLK

629

KLLLKLLK

630

KLLLKLKLKLLK

631

KLLLKLKLKLLK

632

KLLLKLKLKLLK

633

KAAAKAAAKAAK

634

KVVVKVVVKVVK

635

KVVVKVKVKVVK

636

KVVVKVKVKVK

637

KVVVKVKVKVVK

638

KLILKL

639

KVLHLL

640

LKLRLL

641

KPLHLL

642

KLILKLVR

643

KVFHLLHL

644

HKFRILKL

645

KPFHILHL

646

KIiIKIKIKIIK

647

KIIIKIKIKIIK

648

KIIIKIKIKIIK

649

KIPIKIKIKIPK

650

KIPIKIKIKIVK

651

RIIIRIRIRIIR

652

RIIiRIRIRIIR

653

RI[IRIRIRIIR

654

RIVIRIRIRLIR

655

RIIVRIRLRIIR

656

RIGIRLRVRIIR

657

KIVIRIRIRLIR

658

RIAVKWRLRFIK

659

KIGWKLRVRIIR

660

KKIGWLIIRVRR

661

RIVIRIRIRLIRIR

662

RIIVRIRLRIIRVR

663

RIGIRLRVRIIRRV

664

KIVIRIRARLIRIRIR

665

RIIVKIRLRIIKKIRL

666

KIGIKARVRIIRVKII

667

RIIVHIRLRIIHHIRL

668

HIGIKAHVRIIRVHII

669

RIYVKIHLRYIKKIRL

670

KIGHKARVHIIRYKII

671

RIYVKPHPRYIKKIRL

672

KPGHKARPHIIRYKII

673

KIVIRIRIRLIRIRIRKIV

674

RIIVKIRLRIIKKIRLIKK

675

KIGWKLRVRIIRVKIGRLR

676

KI.VIRIRIRLIRIRIRKIVKVKRIR

677

RFAVKIRLRIIKKIRLIKKIRKRVIK

678

KAGWKLRVRIIRVKIGRLRKIGWKKRVRIK

679

RIYVKPHPRYIKKIRL

680

KPGHKARPHIIRYKII

681

KIVIRIRIRLIRIRIRKIV

682

RIIVKIRLRIIKKIRLIKK

683

RIYVSKISIYIKKIRL

684

KIVIFTRIRLTSIRIRSIV

685

KPIHKARPTIIRYKMI

686

cyclicCKGFFALIPKIISSPLFKTLLSAVC

687

CKKGFFALIPKIISSPLFKTLLSAVC

688

CKKKGFFALIPKIISSPLFKTLLSAVC

689

CyclicCRIVIRIRIRLIRIRC

690

CyclicCKPGHKARPHIIRYKIIC

691

CyclicCRFAVKIRLRIIKKIRLIKKIRKRVIKC

692

KLLLKLLL KLLKC

693

KLLLKLLLKLLK

694

KLLLKLKLKLLKC

695

KLLLKLLLKLLK

696

Table 13-VIP-mimetic peptide sequences

Sequence/structure	SEQ ID NO:
HSDAVFYDNYTR LRKQMAVKKYLN SILN	697
Me HSDAVFYDNYTR LRKQMAVKKYLN SILN	698
X_1 X_1' X_1'' X_2	699
X_3SX_4LN	700
KKYL	701
NSILN	702

KKYL

703

KKYA

704

AVKKYL

705

NSILN

706

KKYV

707

SILauN

708

KKYLNIe

709

NSYLN

710

NSIYN

711

KKYLPPNSILN

712

LauKKYL

713

CapKKYL

714

KYL

NR

KKYNIe

715

VKKYL

716

LNSILN

717

YLNSILN

718

KKYLN

719

KKYLNS

720

KKYLNSI

721

KKYLNSIL

722

KKYL

723

KKYDA

724

AVKKYL

725

NSILN

726

KKYV

727

SILauN

728

NSYLN

729

NSIYN

730

KKYLNIe

731

KKYLPPNSILN

732

KKYL

733

KKYDA

734

AVKKYL

735

NSILN

736

IKKYV

737

SILauN

738

LauKKYL

739

CapKKYL

740

KYL

NR

KYL

NR

KKYNIe

741

VKKYL

742

LNSILN

743

YLNSILN

744

KKYLNIe

745

KKYLN

746

KKYLNS

747

KKYLNSI

748

KKYLNSIL

749

KKKYLD

750

cyclicCKKYLC

751

CKKYLK

752

KKYA

753

WWTDTGLW

754

WWTDDGLW

755

WWDTRGLWVWTI

756

FWGNDGIWLESG

757

DWDQFGLWRGAA

758

RWDDNGLWVVVL

759

SGMWSHYGIWMG

760

GGRWDQAGLWVA

761

KLWSEQGIWMGE

762

CWSMHGLWLC

763

GCWDNTGIWVPC

764

DWDTRGLWVY

765

SLWDENGAWI

766

KWDDRGLWMH

767

QAWNERGLWT

768

QWDTRGLWVA

769

WNVHGIWQE

770

SWDTRGLWVE

771

DWDTRGLWVA

772

SWGRDGLWIE

773

EWTDNGLWAL

774

SWDEKGLWSA

775

SWDSSGLWMD

776

Table 14-Mdm/hdm antagonist peptide sequences

Sequence/structure	SEQ ID NO:
TFSDLW	777
QETFSDLWKLLP	778
QPTFSDLWKLLP	779
QETFSDYWKLLP	780
QPTFSDYWKLLP	781
MPRFMDYWEGLN	782

VQNFIDYWTQQF

783

TGPAFTHYWATF

784

IDRAPTFRDHWFALV

785

PRPALVFADYWETLY

786

PAFSRFWSDLSAGAH

787

PAFSRFWSKLSAGAH

788

PXFXDYWXXL

789

QETFSDLWKLLP

790

QPTFSDLWKLLP

791

QETFSDYWKLLP

792

QPTFSDYWKLLP

793

Table 15-Calmodulin antagonist peptide sequences

Sequence/structure	SEQ ID NO:
SCVKWGKKEFCGS	794
SCWKYWGKECGS	795
SCYEWGKLRWCGS	796
SCLRWGKWSNCGS	

797

SCWRWGKYQICGS

798

SCVSWGALKLCGS

799

SCIRWGQNTFCGS

800

SCWQWGNLKICGS

801

SCVRWGQLSICGS

802

LKKFNARRKLKGAILTTMLAK

803

RRWKKNFIAVSAANRFKK

804

RKWQKTGHAVRAIGRLSS

805

INLKALAALAKKIL

806

KIWSILAPLGTTLVKLVA

807

LKKLLKLLKKLLKL

808

LKWKKLLKLLKKLLKKLL

809

AEWPSLTEIKTLSHFSV

810

AEWPSPTRVISTTYFGS

811

AELAHWPPVKTVLRSFT

812

AEGSWLQLLNLMKQMNN

813

AEWPSLTEIK

814

Table 16-Mast cell antagonists/Mast cell protease inhibitor peptide sequences

Sequence/structure	SEQ ID NO:
SGSGVLKRPLPILPVTR	815
RWLSSRPLPPLPLPPRT	816
GSGSYDTLALPSLPLHPMSS	817
GSGSYDTRALPSLPLHPMSS	818
GSGSSGVTMYPKLPPHWSMA	819
GSGSSGVRMYPKLPPHWSMA	820
GSGSSSMRMVPTIPGSAKHG	821
RNR	NR
QT	NR
RQK	NR
NRQ	NR
RQK	NR
RNRQKT	822
RNRQ	823

RNRQK

824

NRQKT

825

RQKT

826

Table 17-SH3 antagonist peptide sequences

Sequence/structure	SEQ ID NO:
RPLPPLP	827
RELPPLP	828
SPLPPLP	829
GPLPPLP	830
RPLPIPP	831
RPLPIPP	832
RRLPPTP	834
RQLPPTP	835
RPLPSRP	836
RPLPTRP	837
SRLPPLP	838
RALPSPP	

839
RRLPRTP
840
RPVPPIT
841
ILAPPVP
842
RPLPMLP
843
RPLPILP
844
RPLPSLP
845
RPLPSLP
846
RPLPMIP
847
RPLPLIP
848
RPLPPTP
849
RSLPPLP
850
RPQPPPP
851
RQLPIPP
852
XXXRPLPPLPXP
853
XXXRPLPPIPXX
854
XXXRPLPPLPXX
855
RXXRPLPPLPXP

856

RXXRPLPPLPPP

857

PPPYPPPPIPXX

858

PPPYPPPPVPXX

859

LXXRPLPXTP

860

ΨXXRPLPXLP

861

PPXΘXPPPΨP

862

+PPΨPXKPXWL

863

RPXΨPΨR+SXP

864

PPVPPRPXXTL

865

ΨPΨLPΨK

866

+ΘDXPLPXLP

867

Table 18-Somatostatin or cortistatin mimetic peptide sequences

Sequence/structure	SEQ ID NO:
X^1X^2 -Asn-Phe-Phe-Trp-Lys-Thr-Phe-X^3-Ser-X^4	868
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	869
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	870

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys

871

Asp Arg Met Pro_Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

872

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

873

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

874

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

875

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys

876

Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys

877

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

878

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

879

Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

880

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys

881

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys

882

Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys

883

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

884

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

885

Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

886

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys

887

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys

889

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys

890

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

891

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

892

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

893

Table 19-UKR antagonist peptide sequences

Sequence/structure	SEQ ID NO:
AEPMPHSLNFSQYLWYT	894
AEHTYSSLWDTYSPLAF	895
AELDLWMRHYPLSFSNR	896
AESSLWTRYAWPSMPSY	897
AEWHPGLSFGSYLWSKT	898
AEPALLNWSFFFNPGLH	899
AEWSFYNLHLPEPQTIF	900
AEPLDLWSLYSLPPLAM	901
AEPTLWQLYQFPLRLSG	902
AEISFSELMWLRSTPAF	

903
AELSEADLWTTWFGMGS
904
AESSLWRIFSPSALMMS
905
AESLPTLTSILWGKESV
906
AETLFMDLWHDKHILLT
907
AEILNFPLWHEPLWSTE
908
AESQTGTLNTLFWNTLR
909
AEPVYQYELDSYLRSYY
910
AELDLSTFYDIQYLLRT
911
AEFFKLGPNGYVYLHSA
912
FKLXXXGYVYL
913
AESTYHHLSLGYMYTLN
914
YHXLXXGYMYT
915

Table 20-Macrophage and/or T-cell inhibiting peptide sequences

Sequence/structure	SEQ ID NO:
Xaa-Yaa-Arg	NR
Arg-Yaa-Xaa	NR

Xaa-Arg-Yaa
NR
Yaa-Arg-Xaa
NR
Ala-Arg
NR
Arg-Arg
NR
Asn-Arg
NR
Asp-Arg
NR
Cys-Arg
NR
GIn-Arg
NR
Glu-Arg
NR
Gly-Arg
NR
His-Arg
NR
Ile-Arg
NR
Leu-Arg
NR
Lys-Arg
NR
Met-Arg
NR
Phe-Arg
NR
Ser-Arg
NR

Thr-Arg

NR

Trp-Arg

NR

Tyr-Arg

NR

Val-Arg

NR

Ala-Glu-Arg

NR

Arg-Glu-Arg

NR

Asn-Glu-Arg

NR

Asp-Glu-Arg

NR

Cys-Glu-Arg

NR

Gln-Glu-Arg

NR

Glu-Glu-Arg

NR

Gly-Glu-Arg

NR

His-Glu-Arg

NR

Ile-Glu-Arg

NR

Leu-Glu-Arg

NR

Lys-Glu-Arg

NR

Met-Glu-Arg

NR

Phe-Glu-Arg

NR

Pro-Glu-Arg

NR

Ser-Glu-Arg

NR

Thr-Glu-Arg

NR

Trp-Glu-Arg

NR

Tyr-Glu-Arg

NR

Val-Glu-Arg

NR

Arg-Ala

NR

Arg-Asp

NR

Arg-Cys

NR

Arg-Gln

NR

Arg-Glu

NR

Arg-Gly

NR

Arg-His

NR

Arg-Ile

NR

Arg-Leu

NR

Arg-Lys

NR

Arg-Met

NR

Arg-Phe

NR

Arg-Pro

NR

Arg-Ser

NR

Arg-Thr

NR

Arg-Trp

NR

Arg-Tyr

NR

Arg-Val

NR

Arg-Glu-Ala

NR

Arg-Glu-Asn

NR

Arg-Glu-Asp

NR

Arg-Glu-Cys

NR

Arg-Glu-Gln

NR

Arg-Glu-Glu

NR

Arg-Glu-Gly

NR

Arg-Glu-His

NR

Arg-Glu-Ile

NR

Arg-Glu-Leu

NR

Arg-Glu-Lys

NR

Arg-Glu-Met

NR

Arg-Glu-Phe

NR

Arg-Glu-Pro

NR

Arg-Glu-Ser

NR

Arg-Glu-Thr

NR

Arg-Glu-Trp

NR

Arg-Glu-Tyr

NR

Arg-Glu-Val

NR

Ala-Arg-Glu

NR

Arg-Arg-Glu

NR

Asn-Arg-Glu

NR

Asp-Arg-Glu

NR

Cys-Arg-Glu

NR

Gln-Arg-Glu

NR

Glu-Arg-Glu

NR

Gly-Arg-Glu

NR

His-Arg-Glu

NR

Ile-Arg-Glu

NR

Leu-Arg-Glu

NR

Lys-Arg-Glu

NR

Met-Arg-Glu

NR

Phe-Arg-Glu

NR

Pro-Arg-Glu

NR

Ser-Arg-Glu

NR

Thr-Arg-Glu

NR

Trp-Arg-Glu

NR

Tyr-Arg-Glu

NR

Val-Arg-Glu

NR

Glu-Arg-Ala

NR

Glu-Arg-Arg

NR

Glu-Arg-Asn

NR

Glu-Arg-Asp

NR

Glu-Arg-Cys

NR

Glu-Arg-Gln

NR

Glu-Arg-Gly

NR

Glu-Arg-His

NR

Glu-Arg-Ile

NR

Glu-Arg-Leu

NR

Glu-Arg-Lys

NR

Glu-Arg-Met

NR

Glu-Arg-Phe

NR

Glu-Arg-Pro

NR

Glu-Arg-Ser

NR

Glu-Arg-Thr

NR

Glu-Arg-Trp

NR

Glu-Arg-Tyr

NR

Glu-Arg-Val

NR

Table 21-Additional Exemplary Pharmacologically Active Peptides

Sequence/Structure	SEQ ID NO:	Activity

VEPNCDIHVMWEWECFERL	916	VEGF-antagonist
GERWCFDGPLTWVCGEES	917	VEGF-antagonist
RGWVEICVADDNGMCVTEAQ	918	VEGF-antagonist
GWDECDVARMWEWECFAGV	919	VEGF- antagonist
GERWCFDGPRAWVCGWEI	920	VEGF- antagonist
EELWCFDGPRAWVCGYVK	921	VEGF- antagonist
RGWVEICAADDYGRCLTEAQ	922	VEGF- antagonist
RGWVEICESDVWGRCL	923	VEGF- antagonist
RGWVEICESDVWGRCL	924	VEGF- antagonist
GGNECDIARMWEWECFERL	925	VEGF- antagonist
RGWVEICAADDYGRCL	926	VEGF-antagonist
CTTHWGFTLC	927	MMP inhibitor
CLRSGXGC	928	MMP inhibitor
CXXHWGFXXC	929	MMP inhibitor
CXPXC	930	MMP inhibitor
CRRHWGFEFC	931	MMP inhibitor
STTHWGFTLS	932	MMP inhibitor
CSLHWGFWWC	933	CTLA4-mimetic
GFVCSGIFAVGVGRC	934	CTLA4-mimetic
APGVRLGCAVLGRYC	935	CTLA4-mimetic
LLGRMK	936	Antiviral (HBV)
ICVVQDWGHHRCTAGHMANLTSHASAI	937	C3b antagonist
ICVVQDWGHHRCT	938	C3b antagonist
CVVQDWGHHAC	939	C3b antagonist
STGGFDDVYDWARGVSSALTTTLVATR	940	Vinculin-binding
STGGFDDVYDWARRVSSALTTTLVATR	941	Vinculin-binding
SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	942	Vinculin-binding
SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	943	Vinculin-binding
SSPSLYTQFLVNYESAATRIQDLLIASRPSR	944	Vinculin-binding
SUGMIDILLGAILQRAADATRTSIPIPSLQNSIR	945	Vinculin-binding
DVYTKKELIECARRVSEK	946	Vinculin-binding
EKGSYYPGSGIAQFHIDYNNVS	947	C4BP-binding
SGIAQFHIDYNNVSSAEGWHVN	948	C41BP-binding

LVTVEKGSYYPGSGIAQFHIDYNNVSSAEGWHVN 949 4BP-binding

SGIAQFHIDYNNVS 950 C4BP-binding

LLGRMK 951 anti-HBV

ALLGRMKG 952 anti-HBV

LDPAFIR 953 anti-HBV

CXXRGDC 954 Inhibition of platelet aggrepation

RPLPPLP 955 Src antagonist

PPVPPR 956 Src antagonist

XFXDXWXXLXX 957 Anti-cancer

KACRRLFGPVDSEQLSRDCD 958 pl 6-mimetic

RERWNFDFVTETPLEGDFAW 959 pl 6-mimetic

KRRQTSMTDFYHSKRRLIFS 960 pl 6-mimetic

TSMTDFYHSKRRLIFSKRKP 961 pl 6-mimetic

RRLIF 962 p16-mimetic

KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK 963 p16-mimetic

KRRLIFSKRQIKIWFQNRRMKWKK 964 pl 6-mimetic

Asn Gin Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arq Phe Val Met Thr Ala Ala Ser Cys Phe Gln 965 CAP37 mimetic/LPs bindin

Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys 499 CAP37 mimetic/LPS binding

Gly Thr Arg Cys Gin Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val 966 CAP37 mimetic/LPS binding

WHWRHRIPLQLAAGR 967 carbohydrate (GID1 alpha) mimetic

LKTPRV 968 I32GPI Ab binding

NTLKTPRV 969 I32GPI Ab binding

NTLKTPRVGGC 970 02GPI Ab binding

KDKATF 971 02GPI Ab binding

KDKATFGCHD 972 P2GPl Ab binding

KDKATFGCHDGC 973 02GPI Ab bindinq

TLRVYK 974 02GPI Ab binding

ATLRVYKG	975	02GPI Ab binding
CATLRVYKGG	976	132GPI Ab binding
INLKALAALAKKIL	977	Membrane transporting
GWT	NR	Membrane transporting
GWTLNSAGYLLG	978	Membrane transporting
GWTLNSAGYLLGKINLKALAALAKKIL	979	Membrane transporting

The present invention is also particularly useful with peptides having activity in treatment of: a VEGF related condition, e.g., but not limited to, cancer, wherein the peptide is a VEGF-mimetic or a VEGF receptor antagonist, a HER2 agonist or antagonist, a CD20 antagonist and the like; asthma, wherein the protein of interest is a CKR3 antagonist, an IL-5 receptor antagonist, and the like; thrombosis, wherein the protein of interest is a GPIIb antagonist, a GPIIIa antagonist, and the like; autoimmune diseases and other conditions involving immune modulation, wherein the protein of interest is an IL-2 receptor antagonist, a CD40 agonist or antagonist, a CD40L agonist or antagonist, a thymopoietin mimetic and the like.

For example, EPO biological activities are well known in the art. See, e.g., Anagnostou A et al Erythropoietin has a mitogenic and positive chemotactic effect on endothelial cells. Proceedings of the National Academy of Science (USA) 87: 5978-82 (1990); Fandrey J and Jelkman WE Interleukin 1 and tumor necrosis factor-alpha inhibit erythropoietin production in vitro. Annals of the New York Academy of Science 628: 250-5 (1991); Geissler K et al Recombinant human erythropoietin: A multipotential hemopoietic growth factor in vivo and in vitro. Contrib. Nephrol. 87: 1-10 (1990); Gregory CJ Erythropoietin sensitivity as a differentiation marker in the hemopoietic system. Studies of three erythropoietic colony responses in culture. Journal of Cellular Physiology 89: 289-301 (1976); Jelkman W et al Monokines inhibiting erythropoietin production in human hepatoma cultures and in isolated perfused rat kidneys. Life Sci. 50: 301-8 (1992); Kimata H et al Human recombinant erythropoietin directly stimulates B cell immunoglobulin production and proliferation in serum-free medium. Clinical and Experimental Immunology 85: 151-6 (1991); Kimata H et al Erythropoietin enhances immunoglobulin production and proliferation by human plasma cells in a serum-free medium. Clin. Immunology Immunopathol. 59: 495-501 (1991); Kimata H et al Effect of recombinant human erythropoietin on human IgE production in vitro Clinical and Experimental Immunology 83: 483-7 (1991); Koury MJ and Bondurant MC Erythropoietin retards DNA breakdown and prevents programmed cell death in erythroid progenitor cells. Science 248: 378-81 (1990); Lim

VS et al Effect of recombinant human erythropoietin on renal function in humans. Kidney International 37: 131-6 (1990); Mitjavila MT et al Autocrine stimulation by erythropoietin and autonomous growth of human erythroid leukemic cells in vitro. Journal of Clinical Investigation 88: 789-97 (1991); Andre M et al Performance of an immunoradiometric assay of erythropoietin and results for specimens from anemic and polycythemic patients. Clinical Chemistry 38: 758-63 (1992); Hankins WD et al Erythropoietin-dependent and erythropoietin-producing cell lines. Implications for research and for leukemia therapy. Annals of the New York Academy of Science 554: 21-8 (1989); Kendall RGT et al Storage and preparation of samples for erythropoietin radioimmunoassay. Clin. Lab. Haematology 13: 189-96 (1991); Krumvieh D et al Comparison of relevant biological assays for the determination of biological active erythropoietin. Dev. Biol. Stand. 69: 15-22 (1988); Ma DD et al Assessment of an EIA for measuring human serum erythropoietin as compared with RIA and an in-vitro bioassay. British Journal of Haematology 80: 431-6 (1992); Noe G et al A sensitive sandwich ELISA for measuring erythropoietin in human serum British Journal of Haematology 80: 285-92 (1992); Pauly JU et al Highly specific and highly sensitive enzyme immunoassays for antibodies to human interleukin 3 (IL3) and human erythropoietin (EPO) in serum. Behring Institut Mitteilungen 90: 112-25 (1991); Sakata S and Enoki Y Improved microbioassay for plasma erythropoietin based on CFU-E colony formation. Ann. Hematology 64: 224-30 (1992); Sanengen T et al Immunoreactive erythropoietin and erythropoiesis stimulating factor(s) in plasma from hypertransfused neonatal and adult mice. Studies with a radioimmunoassay and a cell culture assay for erythropoietin. Acta Physiol. Scand. 135: 11-6 (1989); Widness JA et al A sensitive and specific erythropoietin immunoprecipitation assay: application to pharmacokinetic studies. Journal of Lab. Clin. Med. 119: 285-94 (1992); for further information see also individual cell lines used in individual bioassays. Each of the above references are entirely incorporated herein by reference. EPO can be assayed by employing cell lines such as HCD57 , NFS-60 , TF-1 and UT-7 , which respond to the factor . EPO activity can be assessed also in a Colony formation assay by determining the number of CFU-E from bone marrow cells. An alternative and entirely different detection method is RT-PCR quantitation of cytokines.

A hinge core mimetibody, or specified portion or variant thereof, that partially or preferably substantially provides at least one biological activity of at least one protein or fragment, can bind the protein or fragment ligand and thereby provide at least one activity that is otherwise mediated through the binding of protein to at least one protein ligand or receptor or through other protein-dependent or mediated mechanisms. As used herein, the term "hinge core mimetibody activity" refers to a hinge core mimetibody that can modulate or cause at least

one protein-dependent activity by about 20-10,000%, preferably by at least about 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, 500, 550, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000 % or more depending on the assay.

The capacity of a hinge core mimetibody or specified portion or variant to provide at least one protein-dependent activity is preferably assessed by at least one suitable protein biological assay, as described herein and/or as known in the art. A human hinge core mimetibody or specified portion or variant of the invention can be similar to any class (IgG, IgA, IgM, etc.) or isotype and can comprise at least a portion of a kappa or lambda light chain. In one embodiment, the human hinge core mimetibody or specified portion or variant comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. In another embodiment, the human protein human hinge core mimetibody or specified portion or variant thereof comprises an IgG1 heavy chain and an IgG1 light chain.

At least one hinge core mimetibody or specified portion or variant of the invention binds at least one specified ligand specific to at least one protein, subunit, fragment, portion or any combination thereof. The at least one therapeutic peptide portion (P) of at least one mimetibody of the invention can optionally bind at least one specified ligand epitope of the ligand. The binding epitope can comprise any combination of at least one amino acid sequence of at least 1-3 amino acids to the entire specified portion of contiguous amino acids of the sequences selected from the group consisting of a protein ligand, such as a receptor or portion thereof.

The hinge core mimetibody can comprise at least one N terminal heavy or light chain variable region having a defined amino acid sequence. Mimetibodies that bind to human protein ligands or receptors and that comprise a defined heavy or light chain variable region can be prepared using suitable methods, such as phage display (Katsube, Y., *et al.*, *Int J Mol. Med*, 1(*5*):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. The hinge core mimetibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to mimetibodies, ligand-binding fragments, immunoglobulin chains comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such mimetibodies or ligand-binding fragments and mimetibodies comprising such chains can bind human protein ligands with high affinity (e.g., K_D less than or equal to about 10^{-9} M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid

substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g., charge, structure, polarity, hydrophobicity/ hydrophilicity) that are similar to those of the first amino acid. Conservative substitutions include replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

Amino Acid Codes

The amino acids that make up mimetibodies or specified portions or variants of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New York, 1994), as presented in the following Table 22:

TABLE 22

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU
Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUA, GUC, GUG, GUU
W	Trp	Tryptophan	UGG
Y	Tyr	Tyrosine	UAC, UAU

A hinge core mimetibody or specified portion or variant of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein. Such or other sequences that can be used in the present invention, include, but are not limited to but are not limited to the following sequences presented in Table 23, as further described in Figures 1-42 of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference, with corresponding SEQ ID NOS:31-72. These referenced Figures 1-42 (SEQ ID NOS:31-72) , or Figures 1-41 of PCT US04/19783, show examples of heavy/light chain variable/constant region sequences, frameworks/subdomains and substitutions, portions of which can be used in Ig derived proteins of the present invention, as taught herein.

SEQ ID NO			AA NO	REGIONS						
				FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
980	Heavy chain variable region	Vh1	125	1-31	32	33-46	47	48-79	80	81-125
981		Vh2	97	1-30	31	32-45	46	47-78	79	80-97
982		Vh3a	102	1-30	31	32-45	46	47-78	79	80-102
983		Vh3b	102	1-30	31	32-45	46	47-78	79	80-102
984		Vh3c	94	1-30	31	32-45	46	47-78	79	80-94
985		Vh4	106	1-30	31	32-45	46	47-78	79	80-106
986		Vh5	97	1-30	31	32-45	46	47-78	79	80-97
987		Vh6	91	1-30	31	32-45	46	47-78	79	80-91
988		Vh7	91	1-30	31	32-45	46	47-78	79	80-91
989	Light chain variable region	κ1-4	73	1-23	24	25-39	40	41-72	73	
990		κ2	73	1-23	24	25-39	40	41-72	73	
991		κ3	73	1-23	24	25-39	40	41-72	73	
992		κ5	73	1-23	24	25-39	40	41-72	73	
993		κ new1	67	1-17	18	19-33	34	35-66	67	
994		κ new2	65	1-15	16	17-31	32	33-64	65	
995		λ1a	72	1-22	23	24-38	39	40-71	72	
996		λ1b	73	1-23	24	25-39	40	41-72	73	
997		λ1c	72	1-22	23	24-38	39	40-71	72	
998		λ3a	72	1-22	23	24-38	39	40-71	72	
999		λ3b	72	1-22	23	24-38	39	40-71	72	
1000		λ3c	72	1-22	23	24-38	39	40-71	72	
1001		λ3e	72	1-22	23	24-38	39	40-71	72	
1002		λ4a	72	1-22	23	24-38	39	40-71	72	
1003		λ4b	72	1-22	23	24-38	39	40-71	72	
1004		λ5	75	1-22	23	24-39	40	41-74	75	
1005		λ6	74	1-22	23	24-38	39	40-73	74	

1006		λ7	72	1-22	23	24-38	39	40-71	72	
1007		λ8	72	1-22	23	24-38	39	40-71	72	
1008		λ9	72	1-22	23	24-38	39	40-71	72	
1009		λ10	72	1-22	23	24-38	39	40-71	72	

SEQ ID NO			AA NO	REGIONS						
				CH1	hinge1	hinge2	hinge3	hinge4	CH2	CH3
1010	Heavy chain constant region	IgA1	354	1-102	103-122				123-222	223-354
1011		IgA2	340	1-102	103-108				109-209	210-340
1012		IgD	384	1-101	102-135	136-159			160-267	268-384
1013		IgE	497	1-103					104-210	211-318
1014		IgG1	339	1-98	99-113				114-223	224-339
1015		IgG2	326	1-98	99-110				111-219	220-326
1016		IgG3	377	1-98	99-115	116-130	131-145	146-160	161-270	271-377
1017		IgG4	327	1-98	99-110				111-220	221-327
1018		IgM	476	1-104					105-217	218-323
1019	Light chain constant region	Igκc	107							
1020		Igλc	107							

Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for at least one of a hinge core mimetibody or fragment, e.g., but not limited to, at least one variable, constant, light or heavy chain, or Ig will not be more than 40, 30, 20,19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 amino acids, such as 1-30 or any range or value therein, as specified herein.

The following description of the components of a hinge core mimetibody of the present invention is based on the use of the formula I of the present invention,

((V(m)-P(n)-L(o)-H(p)-CH2(q)-CH3(r))(s),

where V is at least one portion of an N-terminus of an immunoglobulin variable region, P is at least one bioactive peptide, L is at least one linker polypeptide H is at least one portion of at least one immunoglobulin hinge region, CH2 is at least a portion of an immunoglobulin CH2 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, m, n, o, p, q, r and s are independently an integer between 0, 1 or 2 and 10, mimicing different types of immunoglobulin molecules, e.g., but not limited to IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgD, IgE, and the like, or any subclass thereof, or any combination thereof.

In hinge core mimetibodies of the present invention, the optional N-terminal V portion can comprise 1-20 amino acids of at least one heavy chain variable framework 1 (FR1) region, e.g., as presented in Figures 1-9 (SEQ ID NOS:31-39) or at least one LC variable region, e.g., as presented in Figures 10-31 (SEQ ID NOS:40-61), each of such figures of US provisional

application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference, including substitutions, deletions or insertions as presented in these Figures, with those of Figures 5, 6, and 8 preferred. Also preferred are variable sequences that comprise the sequence Q-X-Q.

The P portion can comprise at least one any therapeutic peptide as known in the art or as described herein, such as, but not limited to those presented in Tables 1-21, SEQ ID NOS:1-979, or as known in th e art, or any combination or consensus sequence thereof, or any fusion protein thereof.

The optional linker sequence can be any suitable peptide linker as known in the art. Preferred sequence include any combination of G and S, e.g., X1-X2-X3-X4-Xn, where X can be G or S, and n can be 5-30. Non-limiting examples include, GS, GGGS, GSGGGS, GSGGGSGG, and the like.

In the present invention, the CH1 portion is not used and a variable number of amino acids from the N-terminus of the hinge region are deleted, e.g., as referenced to Figures 1-42 of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference, and Table 3. The variable number of amino acids used for the hinge core portion of a mimetibody of the present invention include, but are not limited to, deletion of any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 1-3, 2-5, 2-7, 2-8, 3-9, 4-10, 5-9, 5-10, 5-15, 10-20, 2-30, 20-40, 10-50, or any range or value therein, of the N-terminal amino acids of at least one hinge region, e.g., as presented in Figures 32-40 of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference, or Table 3 above, e.g., but not limited to, deletion of any to all of the amino acids 99-101 to 105-157 of amino acids 99-105, 99-108, 99-111, 99-112, 99-113, 99-114, 99-115, 99-119, 99-125, 99-128, 99-134, 99-140, 99-143, 99-149, 99-155 and 99-158 of Figures 32-40 of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference, corresponding to SEQ ID NOS:62-70, including the substitutions, insertions or deletions described in Figures 32-40 of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to

Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference. In preferred embodiments, a hinge core regions of the present invention includes a deletion of the N-terminous of the hinge region to provide a hinge core region that includes a deletion up to but not including a Cys residue or up to but not including a sequence Cys-Pro-Xaa-Cys. In further preferred embodiment, such hinge core sequences used in a hinge core mimetibody of the present invention include amino acids 109-113 or 112-113 of Fig. 36 (SEQ ID NO:66) (IgG1); 105-110 or 109-110 of Fig. 37 (SEQ ID NO:67) (IgG2); 111-160, 114-160, 120-160, 126-160, 129-160, 135-160, 141-160, 144-160, 150-160, 156-160 and 159-160 of Fig. 38 (SEQ ID NO:68) (IgG3); or 106-110 or 109-110 of Fig. 39 (SEQ ID NO:69) (IgG4), of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference.

The CH2, CH3 and optional CH4 sequence can be any suitable human or human compatable sequence, e.g., as presented in Figures 1-41 and Table 23 of US provisional application 60/507,349, filed 30/09/2003, entirely incorporated by reference herein, corresponding to Figures 1-41 of PCT Appl. No. US04/19783, filed June 17, 2004, entirely incorporated herein by reference, or as known in the art, or any combination or consensus sequence thereof, or any fusion protein thereof.

Amino acids in a hinge core mimetibody or specified portion or variant of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to at least one protein related activity, as specified herein or as known in the art. Sites that are critical for hinge core mimetibody or specified portion or variant binding can also be identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

Mimetibodies or specified portions or variants of the present invention can comprise as P portion of Formula (I), but are not limited to, at least one portion, sequence or combination selected from 3 to all the of at least one of SEQ ID NOS:1-979. Non-limiting variants that can enhance or maintain at least one of the listed activities include, but are not limited to, any of the above polypeptides, further comprising at least one mutation corresponding to at least one

substitution, insertion or deletion that does not significantly affect the suitable biological activtities or functions of said hinge core mimetibody.

A hinge core mimetibody or specified portion or variant can further optionally comprise at least one functional portion of at least one polypeptide as P portion of Formula (I), at least one of 90-100% of SEQ ID NOS:1-979. A hinge core mimetibody can further optionally comprise an amino acid sequence for the P portion of Formula (I), selected from one or more of SEQ ID NOS:1-979.

In one embodiment, the P amino acid sequence of an immunoglobulin chain, or portion thereof has about 90-100% identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the corresponding amino acid sequence of the corresponding portion of at least one of SEQ ID NOS: 1-979. Preferably, 90-100% amino acid identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

Mimetibodies or specified portions or variants of the present invention can comprise any number of contiguous amino acid residues from a hinge core mimetibody or specified portion or variant of the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in a hinge core mimetibody. Optionally, this subsequence of contiguous amino acids is at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more.

As those of skill will appreciate, the present invention includes at least one biologically active hinge core mimetibody or specified portion or variant of the present invention. Biologically active mimetibodies or specified portions or variants have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related and known inserted or fused protein or specified portion or variant. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity are well known to those of skill in the art.

In another aspect, the invention relates to human mimetibodies and ligand-binding fragments, as described herein, which are modified by the covalent attachment of an organic moiety. Such modification can produce a hinge core mimetibody or ligand-binding fragment with improved pharmacokinetic properties (e.g., increased *in vivo* serum half-life). The

organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

The modified mimetibodies and ligand-binding fragments of the invention can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the hinge core mimetibody or specified portion or variant. Each organic moiety that is bonded to a hinge core mimetibody or ligand-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, a hinge core mimetibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying mimetibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrolidone. Preferably, the hydrophilic polymer that modifies the hinge core mimetibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example, PEG_{2500}, PEG_{5000}, PEG_{7500}, PEG_{9000}, PEG_{10000}, PEG_{12500}, PEG_{15000}, and $PEG_{20,000}$, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used.

The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N,N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

Fatty acids and fatty acid esters suitable for modifying mimetibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying mimetibodies of the invention include, for example, n-dodecanoate (C_{12},

laurate), n-tetradecanoate (C_{14}, myristate), n-octadecanoate (C_{18}, stearate), n-eicosanoate (C_{20}, arachidate), n-docosanoate (C_{22}, behenate), n-triacontanoate (C_{30}), n-tetracontanoate (C_{40}), *cis*-Δ9-octadecanoate (C_{18}, oleate), all *cis*-Δ 5,8,11,14-eicosatetraenoate (C_{20}, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

The modified human mimetibodies and ligand-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C_1-C_{12} group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, $-(CH_2)_3-$, $-NH-(CH_2)_6-NH-$, $-(CH_2)_2-NH-$ and $-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH-NH-$. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for

example, Thompson, *et al.*, WO 92/16221 the entire teachings of which are incorporated herein by reference.)

The modified mimetibodies of the invention can be produced by reacting an human hinge core mimetibody or ligand-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the hinge core mimetibody in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified human mimetibodies or ligand-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of a hinge core mimetibody or ligand-binding fragment. The reduced hinge core mimetibody or ligand-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified hinge core mimetibody of the invention. Modified human mimetibodies and ligand-binding fragments comprising an organic moiety that is bonded to specific sites of a hinge core mimetibody or specified portion or variant of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch *et al., Bioconjugate Chem.*, 3:147-153 (1992); Werlen *et al.*, *Bioconjugate Chem.*, 5:411-417 (1994); Kumaran *et al.*, *Protein Sci.* 6(10):2233-2241 (1997); Itoh *et al.*, *Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas *et al.*, *Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

HINGE CORE MIMETIBODY COMPOSITIONS

The present invention also provides at least one hinge core mimetibody or specified portion or variant composition comprising at least one, at least two, at least three, at least four, at least five, at least six or more mimetibodies or specified portions or variants thereof, as described herein and/or as known in the art that are provided in a non-naturally occurring composition, mixture or form. Such composition percentages are by weight, volume, concentration, molarity, or molality as liquid or dry solutions, mixtures, suspension, emulsions or colloids, as known in the art or as described herein.

Such compositions can comprise 0.00001-99.9999 percent by weight, volume, concentration, molarity, or molality as liquid, gas, or dry solutions, mixtures, suspension, emulsions or colloids, as known in the art or as described herein, on any range or value therein, such as but not limited to 0.00001, 0.00003, 0.00005, 0.00009, 0.0001, 0.0003, 0.0005, 0.0009, 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88,

89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 %. Such compositions of the present invention thus include but are not limited to 0.00001-100 mg/ml and/or 0.00001-100 mg/g.

The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see, e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmcotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).

The anti-infective drug can be at least one selected from amebicides or at least one antiprotozoals, anthelmintics, antifungals, antimalarials, antituberculotics or at least one antileprotics, aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides, fluoroquinolones, antivirals, macrolide anti-infectives, miscellaneous anti-infectives. The CV drug can be at least one selected from inotropics, antiarrhythmics, antianginals, antihypertensives, antilipemics, and miscellaneous cardiovascular drugs. The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opiod analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The respiratory tract drug can be at least one selected from antihistamines, bronchodilators, expectorants or at least one antitussives, miscellaneous respiratory drugs. The GI tract drug can be at least one selected from antacids or at least one adsorbents or at least one antiflatulents, digestive enzymes or at least one gallstone solubilizers, antidiarrheals, laxatives, antiemetics, antiulcer drugs. The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroids, estrogens or at least one progestins, gonadotropins, antidiabetic drugs or at least one glucagon, thyroid hormones, thyroid hormone antagonists, pituitary hormones, parathyroid-like drugs. The drug

for fluid and electrolyte balance can be at least one selected from diuretics, electrolytes or at least one replacement solutions, acidifiers or at least one alkalinizers. The hematologic drug can be at least one selected from hematinics, anticoagulants, blood derivatives, thrombolytic enzymes. The antineoplastics can be at least one selected from alkylating drugs, antimetabolites, antibiotic antineoplastics, antineoplastics that alter hormone balance, miscellaneous antineoplastics. The immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least one toxoids, antitoxins or at least one antivenins, immune serums, biological response modifiers. The ophthalmic, otic, and nasal drugs can be at least one selected from ophthalmic anti-infectives, ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous ophthalmics, otics, nasal drugs. The topical drug can be at least one selected from local anti-infectives, scabicides or at least one pediculicides, topical corticosteroids. The nutritional drug can be at least one selected from vitamins, minerals, or calorics. See, e.g., contents *of Nursing 2001 Drug Handbook, supra.*

The at least one amebicide or antiprotozoal can be at least one selected from atovaquone, chloroquine hydrochloride, chloroquine phosphate, metronidazole, metronidazole hydrochloride, pentamidine isethionate. The at least one anthelmintic can be at least one selected from mebendazole, pyrantel pamoate, thiabendazole. The at least one antifungal can be at least one selected from amphotericin B, amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposomal, fluconazole, flucytosine, griseofulvin microsize, griseofulvin ultramicrosize, itraconazole, ketoconazole, nystatin, terbinafine hydrochloride. The at least one antimalarial can be at least one selected from chloroquine hydrochloride, chloroquine phosphate, doxycycline, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine phosphate, pyrimethamine, pyrimethamine with sulfadoxine. The at least one antituberculotic or antileprotic can be at least one selected from clofazimine, cycloserine, dapsone, ethambutol hydrochloride, isoniazid, pyrazinamide, rifabutin, rifampin, rifapentine, streptomycin sulfate. The at least one aminoglycoside can be at least one selected from amikacin sulfate, gentamicin sulfate, neomycin sulfate, streptomycin sulfate, tobramycin sulfate. The at least one penicillin can be at least one selected from amoxcillin/clavulanate potassium, amoxicillin trihydrate, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin sodium/sulbactam sodium, cloxacillin sodium, dicloxacillin sodium, mezlocillin sodium, nafcillin sodium, oxacillin sodium, penicillin G benzathine, penicillin G potassium, penicillin G procaine, penicillin G sodium, penicillin V potassium, piperacillin sodium, piperacillin sodium/tazobactam sodium, ticarcillin disodium, ticarcillin disodium/clavulanate potassium. The at least one cephalosporin can be at least one selected

from at least one of cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalexin hydrochloride, cephalexin monohydrate, cephradine, loracarbef. The at least one tetracycline can be at least one selected from demeclocycline hydrochloride, doxycycline calcium, doxycycline hyclate, doxycycline hydrochloride, doxycycline monohydrate, minocycline hydrochloride, tetracycline hydrochloride. The at least one sulfonamide can be at least one selected from co-trimoxazole, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfisoxazole acetyl. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one antiviral can be at least one selected from abacavir sulfate, acyclovir sodium, amantadine hydrochloride, amprenavir, cidofovir, delavirdine mesylate, didanosine, efavirenz, famciclovir, fomivirsen sodium, foscarnet sodium, ganciclovir, indinavir sulfate, lamivudine, lamivudine/zidovudine, nelfinavir mesylate, nevirapine, oseltamivir phosphate, ribavirin, rimantadine hydrochloride, ritonavir, saquinavir, saquinavir mesylate, stavudine, valacyclovir hydrochloride, zalcitabine, zanamivir, zidovudine. The at least one macroline anti-infective can be at least one selected from azithromycin, clarithromycin, dirithromycin, erythromycin base, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin stearate. The at least one miscellaneous anti-infective can be at least one selected from aztreonam, bacitracin, chloramphenicol sodium sucinate, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, imipenem and cilastatin sodium, meropenem, nitrofurantoin macrocrystals, nitrofurantoin microcrystals, quinupristin/dalfopristin, spectinomycin hydrochloride, trimethoprim, vancomycin hydrochloride. (See, e.g., pp. 24-214 of *Nursing 2001 Drug Handbook.*)

The at least one inotropic can be at least one selected from amrinone lactate, digoxin, milrinone lactate. The at least one antiarrhythmic can be at least one selected from adenosine, amiodarone hydrochloride, atropine sulfate, bretylium tosylate, diltiazem hydrochloride, disopyramide, disopyramide phosphate, esmolol hydrochloride, flecainide acetate, ibutilide fumarate, lidocaine hydrochloride, mexiletine hydrochloride, moricizine hydrochloride,

phenytoin, phenytoin sodium, procainamide hydrochloride, propafenone hydrochloride, propranolol hydrochloride, quinidine bisulfate, quinidine gluconate, quinidine polygalacturonate, quinidine sulfate, sotalol, tocainide hydrochloride, verapamil hydrochloride. The at least one antianginal can be at least one selected from amlodipidine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, isosorbide mononitrate, nadolol, nicardipine hydrochloride, nifedipine, nitroglycerin, propranolol hydrochloride, verapamil, verapamil hydrochloride. The at least one antihypertensive can be at least one selected from acebutolol hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol hydrochloride, bisoprolol fumarate, candesartan cilexetil, captopril, carteolol hydrochloride, carvedilol, clonidine, clonidine hydrochloride, diazoxide, diltiazem hydrochloride, doxazosin mesylate, enalaprilat, enalapril maleate, eprosartan mesylate, felodipine, fenoldopam mesylate, fosinopril sodium, guanabenz acetate, guanadrel sulfate, guanfacine hydrochloride, hydralazine hydrochloride, irbesartan, isradipine, labetalol hydrchloride, lisinopril, losartan potassium, methyldopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril hydrochloride, nadolol, nicardipine hydrochloride, nifedipine, nisoldipine, nitroprusside sodium, penbutolol sulfate, perindopril erbumine, phentolamine mesylate, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, telmisartan, terazosin hydrochloride, timolol maleate, trandolapril, valsartan, verapamil hydrochloride The at least one antilipemic can be at least one selected from atorvastatin calcium, cerivastatin sodium, cholestyramine, colestipol hydrochloride, fenofibrate (micronized), fluvastatin sodium, gemfibrozil, lovastatin, niacin, pravastatin sodium, simvastatin. The at least one miscellaneous CV drug can be at least one selected from abciximab, alprostadil, arbutamine hydrochloride, cilostazol, clopidogrel bisulfate, dipyridamole, eptifibatide, midodrine hydrochloride, pentoxifylline, ticlopidine hydrochloride, tirofiban hydrochloride. (See, e.g., pp. 215-336 of *Nursing 2001 Drug Handbook.*)

The at least one nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, diflunisal, magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opiod analgesic can be at least one selected from alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate,

fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride, morphine hydrochloride, morphine sulfate, morphine tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine hydrochloride and naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanil hydrochloride, sufentanil citrate, tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, temazepam, triazolam, zaleplon, zolpidem tartrate. The at least one anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximde, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, valproate sodium, valproic acid. The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate, sertraline hydrochloride, tranylcypromine sulfate, trimipramine maleate, venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephrobamate, midazolam hydrochloride, oxazepam. The at least one antipsychotic drug can be at least one selected from chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluephenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride, methylphenidate hydrochloride, modafinil, pemoline, phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from

amantadine hydrochloride, benztropine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. The at least one miscellaneous central nervous system drug can be at least one selected from bupropion hydrochloride, donepezil hydrochloride, droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex, nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, zolmitriptan. (See, e.g., pp. 337-530 of *Nursing 2001 Drug Handbook.*)

The at least one cholinergic (e.g., parasymathomimetic) can be at least one selected from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine salicylate, pyridostigmine bromide. The at least one anticholinergics can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, scopolamine hydrobromide. The at least one adrenergics (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate. The at least one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, propranolol hydrochloride. The at least one skeletal muscle relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, tizanidine hydrochloride. The at least one neuromuscular blockers can be at least one selected from atracurium besylate, cisatracurium besylate, doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, vecuronium bromide. (See, e.g., pp. 531-84 of *Nursing 2001 Drug Handbook.*)

The at least one antihistamine can be at least one selected from brompheniramine maleate, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cyproheptadine hydrochloride, diphenhydramine hydrochloride, fexofenadine hydrochloride, loratadine, promethazine hydrochloride, promethazine theoclate, triprolidine hydrochloride. The at least one bronchodilators can be at least one selected from albuterol, albuterol sulfate, aminophylline, atropine sulfate, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephrine hydrochloride, ipratropium bromide, isoproterenol, isoproterenol hydrochloride,

isoproterenol sulfate, levalbuterol hydrochloride, metaproterenol sulfate, oxtriphylline, pirbuterol acetate, salmeterol xinafoate, terbutaline sulfate, theophylline. The at least one expectorants or antitussives can be at least one selected from benzonatate, codeine phosphate, codeine sulfate, dextramethorphan hydrobromide, diphenhydramine hydrochloride, guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant, budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetonide, zafirlukast, zileuton. (See, e.g., pp. 585-642 of *Nursing 2001 Drug Handbook.*)

The at least one antacid, adsorbents, or antiflatulents can be at least one selected from aluminum carbonate, aluminum hydroxide, calcium carbonate, magaldrate, magnesium hydroxide, magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enymes or gallstone solubilizers can be at least one selected from pancreatin, pancrelipase, ursodiol. The at least one antidiarrheal can be at least one selected from attapulgite, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincure (camphorated). The at least one laxative can be at least one selected from bisocodyl, calcium polycarbophil, cascara sagrada, cascara sagrada aromatic fluidextract, cascara sagrada fluidextract, castor oil, docusate calcium, docusate sodium, glycerin, lactulose, magnesium citrate, magnesium hydroxide, magnesium sulfate, methylcellulose, mineral oil, polyethylene glycol or electrolyte solution, psyllium, senna, sodium phosphates. The at least one antiemetic can be at least one selected from chlorpromazine hydrochloride, dimenhydrinate, dolasetron mesylate, dronabinol, granisetron hydrochloride, meclizine hydrochloride, metoclopramide hydrochloride, ondansetron hydrochloride, perphenazine, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, scopolamine, thiethylperazine maleate, trimethobenzamide hydrochloride. The at least one antiulcer drug can be at least one selected from cimetidine, cimetidine hydrochloride, famotidine, lansoprazole, misoprostol, nizatidine, omeprazole, rabeprozole sodium, rantidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook.*)

The at least one coricosteroids can be at least one selected from betamethasone, betamethasone acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone,

methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate. The at least one androgen or anabolic steroids can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone transdermal system. The at least one estrogen or progestin can be at least one selected from esterified estrogens, estradiol, estradiol cypionate, estradiol/norethindrone acetate transdermal system, estradiol valerate, estrogens (conjugated), estropipate, ethinyl estradiol, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and levonorgestrel, ethinyl estradiol and norethindrone, ethinyl estradiol and norethindrone acetate, ethinyl estradiol and norgestimate, ethinyl estradiol and norgestrel, ethinyl estradiol and norethindrone and acetate and ferrous fumarate, levonorgestrel, medroxyprogesterone acetate, mestranol and norethindron, norethindrone, norethindrone acetate, norgestrel, progesterone. The at least one gonadroptropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucaon can be at least one selected from acarbose, chlorpropamide, glimepiride, glipizide, glucagon, glyburide, insulins, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, troglitazone. The at least one thyroid hormone can be at least one selected from levothyroxine sodium, liothyronine sodium, liotrix, thyroid. The at least one thyroid hormone antagonist can be at least one selected from methimazole, potassium iodide, potassium iodide (saturated solution), propylthiouracil, radioactive iodine (sodium iodide ^{131}I), strong iodine solution. The at least one pituitary hormone can be at least one selected from corticotropin, cosyntropin, desmophressin acetate, leuprolide acetate, repository corticotropin, somatrem, somatropin, vasopressin. The at least one parathyroid-like drug can be at least one selected from calcifediol, calcitonin (human), calcitonin (salmon), calcitriol, dihydrotachysterol, etidronate disodium. (See, e.g., pp. 696-796 of *Nursing 2001 Drug Handbook.*)

The at least one diuretic can be at least one selected from acetazolamide, acetazolamide sodium, amiloride hydrochloride, bumetanide, chlorthalidone, ethacrynate sodium, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol, metolazone, spironolactone, torsemide, triamterene, urea. The at least one electrolyte or replacement solution can be at least one selected from calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, calcium lactate,

calcium phosphate (dibasic), calcium phosphate (tribasic), dextran (high-molecular-weight), dextran (low-molecular-weight), hetastarch, magnesium chloride, magnesium sulfate, potassium acetate, potassium bicarbonate, potassium chloride, potassium gluconate, Ringer's injection, Ringer's injection (lactated), sodium chloride. The at least one acidifier or alkalinizer can be at least one selected from sodium bicarbonate, sodium lactate, tromethamine. (See, e.g., pp. 797-833 of *Nursing 2001 Drug Handbook.*)

The at least one hematinic can be at least one selected from ferrous fumarate, ferrous gluconate, ferrous sulfate, ferrous sulfate (dried), iron dextran, iron sorbitol, polysaccharide-iron complex, sodium ferric gluconate complex. The at least one anticoagulant can be at least one selected from ardeparin sodium, dalteparin sodium, danaparoid sodium, enoxaparin sodium, heparin calcium, heparin sodium, warfarin sodium. The at least one blood derivative can be at least one selected from albumin 5%, albumin 25%, antihemophilic factor, anti-inhibitor coagulant complex, antithrombin III (human), factor IX (human), factor IX complex, plasma protein fractions. The at least one thrombolytic enzyme can be at least one selected from alteplase, anistreplase, reteplase (recombinant), streptokinase, urokinase. (See, e.g., pp. 834-66 of *Nursing 2001 Drug Handbook.*)

The at least one alkylating drug can be at least one selected from busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine, mechlorethamine hydrochloride, melphalan, melphalan hydrochloride, streptozocin, temozolomide, thiotepa. The at least one antimetabolite can be at least one selected from capecitabine, cladribine, cytarabine, floxuridine, fludarabine phosphate, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, methotrexate sodium, thioguanine. The at least one antibiotic antineoplastic can be at least one selected from bleomycin sulfate, dactinomycin, daunorubicin citrate liposomal, daunorubicin hydrochloride, doxorubicin hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, pentostatin, plicamycin, valrubicin. The at least one antineoplastics that alter hormone balance can be at least one selected from anastrozole, bicalutamide, estramustine phosphate sodium, exemestane, flutamide, goserelin acetate, letrozole, leuprolide acetate, megestrol acetate, nilutamide, tamoxifen citrate, testolactone, toremifene citrate. The at least one miscellaneous antineoplastic can be at least one selected from asparaginase, bacillus Calmette-Guerin (BCG) (live intravesical), dacarbazine, docetaxel, etoposide, etoposide phosphate, gemcitabine hydrochloride, irinotecan hydrochloride, mitotane, mitoxantrone hydrochloride, paclitaxel, pegaspargase, porfimer sodium, procarbazine hydrochloride, rituximab, teniposide, topotecan hydrochloride, trastuzumab, tretinoin, vinblastine sulfate,

vincristine sulfate, vinorelbine tartrate. (See, e.g., pp. 867-963 of *Nursing 2001 Drug Handbook.*)

The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, tacrolimus. The at least one vaccine or toxoid can be at least one selected from BCG vaccine, cholera vaccine, diphtheria and tetanus toxoids (adsorbed), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, diphtheria and tetanus toxoids and whole-cell pertussis vaccine, *Haemophilius* b conjugate vaccines, hepatitis A vaccine (inactivated), hepatisis B vaccine (recombinant), influenza virus vaccine 1999-2000 trivalent types A & B (purified surface antigen), influenza virus vaccine 1999-2000 trivalent types A & B (subvirion or purified subvirion), influenza virus vaccine 1999-2000 trivalent types A & B (whole virion), Japanese encephalitis virus vaccine (inactivated), Lyme disease vaccine (recombinant OspA), measles and mumps and rubella virus vaccine (live), measles and mumps and rubella virus vaccine (live attenuated), measles virus vaccine (live attenuated), meningococcal polysaccharide vaccine, mumps virus vaccine (live), plague vaccine, pneumococcal vaccine (polyvalent), poliovirus vaccine (inactivated), poliovirus vaccine (live, oral, trivalent), rabies vaccine (adsorbed), rabies vaccine (human diploid cell), rubella and mumps virus vaccine (live), rubella virus vaccine (live, attenuated), tetanus toxoid (adsorbed), tetanus toxoid (fluid), typhoid vaccine (oral), typhoid vaccine (parenteral), typhoid Vi polysaccharide vaccine, varicella virus vaccine, yellow fever vaccine. The at least one antitoxin or antivenin can be at least one selected from black widow spider antivenin, Crotalidae antivenom (polyvalent), diphtheria antitoxin (equine), *Micrurus fulvius* antivenin). The at least one immune serum can be at least one selected from cytomegalovirus immune globulin (intraveneous), hepatitis B immune globulin (human), immune globulin intramuscular, immune globulin intravenous, rabies immune globulin (human), respiratory syncytial virus immune globulin intravenous (human), $Rh_0(D)$ immune globulin (human), $Rh_0(D)$ immune globulin intravenous (human), tetanus immune globulin (human), varicella-zoster immune globulin. The at least one biological response modifiers can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin, sargramostim. (See, e.g., pp. 964-1040 of *Nursing 2001 Drug Handbook.*)

The at least one ophthalmic anti-infectives can be selected form bacitracin,

chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, vidarabine. The at least one ophthalmic anti-inflammatories can be at least one selected from dexamethasone, dexamethasone sodium phosphate, diclofenac sodium 0.1%, fluorometholone, flurbiprofen sodium, ketorolac tromethamine, prednisolone acetate (suspension) prednisolone sodium phosphate (solution). The at least one miotic can be at least one selected from acetylocholine chloride, carbachol (intraocular), carbachol (topical), echothiophate iodide, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate. The at least one mydriatic can be at least one selected from atropine sulfate, cyclopentolate hydrochloride, epinephrine hydrochloride, epinephryl borate, homatropine hydrobromide, phenylephrine hydrochloride, scopolamine hydrobromide, tropicamide. The at least one ophthalmic vasoconstrictors can be at least one selected from naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride. The at least one miscellaneous ophthalmics can be at least one selected from apraclonidine hydrochloride, betaxolol hydrochloride, brimonidine tartrate, carteolol hydrochloride, dipivefrin hydrochloride, dorzolamide hydrochloride, emedastine difumarate, fluorescein sodium, ketotifen fumarate, latanoprost, levobunolol hydrochloride, metipranolol hydrochloride, sodium chloride (hypertonic), timolol maleate. The at least one otic can be at least one selected from boric acid, carbamide peroxide, chloramphenicol, triethanolamine polypeptide oleate-condensate. The at least one nasal drug can be at least one selected from beclomethasone dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, xylometazoline hydrochloride. (See, e.g., pp. 1041-97 of *Nursing 2001 Drug Handbook.*)

The at least one local anti-infectives can be at least one selected from acyclovir, amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, tolnaftate. The at least one scabicide or pediculicide can be at least one selected from crotamiton, lindane, permethrin, pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone

acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcionide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocorisone valerate, mometasone furoate, triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook.*)

The at least one vitamin or mineral can be at least one selected from vitamin A, vitamin B complex, cyanocobalamin, folic acid, hydroxocobalamin, leucovorin calcium, niacin, niacinamide, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, vitamin C, vitamin D, cholecalciferol, ergocalciferol, vitamin D analogue, doxercalciferol, paricalcitol, vitamin E, vitamin K analogue, phytonadione, sodium fluoride, sodium fluoride (topical), trace elements, chromium, copper, iodine, manganese, selenium, zinc. The at least one calorics can be at least one selected from amino acid infusions (crystalline), amino acid infusions in dextrose, amino acid infusions with electrolytes, amino acid infusions with electrolytes in dextrose, amino acid infusions for hepatic failure, amino acid infusions for high metabolic stress, amino acid infusions for renal failure, dextrose, fat emulsions, medium-chain triglycerides. (See, e.g., pp. 1137-63 of *Nursing 2001 Drug Handbook.*)

Hinge core mimetibody antibody or polypeptide compositions of the present invention can further comprise at least one of any suitable and/or effective amount of a composition or pharmaceutical composition comprising at least one hinge core mimetibody protein or antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, enteracept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropieitin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine,

daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limted to, any of IL-1 to IL-23. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Such compositions can also include toxin molecules that are associated, bound, co-formulated or co-administered with at least one antibody or polypeptide of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7), Staphylococcus species (e.g., *Staphylococcus aureus, Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae, Shigella flexneri, Shigella boydii, and Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi, Salmonella cholera-suis, Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens, Clostridium dificile, Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni, Camphlobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria, Aeromonas hydrophila, Aeromonas caviae*), *Pleisomonas shigelloides, Yersina enterocolitica, Vibrios* species (e.g., *Vibrios cholerae, Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed.,

INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.

hinge core mimetibody or specified portion or variant compositions of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the hinge core mimetibody composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include but are not limited to proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/hinge core mimetibody or specified portion or variant components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

hinge core mimetibody compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as citrate.

Additionally, the hinge core mimetibody or specified portion or variant compositions of the invention can include polymeric excipients/additives such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (*e.g.*, phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the hinge core mimetibody compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferrred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents.

Formulations

As noted above, the invention provides for stable formulations, which can preferably include a suitable buffer with saline or a chosen salt, as well as optional preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one hinge core mimetibody or specified portion or variant in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4., 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3,

1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3. 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1., 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one hinge core mimetibody or specified portion or variant with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one hinge core mimetibody or specified portion or variant, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the at least one hinge core mimetibody or specified portion or variant in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

The at least one hinge core mimetibody or specified portion or variant used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

The range of amounts of at least one hinge core mimetibody or specified portion or variant in the product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 μg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative

used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

Other excipients, e.g. isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyls, other block co-polymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

The formulations of the present invention can be prepared by a process which comprises mixing at least one hinge core mimetibody or specified portion or variant and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one hinge core mimetibody or specified portion or variant and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one hinge core mimetibody or specified portion or variant in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the protein and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that may be optimized

for the concentration and means of administration used.

The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one hinge core mimetibody or specified portion or variant that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be safely stored at temperatures of from about 2 to about 40°C and retain the biologically activity of the protein for extended periods of time, thus, allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to at least one of 1-12 months, one-half, one and a half, and/or two years.

The solutions of at least one hinge core mimetibody or specified portion or variant in the invention can be prepared by a process that comprises mixing at least one hinge core mimetibody or specified portion or variant in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one hinge core mimetibody or specified portion or variant in water or buffer is combined in quantities sufficient to provide the protein and optionally a preservative or buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that may be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one hinge core mimetibody or specified portion or variant that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to

pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one hinge core mimetibody or specified portion or variant that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger in size, providing a large reservoir from which smaller portions of the at least one hinge core mimetibody or specified portion or variant solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as Humaject®, NovoPen®, B-D®Pen, AutoPen®, and OptiPen®. Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution such as the HumatroPen®.

The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which the product can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the at least one hinge core mimetibody or specified portion or variant in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical product use.

The formulations of the present invention can be prepared by a process that comprises mixing at least one hinge core mimetibody or specified portion or variant and a selected buffer, preferably a phosphate buffer containing saline or a chosen salt. Mixing the at least one hinge core mimetibody or specified portion or variant and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one hinge core mimetibody or specified portion or variant in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed stable or preserved formulations can be provided to patients as

clear solutions or as dual vials comprising a vial of lyophilized at least one hinge core mimetibody or specified portion or variant that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

At least one hinge core mimetibody or specified portion or variant in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

Therapeutic Applications

The present invention for mimetibodies also provides a method for modulating or treating anemia, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of any anemia, cancer treatment related anemia, radiotherapy or chemotherapy related anemia, viral or bacterial infection treatment related anemia, renal anemia, anemia of prematurity, pediatric and/or adult cancer-associated anemia, anemia associated with lymphoma, myeloma, multple myeloma, AIDS-associated anemia, concomitant treatment for patients with or without autologous blood donation awaiting elective surgery, preoperatve and post operative for surgery, autologous blood donation or transfusion, perioperative management, cyclic neutropenia or Kostmann syndrome (congenital agranulocytosis), end-stage renal disease, anemia associated with dialysis, chronic renal insufficiency, primary hemopoietic diseases, such as congenital hypoplastic anemia, thalassemia major, or sickle cell disease, vaso-occlusive complications of sickle cell disease. Furman et al., Pediatrics 1992; 90: 716-728, Goldberg Science. 1988;242:1412-1415; Paul et al., Exp Hematol. 1984;12:825-830; Erslev et al., Arch Intern Med. 1968;122:230-235; Ersley et al., Ann Clin Lab Sci. 1980;10:250-257; Jacobs et al., Nature. 1985;313:806-810; Lin et al., Proc Natl Acad Sci USA. 1985;82:7580-7584; Law et al., Proc Natl Acad Sci USA. 1986;83:6920-6924; Goldwasser et al., J Biol Chem. 1974;249:4202-4206; Eaves et a., Blood. 1978;52:1196-1210; Sawyer et al., Blood. 1989;74:103-109; Winearls et al., Lancet. 1986;2:1175-1178; Eschbach et al., N Engl J Med. 1987;316:73-78; Eschbach et al., Ann Intern Med. 1989;111:992-1000, each reference entirely incoporated herein by reference.

Mimetibodies of the present invention can also be used for non-renal forms of anemia

induced, for example, by chronic infections, inflammatory processes, radiation therapy, and cytostatic drug treatment, and encouraging results in patients with non-renal anemia have been reported. See, e.g., Abels RI and Rudnick SA Erythropoietin: evolving clinical applications. Experimental Hematology 19: 842-50 (1991); Graber SE and Krantz SB Erythropoietin: biology and clinical use. Hematology/Oncol. Clin. North Amer. 3: 369-400 (1989); Jelkman W and Gross AJ (eds) Erythropoietin. Springer, Berlin 1989; Koury MJ and Bondurant MC The molecular mechanism of erythropoietin action. European Journal of Biochemistry 210: 649-63 (1992); Krantz SB Erythropoietin. Blood 77: 419-34 (1991); Tabbara IA Erythropoietin. Biology and clinical applications. Archives of Internal Medicine 153: 298-304 (1993), each entirely incorporated herein by reference.

The present invention also provides a method for modulating or treating an anemia or blood cell related condition, in a cell, tissue, organ, animal, or patient, wherein said anemia or blood cell related condition is associated with at least one including, but not limited to, at least one of immune related disease, cardiovascular disease, infectious, malignant and/or neurologic disease. Such a method can optionally comprise administering an effective amount of at least one composition or pharmaceutical composition comprising at least one hinge core mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating cancer/infecteous disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection/HIV neuropathy, meningitis, hepatitis, septic arthritis, peritonitis, pneumonia , epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis/epidydimitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitis/aseptic meningitis, and the like; (ii) leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chromic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodyplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignamt lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant

histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, adenocarcinomas, sarcomas, malignant melanoma, and the like; or (iii) neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one TNF antibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16th Edition, Merck & Company, Rahway, NJ (1992)

Such a method can optionally comprise administering an effective amount of at least one composition or pharmaceutical composition comprising at least one hinge core mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, diabetic ateriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system, heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal),

chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrythmias, ventricular fibrillation, His bundle arrythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aordic and peripheral aneuryisms, aortic dissection, inflammation of the aorta, occulsion of the abdominal aorta and its branches, peripheral vascular disorders, occulsive arterial disorders, peripheral atherlosclerotic disease, thromboangitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphederma, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one hinge core mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one hinge core mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such immune diseases, wherein the administering of said at least one hinge core mimetibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist), an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropieitin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite,

a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Mimetibodies can also be used ex vivo, such as in autologous marrow culture. Briefly, bone marrow is removed from a patient prior to chemotherapy and treated with TPO and/or EPO, optionally in combination with mimetibodies, optionally in combination with one or more additional cytokines. The treated marrow is then returned to the patient after chemotherapy to speed the recovery of the marrow. In addition, TPO, alone and in combination with EPO mimetibodies and/or EPO, can also be used for the ex vivo expansion of marrow or peripheral blood progenitor (PBPC) cells. Prior to chemotherapy treatment, marrow can be stimulated with stem cell factor (SCF) or G-CSF to release early progenitor cells into peripheral circulation. These progenitors are optionally collected and concentrated from peripheral blood and then treated in culture with TPO and mimetibodies, optionally in combination with one or more other cytokines, including but not limited to SCF, G-CSF, IL-3, GM-CSF, IL-6 or IL-11, to differentiate and proliferate into high-density megakaryocyte cultures, which are optionally then be returned to the patient following high-dose chemotherapy. Doses of TPO for ex vivo treatment of bone marrow will be in the range of 100 pg/ml to 10 ng/ml, preferably 500 pg/ml to 3 ng/ml. Doses of mimetibodies will be equivalent in activity to EPO which can be used from 0.1 units/ml to 20 units/ml, preferably from 0.5 units/ml to 2 units/ml, or any range or value therein.

TNF antagonists suitable for compositions, combination therapy, co-administration, devices and/or methods of the present invention (further comprising at least one anti body, specified portion and variant thereof, of the present invention), include, but are not limited to, anti-TNF antibodies, ligand-binding fragments thereof, and receptor molecules which bind specifically to TNF; compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g, pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen

activated protein (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metalloproteinase inhibitors; compounds which block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril); and compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

As used herein, a "tumor necrosis factor antibody," "TNF antibody," "TNFα antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNFα activity *in vitro, in* situ and/or preferably in *vivo*. For example, a suitable TNF human antibody of the present invention can bind TNFα and includes anti-TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNFα. A suitable TNF antibody or fragment can also decrease block, abrogate, interfere, prevent and/or inhibit TNF RNA, DNA or protein synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse anti-human TNFα IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric antibody cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNFα in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNFα, the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} M^{-1}$. Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow, *et al.*, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology,* Greene Publishing Assoc. and Wiley Interscience, New York, (1992-2003); Kozbor *et al.*, *Immunol. Today, 4*:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology,* Wiley Interscience, New York (1987-2003); and Muller, *Meth. Enzymol., 92*:589-601 (1983), which references are entirely incorporated herein by reference.

In a particular embodiment, murine monoclonal antibody A2 is produced by a cell line designated c134A. Chimeric antibody cA2 is produced by a cell line designated c168A.

Additional examples of monoclonal anti-TNF antibodies that can be used in the present invention are described in the art (see, e.g., U.S. Patent No. 5,231,024; Möller, A. *et al.*, *Cytokine 2*(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication No. 0 218 868 (published April 22, 1987); Yone *et al.*, EPO Patent Publication No. 0 288 088 (October 26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm. 137*:847-854 (1986); Meager, *et al.*, *Hybridoma 6*:305-311 (1987); Fendly *et al.*, *Hybridoma 6*:359-369 (1987); Bringman, *et al.*, *Hybridoma 6*:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth. 96*:57-62 (1987), which references are entirely incorporated herein by reference).

TNF Receptor Molecules

Preferred TNF receptor molecules useful in the present invention are those that bind TNFα with high affinity (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell 61*:361-370 (1990); and Loetscher *et al.*, *Cell 61*:351-359 (1990), which references are entirely incorporated herein by reference) and optionally possess low immunogenicity. In particular, the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors are useful in the present invention. Truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem. 223*:831-840 (1994)), are also useful in the present invention. Truncated forms of the TNF receptors, comprising the ECD, have been detected in urine and serum as 30 kDa and 40 kDa TNFα inhibitory binding proteins (Engelmann, H. *et al.*, *J. Biol. Chem. 265*:1531-1536 (1990)). TNF receptor multimeric molecules and TNF immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNF receptor molecules which are useful in the methods and compositions of the present invention. The TNF receptor molecules which can be used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, may contribute to the therapeutic results achieved.

TNF receptor multimeric molecules useful in the present invention comprise all or a functional portion of the ECD of two or more TNF receptors linked via one or more polypeptide linkers or other nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted protein to direct expression of the multimeric molecule. These multimeric molecules and methods for their

production have been described in U.S. Application No. 08/437,533 (filed May 9, 1995), the content of which is entirely incorporated herein by reference.

TNF immunoreceptor fusion molecules useful in the methods and compositions of the present invention comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF receptors. These immunoreceptor fusion molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can also be monovalent or multivalent. An example of such a TNF immunoreceptor fusion molecule is TNF receptor/IgG fusion protein. TNF immunoreceptor fusion molecules and methods for their production have been described in the art (Lesslauer *et al.*, *Eur. J. Immunol. 21*:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA 88*:10535-10539 (1991); Peppel *et al.*, *J. Exp. Med. 174*:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA 91*:215-219 (1994); Butler *et al.*, *Cytokine 6*(6):616-623 (1994); Baker *et al.*, *Eur. J. Immunol. 24*:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and U.S. Application No. 08/442,133 (filed May 16, 1995), each of which references are entirely incorporated herein by reference). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*, *Nature 337*:525-531 (1989), which references are entirely incorporated herein by reference.

A functional equivalent, derivative, fragment or region of TNF receptor molecule refers to the portion of the TNF receptor molecule, or the portion of the TNF receptor molecule sequence which encodes TNF receptor molecule, that is of sufficient size and sequences to functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNFα with high affinity and possess low immunogenicity). A functional equivalent of TNF receptor molecule also includes modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNFα with high affinity and possess low immunogenicity). For example, a functional equivalent of TNF receptor molecule can contain a "SILENT" codon or one or more amino acid substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1987-2003).

Cytokines include, but are not limited to all known cytokines. See, e.g., CopewithCytokines.com. Cytokine antagonists include, but are not limited to, any antibody,

fragment or mimetic, any soluble receptor, fragment or mimetic, any small molecule antagonist, or any combination thereof.

Any method of the present invention can comprise a method for treating a protein mediated disorder, comprising administering an effective amount of a composition or pharmaceutical composition comprising at least one hinge core mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such immune diseases, wherein the administering of said at least one hinge core mimetibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one other cytokines such as IL-3, IL -6 and IL -11; stem cell factor; G-CSF and GM-CSF. Combination therapy with GM-CSF, for example, is indicated in patients with low neutrophil levels.

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one hinge core mimetibody composition that total, on average, a range from at least about 0.01 to 500 milligrams of at least one hinge core mimetibody or specified portion or variant /kilogram of patient per dose, and preferably from at least about 0.1 to 100 milligrams hinge core mimetibody or specified portion or variant /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.1-5000 µg/ml serum concentration per single or multiple adminstration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses can optionally include 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 009, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and/or 30 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5., 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5,

19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 μg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one hinge core mimetibody or specified portion or variant of the present invention 0.01 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.0001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

For parenteral administration, the hinge core mimetibody or specified portion or variant can be formulated as a solution, suspension, emulsion or lyophilized powder in association, or separately provided, with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The vehicle or lyophilized powder may contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Therapeutic Administration

Many known and developed modes of can be used according to the present invention for administering pharmaceutically effective amounts of at least one hinge core mimetibody or specified portion or variant according to the present invention. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results.

A hinge core mimetibody of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

Parenteral Formulations and Administration

Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent such as aquous solution or a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthtetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

Alternative Delivery

The invention further relates to the administration of at least one hinge core mimetibody or specified portion or variant by parenteral, subcutaneous, intramuscular, intravenous, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. Protein, hinge core mimetibody or specified portion or variant compositions can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) administration particularly in the form of liquid solutions or suspensions; for use in vaginal or rectal administration

particularly in semisolid forms such as creams and suppositories; for buccal, or sublingual administration particularly in the form of tablets or capsules; or intranasally particularly in the form of powders, nasal drops or aerosols or certain agents; or transdermally particularly in the form of a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure or to increase the drug concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement"; Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with oxidizing agents that enable the application of formulations containing proteins and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways such as electroporation, or to increase the mobility of charged drugs through the skin such as iontophoresis, or application of ultrasound such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated herein by reference).

Pulmonary/Nasal Administration

For pulmonary administration, preferably at least one hinge core mimetibody or specified portion or variant composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one hinge core mimetibody or specified portion or variant can be delivered by any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of hinge core mimetibody or specified portion or variants are also known in the art. All such devices can use of formulations suitable for the administration for the dispensing of hinge core mimetibody or specified portion or variant in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin® metered dose inhaler, typically use a propellent gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers like Turbuhaler™ (Astra), Rotahaler® (Glaxo), Diskus® (Glaxo), Spiros™ inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler® powder inhaler (Fisons), use breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO 94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference). Nebulizers like AERx™ Aradigm, the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer

(Marquest Medical Products) (US 5404871 Aradigm, WO 97/22376), the above references entirely incorporated herein by reference, produce aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. generate small particle aerosols. These specific examples of commercially available inhalation devices are intended to be a representative of specific devices suitable for the practice of this invention, and are not intended as limiting the scope of the invention. Preferably, a composition comprising at least one hinge core mimetibody or specified portion or variant is delivered by a dry powder inhaler or a sprayer. There are a several desirable features of an inhalation device for administering at least one hinge core mimetibody or specified portion or variant of the present invention. For example, delivery by the inhalation device is advantageously reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles, e.g. less than about 10 μm, preferably about 1-5 μm, for good respirability.

Administration of hinge core mimetibody or specified portion or variant Compositions as a Spray

A spray including hinge core mimetibody or specified portion or variant composition protein can be produced by forcing a suspension or solution of at least one hinge core mimetibody or specified portion or variant through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output and particle size. An electrospray can be produced, for example, by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of at least one hinge core mimetibody or specified portion or variant composition protein delivered by a sprayer have a particle size less than about 10 μm, preferably in the range of about 1 μm to about 5 μm, and most preferably about 2 μm to about 3 μm.

Formulations of at least one hinge core mimetibody or specified portion or variant composition protein suitable for use with a sprayer typically include hinge core mimetibody or specified portion or variant composition protein in an aqueous solution at a concentration of about 1 mg to about 20 mg of at least one hinge core mimetibody or specified portion or variant composition protein per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the hinge core mimetibody or specified portion or variant composition protein, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating hinge core mimetibody or specified portion or variant composition proteins include albumin, protamine,

or the like. Typical carbohydrates useful in formulating hinge core mimetibody or specified portion or variant composition proteins include sucrose, mannitol, lactose, trehalose, glucose, or the like. The hinge core mimetibody or specified portion or variant composition protein formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the hinge core mimetibody or specified portion or variant composition protein caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein such as mimetibodies, or specified portions or variants, can also be included in the formulation.

Administration of hinge core mimetibody or specified portion or variant compositions by a Nebulizer

hinge core mimetibody or specified portion or variant composition protein can be administered by a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of hinge core mimetibody or specified portion or variant composition protein through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of hinge core mimetibody or specified portion or variant composition protein either directly or through a coupling fluid, creating an aerosol including the hinge core mimetibody or specified portion or variant composition protein. Advantageously, particles of hinge core mimetibody or specified portion or variant composition protein delivered by a nebulizer have a particle size less than about 10 μm, preferably in the range of about 1 μm to about 5 μm, and most preferably about 2 μm to about 3 μm.

Formulations of at least one hinge core mimetibody or specified portion or variant suitable for use with a nebulizer, either jet or ultrasonic, typically include hinge core

mimetibody or specified portion or variant composition protein in an aqueous solution at a concentration of about 1 mg to about 20 mg of at least one hinge core mimetibody or specified portion or variant protein per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the at least one hinge core mimetibody or specified portion or variant composition protein, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating at least one hinge core mimetibody or specified portion or variant composition proteins include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one hinge core mimetibody or specified portion or variant include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one hinge core mimetibody or specified portion or variant formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one hinge core mimetibody or specified portion or variant caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbital fatty acid esters. Amounts will generally range between 0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein such as hinge core mimetibody or specified portion or variant protein can also be included in the formulation.

Administration of hinge core mimetibody or specified portion or variant compositions By A Metered Dose Inhaler

In a metered dose inhaler (MDI), a propellant, at least one hinge core mimetibody or specified portion or variant, and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases the mixture as an aerosol, preferably containing particles in the size range of less than about 10 μm, preferably about 1 μm to about 5 μm, and most preferably about 2 μm to about 3 μm. The desired aerosol particle size can be obtained by employing a formulation of hinge core mimetibody or specified portion or variant composition protein produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

Formulations of at least one hinge core mimetibody or specified portion or variant for

use with a metered-dose inhaler device will generally include a finely divided powder containing at least one hinge core mimetibody or specified portion or variant as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluroalkane-134a), HFA-227 (hydrofluroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one hinge core mimetibody or specified portion or variant as a suspension in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a protein such as protein can also be included in the formulation.

One of ordinary skill in the art will recognize that the methods of the current invention can be achieved by pulmonary administration of at least one hinge core mimetibody or specified portion or variant compositions via devices not described herein.

Mucosal Formulations and Administration

For absorption through mucosal surfaces, compositions and methods of administering at least one hinge core mimetibody or specified portion or variant include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. Nos. 5,514,670). Mucous surfaces suitable for application of the emulsions of the present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g. suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include sugars, calcium stearate, magnesium stearate, pregelinatined starch, and the like (U.S. Pat. No. 5,849,695).

Oral Formulations and Administration

Formulations for oral rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether)

to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations may contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,5,871,753 are used to deliver biologically active agents orally are known in the art.

Transdermal Formulations and Administration

For transdermal administration, the at least one hinge core mimetibody or specified portion or variant is encapsulated in a delivery device such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known, including microparticles made of synthetic polymers such as polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other proteins, alginate and other polysaccharides, and combinations thereof (U.S. Pat. No. 5,814,599).

Prolonged Administration and Formulations

It can be sometimes desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms can be utilized.

For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow release, depot or implant formulations, e.g. gas or liquid liposomes are known in the literature (U.S. Pat. No. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Example 1: Cloning and Expression of hinge core mimetibody in Mammalian Cells

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the hinge core mimetibody or specified portion or variant coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pIRES1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clonetech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded hinge core mimetibody or specified portion or variant. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of hinge core mimetibody or specified portion or variants.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the

restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

Cloning and Expression in CHO Cells

The vector pC4 is used for the expression of hinge core mimetibody or specified portion or variant. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., J. Biol. Chem. 253:1357-1370 (1978); J. L. Hamlin and C. Ma, Biochem. et Biophys. Acta 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, Biotechnology 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains for expressing the gene of interest the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) (Boshart, et al., Cell 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLVI. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the EPO in a regulated way in mammalian cells (M. Gossen, and H. Bujard, Proc. Natl. Acad. Sci. USA 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a

selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

The DNA sequence encoding the complete hinge core mimetibody or specified portion or variant is used, corresponding to HC and LC variable regions of a hinge core mimetibody of the present invention, according to known method steps. Isolated nucleic acid encoding a suitable human constant region (i.e., HC and LC regions) is also used in this construct.

The isolated variable and constant region encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. 5 μg of the expression plasmid pC4 is cotransfected with 0.5 μg of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 μg /ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 μg /ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Additional constructs can be expressed with single or multiple amino acid changes in order to avoid undesirable activities. These changes may be expressed alone or multiple changes combined in a single construct. The cysteine normally involved in a disulfide bridge between the HC and LC will be mutated to an alanine. While this cysteine may be involved in stabilizing the construct by forming a third disulfide bridge, it is possible that it may aberrantly form a disulfide bond with other cyseines within the construct, or it could form a disulfide

linkage between two constructs. By removing the cysteine, proper folding and assembly could be enhanced and the possibility of self-association diminished.

It has been shown that mutation of two lysine (L) residues, L234 & L235, in the IgG1 lower hinge region to alanine (A) will abrogate the ability of the immunoglobulin to mediate complement dependent cytotoxicity (CDC) and antibody dependant cellular cytotoxicity (ADCC) (Hezereh et al., 2001, J. Virol., vol. **75** (24), 12161-68). Similar changes can be made in the hinge region of other immunoglobulin classes and subclasses.

Another modification that would result in a decrease in mediation of immune effector functions is the removal of the glycosylation attachment site. This can be accomplished by mutation of the asparagine to glutamine (Q). Aglycosylated versions of the IgG1 subclass are known to be poor mediators of immune effector function (Jefferis et al. 1998, Immol. Rev., vol. **163**, 50-76).

An additional modification that is currently being pursued is the replacement of the IgG1 CH2 and CH3 regions with the same regions of the IgG4 subtype while retaining the G1 hinge region. As discussed previously, the ability of the IgG4 subclass to mediate immune effector functions is much lower than that of the G1 subclass. So this construct is expected to retain activity without the concerns of potential immune effector functions.

Other envisioned modifications are those that would decrease the potential immunogenicity of the constructs. One important determinant of immunogenicity is the ability of peptides derived from a protein to be efficiently bound and presented by MHC molecules to T cells and to elicit a cell based immune response or T cell help for an antibody response. Using publicly available web based algorithms for MHC binding (SYFPETHI, Ramensee et al., 1999, Immunogenetics, vol. 50, 213-19 and BIMAS) potential MHC binding epitopes within the mimetibody were analyzed. Mutations that would decrease the predicted immunogenicity of one or more peptides are evaluated for *in vivo* effect on immunogenicity.

Advantages: The mimetibody constructs described above offers an alternative way of displaying bioactive peptides. In addition, proposed modifications are expected to, in combination and in addition to the novel features of mimetibodies of the present invention, enhance their utility.

It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the present invention

WHAT IS CLAIMED IS:

1. At least one hinge core mimetibody nucleic acid, comprising at least one polynucleotide encoding a polypeptide according to Formula (I):

((V(m)-P(n)-L(o)-H(p)-CH2(q)-CH3(r))(s),

where V is at least one portion of an N-terminus of an immunoglobulin variable region, P is at least one bioactive peptide, L is linker sequence, H is at least a portion of an immunoglobulin variable hinge region, CH2 is at least one portion of an immunoglobulin CH2 constant region, CH3 is at least one portion of an immunoglobulin CH3 constant region, and m, n, o, p, q, r and s, can independently be any integer between 0, 1 or 2 and 10.

2. At least one hinge core mimetibody polypeptide, comprising a polypeptide according to Formula (I):

((V(m)-P(n)-L(o)-H(p)-CH2(q)-CH3(r))(s),

where V is at least one portion of an N-terminus of an immunoglobulin variable region, P is at least one bioactive peptide selected from SEQ ID NOS:43-518, L is linker sequence, H is at least a portion of an immunoglobulin variable hinge region, CH2 is at least a portion of an immunoglobulin CH2 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, n and m can be independently an integer between 0, 1 or 2 and 10.

3. At least one hinge core mimetibody polypeptide, comprising a polypeptide according to Formula (I):

((V(m)-P(n)-L(o)-H(p)-CH2(q)-CH3(r))(s),

where V is at least one portion of an N-terminus of an immunoglobulin variable region, P is at least one bioactive peptide selected from SEQ ID NOS:519-979, L is linker sequence, H is at least a portion of an immunoglobulin variable hinge region, CH2 is at least a portion of an immunoglobulin CH2 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, n and m can be independently an integer between 0, 1 or 2 and 10.

4. A(n) hinge core mimetibody nucleic acid or hinge core mimetibody polypeptide according to claim 1, wherein said polypeptide has at least one activity of at least one P polypeptide.

5. A hinge core mimetibody antibody, comprising a monoclonal or polyclonal antibody, fusion protein, or fragment thereof, that specifically binds at least one hinge core mimetibody polypeptide according to claim 1.

6. A hinge core mimetibody nucleic acid encoding at least one hinge core mimetibody polypeptide or hinge core mimetibody antibody according to claim 1.

7. A hinge core mimetibody vector comprising at least one

isolated nucleic acid according to claim 6.

8. A hinge core mimetibody host cell comprising an isolated nucleic acid according to claim 7.

9. A hinge core mimetibody host cell according to claim 8, wherein said host cell is at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, NSO, DG44 CHO, CHO K1, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof.

10. A method for producing at least one hinge core mimetibody polypeptide or hinge core mimetibody antibody, comprising translating a nucleic acid according to claim 6 under conditions in vitro, in vivo or in situ, such that the hinge core mimetibody or antibody is expressed in detectable or recoverable amounts.

11. A composition comprising at least one hinge core mimetibody nucleic acid, hinge core mimetibody polypeptide, or hinge core mimetibody antibody according to claim 1.

12. A composition according to claim 11, wherein said composition further comprises at least one pharmaceutically acceptable carrier or diluent.

13. A composition according to claim 11, further comprising at least one composition comprising an therapeutically effective amount of at least one compound, composition or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

14. A composition according to claim 11, in a form of at least one selected from a liquid, gas, or dry, solution, mixture, suspension, emulsion or colloid, a lyophilized preparation, or a powder.

15. A method for diagnosing or treating a hinge core mimetibody ligand related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one hinge core mimetibody nucleic acid, polypeptide or antibody according to claim 1, with, or to, said cell, tissue, organ or animal.

16. A method according to claim 15, wherein said effective amount is 0.001-50 mg of hinge core mimetibody antibody; 0.000001-500 mg of said hinge

core mimetibody; or 0.0001-100μg of said hinge core mimetibody nucleic acid per kilogram of said cells, tissue, organ or animal.

17. A method according to claim 15, wherein said contacting or said administrating is by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

18. A method according to claim 15, further comprising administering, prior, concurrently or after said (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

19. A device, comprising at least one isolated hinge core mimetibody polypeptide, antibody or nucleic acid according to claim 1, wherein said device is suitable for contacting or administerting said at least one of said hinge core mimetibody polypeptide, antibody or nucleic acid, by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

20. An article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising at least one isolated hinge core mimetibody polypeptide, antibody or nucleic acid according to claim 1.

21. The article of manufacture of claim 20, wherein said container

is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

22. A method for producing at least one isolated hinge core mimetibody polypeptide, antibody or nucleic acid according to claim 1, comprising providing at least one host cell, transgenic animal, transgenic plant, plant cell capable of expressing in detectable or recoverable amounts said polypeptide, antibody or nucleic acid.

23. At least one hinge core mimetibody polypeptide, antibody or nucleic acid, produced by a method according to claim 22.

24. Any invention based on the disclosure presented herein.

Sequence Listing

<110> Huang, ChiChi;Heavner, George, A.;Knight, David, M.;Ghrayeb, John;Scallon, Bernard, J.;Nesspor, Thomas, C.; Centocor, Inc.

<120> HUMAN HINGE CORE MIMETIBODIES, COMPOSITIONS, METHODS AND USES

<130> CEN5038 PCT

<150> 60/507,231
<151> 2003-09-30

<160> 979

<170> PatentIn Ver 3.0

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Pro Gln

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Arg Pro Ser Pro Lys Ala
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Tyr Ala Leu Pro Leu
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Gly Leu

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Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
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Tyr Ala Leu Pro Leu
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Tyr Ala Leu Pro Leu
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Val Thr Asp Phe Tyr
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1 5 10 15

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<400> 248

Arg Ser Thr Ala Ser Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 249
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<213> Homo sapiens
<400> 249

Glu Ser Lys Glu Asp Gln Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 250
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<213> Homo sapiens
<400> 250

Glu Gly Leu Thr Met Lys Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 251
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<400> 251

Glu Gly Ser Arg Glu Gly Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 252
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<400> 252

Val Ile Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 253
<211> 12
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<213> Homo sapiens
<400> 253

Val Trp Tyr Trp Glu Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 254
<211> 12
<212> PRT
<213> Homo sapiens
<400> 254

Ala Ser Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 255
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<213> Homo sapiens
<400> 255

Phe Tyr Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 256
<211> 12
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<213> Homo sapiens
<400> 256

Glu Gly Trp Trp Val Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 257
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<212> PRT
<213> Homo sapiens
<400> 257

Trp Gly Glu Trp Leu Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 258
<211> 12
<212> PRT
<213> Homo sapiens
<400> 258

Asp Tyr Val Trp Glu Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 259
<211> 12
<212> PRT
<213> Homo sapiens
<400> 259

Ala His Thr Trp Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 260
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<400> 260

Phe Ile Glu Trp Phe Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 261
<211> 12
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<400> 261

Trp Leu Ala Trp Glu Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 262
<211> 12
<212> PRT
<213> Homo sapiens
<400> 262

Val Met Glu Trp Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 263
<211> 11
<212> PRT
<213> Homo sapiens
<400> 263

Glu Arg Met Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 264
<211> 12
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<213> Homo sapiens
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<223> Xaa at postitions 2, 3, 5, and 6 is any amino acid
<400> 264

Asn Xaa Xaa Trp Xaa Xaa Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 265
<211> 12
<212> PRT
<213> Homo sapiens
<400> 265

Trp Gly Asn Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 266
<211> 12
<212> PRT
<213> Homo sapiens
<400> 266

Thr Leu Tyr Trp Glu Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 267
<211> 12
<212> PRT
<213> Homo sapiens
<400> 267

Val Trp Arg Trp Glu Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 268
<211> 11
<212> PRT
<213> Homo sapiens
<400> 268

Leu Leu Trp Thr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 269
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postitions 5 and 6 is any amino acid
<400> 269

Ser Arg Ile Trp Xaa Xaa Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 270
<211> 12
<212> PRT
<213> Homo sapiens
<400> 270

Ser Asp Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 271

<211> 12
<212> PRT
<213> Homo sapiens
<220>
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<400> 271

Trp Gly Tyr Tyr Xaa Xaa Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 272
<211> 12
<212> PRT
<213> Homo sapiens
<400> 272

Thr Ser Gly Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 273
<211> 12
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<400> 273

Val His Pro Tyr Xaa Xaa Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 274
<211> 12
<212> PRT
<213> Homo sapiens
<400> 274

Glu His Ser Tyr Phe Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 275
<211> 12
<212> PRT
<213> Homo sapiens
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<400> 275

Xaa Xaa Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 276
<211> 12
<212> PRT
<213> Homo sapiens
<400> 276

Ala Gln Leu His Ser Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 277
<211> 12
<212> PRT
<213> Homo sapiens
<400> 277

Trp Ala Asn Trp Phe Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 278
<211> 12
<212> PRT
<213> Homo sapiens
<400> 278

Ser Arg Leu Tyr Ser Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 279
<211> 12
<212> PRT
<213> Homo sapiens
<400> 279

Gly Val Thr Phe Ser Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 280
<211> 12
<212> PRT
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<400> 280

Ser Ile Val Trp Ser Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 281
<211> 12
<212> PRT
<213> Homo sapiens
<400> 281

Ser Arg Asp Leu Val Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 282
<211> 17
<212> PRT
<213> Homo sapiens
<400> 282

His Trp Gly His Val Tyr Trp Gln Pro Tyr Ser Val Gln Asp Asp Leu
1 5 10 15

Gly

<210> 283
<211> 17
<212> PRT
<213> Homo sapiens
<400> 283

Ser Trp His Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Val Pro
1 5 10 15

Glu

<210> 284
<211> 17
<212> PRT
<213> Homo sapiens
<400> 284

Trp Arg Asp Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Pro Glu Ser
1 5 10 15

Ala

<210> 285
<211> 17
<212> PRT
<213> Homo sapiens
<400> 285

Thr Trp Asp Ala Val Tyr Trp Gln Pro Tyr Ser Val Gln Lys Trp Leu
1 5 10 15

Asp

<210> 286
<211> 17
<212> PRT
<213> Homo sapiens
<400> 286

Thr Pro Pro Trp Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Leu Asp
1 5 10 15

Pro

<210> 287
<211> 17
<212> PRT
<213> Homo sapiens
<400> 287

Tyr Trp Ser Ser Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Val His
1 5 10 15

Ser

<210> 288
<211> 10
<212> PRT
<213> Homo sapiens
<400> 288

Tyr Trp Tyr Gln Pro Tyr Ala Leu Gly Leu
1 5 10

<210> 289
<211> 10
<212> PRT
<213> Homo sapiens
<400> 289

Tyr Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 290
<211> 10
<212> PRT
<213> Homo sapiens
<400> 290

Glu Trp Ile Gln Pro Tyr Ala Thr Gly Leu
1 5 10

<210> 291
<211> 10
<212> PRT
<213> Homo sapiens
<400> 291

Asn Trp Glu Gln Pro Tyr Ala Lys Pro Leu
1 5 10

<210> 292
<211> 10
<212> PRT
<213> Homo sapiens
<400> 292

Ala Phe Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 293
<211> 10
<212> PRT
<213> Homo sapiens
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Phe Leu Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 294
<211> 10
<212> PRT
<213> Homo sapiens
<400> 294

Val Cys Lys Gln Pro Tyr Leu Glu Trp Cys
1 5 10

<210> 295
<211> 21
<212> PRT
<213> Homo sapiens
<400> 295

Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 296
<211> 21
<212> PRT
<213> Homo sapiens
<400> 296

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

Tyr Ala Leu Pro Leu
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<210> 297
<211> 21
<212> PRT
<213> Homo sapiens
<400> 297

Phe Ser Glu Ala Gly Tyr Thr Trp Pro Glu Asn Thr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 298
<211> 21
<212> PRT
<213> Homo sapiens
<400> 298

Thr Glu Ser Pro Gly Gly Leu Asp Trp Ala Lys Ile Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 299

<211> 21
<212> PRT
<213> Homo sapiens
<400> 299

Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 300
<211> 21
<212> PRT
<213> Homo sapiens
<400> 300

Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 301
<211> 21
<212> PRT
<213> Homo sapiens
<400> 301

Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 302
<211> 21
<212> PRT
<213> Homo sapiens
<400> 302

Met Asn Asp Gln Thr Ser Glu Val Ser Thr Phe Pro Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 303
<211> 21
<212> PRT
<213> Homo sapiens
<400> 303

Ser Trp Ser Glu Ala Phe Glu Gln Pro Arg Asn Leu Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
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<210> 304
<211> 21
<212> PRT
<213> Homo sapiens
<400> 304

Gln Tyr Ala Glu Pro Ser Ala Leu Asn Asp Trp Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 305
<211> 21
<212> PRT
<213> Homo sapiens
<400> 305

Asn Gly Asp Trp Ala Thr Ala Asp Trp Ser Asn Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
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<210> 306
<211> 15
<212> PRT
<213> Homo sapiens
<400> 306

Thr His Asp Glu His Ile Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 307
<211> 21
<212> PRT
<213> Homo sapiens
<400> 307

Met Leu Glu Lys Thr Tyr Thr Thr Trp Thr Pro Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 308
<211> 20
<212> PRT
<213> Homo sapiens
<400> 308

Trp Ser Asp Pro Leu Thr Arg Asp Ala Asp Leu Tyr Trp Gln Pro Tyr
1 5 10 15

Ala Leu Pro Leu
20

<210> 309
<211> 21
<212> PRT
<213> Homo sapiens
<400> 309

Ser Asp Ala Phe Thr Thr Gln Asp Ser Gln Ala Met Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 310
<211> 21
<212> PRT
<213> Homo sapiens
<400> 310

Gly Asp Asp Ala Ala Trp Arg Thr Asp Ser Leu Thr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 311
<211> 21
<212> PRT
<213> Homo sapiens
<400> 311

Ala Ile Ile Arg Gln Leu Tyr Arg Trp Ser Glu Met Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 312
<211> 21
<212> PRT
<213> Homo sapiens
<400> 312

Glu Asn Thr Tyr Ser Pro Asn Trp Ala Asp Ser Met Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 313
<211> 21
<212> PRT
<213> Homo sapiens
<400> 313

Met Asn Asp Gln Thr Ser Glu Val Ser Thr Phe Pro Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu

20

<210> 314
<211> 21
<212> PRT
<213> Homo sapiens
<400> 314

Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 315
<211> 21
<212> PRT
<213> Homo sapiens
<400> 315

Gln Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 316
<211> 21
<212> PRT
<213> Homo sapiens
<400> 316

Glu Asn Pro Phe Thr Trp Gln Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 317
<211> 21
<212> PRT
<213> Homo sapiens
<400> 317

Val Thr Pro Phe Thr Trp Glu Asp Ser Asn Val Phe Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 318
<211> 21
<212> PRT
<213> Homo sapiens
<400> 318

Gln Ile Pro Phe Thr Trp Glu Gln Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 319
<211> 21
<212> PRT
<213> Homo sapiens
<400> 319

Gln Ala Pro Leu Thr Trp Gln Glu Ser Ala Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 320
<211> 21
<212> PRT
<213> Homo sapiens
<400> 320

Glu Pro Thr Phe Thr Trp Glu Glu Ser Lys Ala Thr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 321
<211> 21
<212> PRT
<213> Homo sapiens
<400> 321

Thr Thr Thr Leu Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 322
<211> 21
<212> PRT
<213> Homo sapiens
<400> 322

Glu Ser Pro Leu Thr Trp Glu Glu Ser Ser Ala Leu Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 323
<211> 21
<212> PRT
<213> Homo sapiens
<400> 323

Glu Thr Pro Leu Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 324
<211> 21
<212> PRT
<213> Homo sapiens
<400> 324

Glu Ala Thr Phe Thr Trp Ala Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 325
<211> 21
<212> PRT
<213> Homo sapiens
<400> 325

Glu Ala Leu Phe Thr Trp Lys Glu Ser Thr Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 326
<211> 20
<212> PRT
<213> Homo sapiens
<400> 326

Ser Thr Pro Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro Tyr
1 5 10 15

Ala Leu Pro Leu
20

<210> 327
<211> 21
<212> PRT
<213> Homo sapiens
<400> 327

Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 328
<211> 21
<212> PRT
<213> Homo sapiens

<400> 328

Lys Ala Pro Phe Thr Trp Glu Glu Ser Gln Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 329
<211> 21
<212> PRT
<213> Homo sapiens
<400> 329

Ser Thr Ser Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 330
<211> 21
<212> PRT
<213> Homo sapiens
<400> 330

Asp Ser Thr Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 331
<211> 21
<212> PRT
<213> Homo sapiens
<400> 331

Tyr Ile Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 332
<211> 21
<212> PRT
<213> Homo sapiens
<400> 332

Gln Thr Ala Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 333
<211> 21

<212> PRT
<213> Homo sapiens
<400> 333

Glu Thr Leu Phe Thr Trp Glu Glu Ser Asn Ala Thr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 334
<211> 21
<212> PRT
<213> Homo sapiens
<400> 334

Val Ser Ser Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 335
<211> 7
<212> PRT
<213> Homo sapiens
<400> 335

Gln Pro Tyr Ala Leu Pro Leu
1 5

<210> 336
<211> 9
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 4 is any amino acid
<400> 336

Pro Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5

<210> 337
<211> 21
<212> PRT
<213> Homo sapiens
<400> 337

Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 338
<211> 15
<212> PRT
<213> Homo sapiens

<400> 338

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 339
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 339

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 340
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 340

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 341
<211> 21
<212> PRT
<213> Homo sapiens
<400> 341

Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 342
<211> 18
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 13 is any amino acid
<400> 342

Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 343
<211> 16
<212> PRT
<213> Homo sapiens
<400> 343

Ala Asp Val Leu Tyr Trp Gln Pro Tyr Ala Pro Val Thr Leu Trp Val
1 5 10 15

<210> 344
<211> 17
<212> PRT
<213> Homo sapiens
<400> 344

Gly Asp Val Ala Glu Tyr Trp Gln Pro Tyr Ala Leu Pro Leu Thr Ser
1 5 10 15

Leu

<210> 345
<211> 18
<212> PRT
<213> Homo sapiens
<400> 345

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

Gly Leu

<210> 346
<211> 15
<212> PRT
<213> Homo sapiens
<400> 346

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 347
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 347

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 348
<211> 15
<212> PRT
<213> Homo sapiens
<400> 348

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 349
<211> 15
<212> PRT

<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 349

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 350
<211> 15
<212> PRT
<213> Homo sapiens
<400> 350

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 351
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 351

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 352
<211> 21
<212> PRT
<213> Homo sapiens
<400> 352

Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 353
<211> 18
<212> PRT
<213> Homo sapiens
<400> 353

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

Gly Leu

<210> 354
<211> 21
<212> PRT
<213> Homo sapiens
<400> 354

Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Trp Ala Ile Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 355
<211> 21
<212> PRT
<213> Homo sapiens
<400> 355

Glu Asn Thr Tyr Ser Pro Asn Trp Ala Asp Ser Met Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 356
<211> 21
<212> PRT
<213> Homo sapiens
<400> 356

Ser Val Gly Glu Asp His Asn Phe Trp Thr Ser Glu Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 357
<211> 21
<212> PRT
<213> Homo sapiens
<400> 357

Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 358
<211> 15
<212> PRT
<213> Homo sapiens
<400> 358

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10 15

<210> 359
<211> 11
<212> PRT
<213> Homo sapiens
<400> 359

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr

1 5 10

<210> 360
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 360

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 361
<211> 10
<212> PRT
<213> Homo sapiens
<400> 361

Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr
1 5 10

<210> 362
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 362

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
1 5 10

<210> 363
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 363

Ala Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 364
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 364

Phe Ala Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 365
<211> 11

<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 365

Phe Glu Ala Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 366
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 366

Phe Glu Trp Ala Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 367
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 367

Phe Glu Trp Thr Ala Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 368
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 368

Phe Glu Trp Thr Pro Ala Tyr Trp Gln Xaa Tyr
1 5 10

<210> 369
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 369

Phe Glu Trp Thr Pro Gly Ala Trp Gln Xaa Tyr
1 5 10

<210> 370
<211> 11
<212> PRT
<213> Homo sapiens
<220>

<223> Xaa at postition 10 is any amino acid
<400> 370

Phe Glu Trp Thr Pro Gly Tyr Ala Gln Xaa Tyr
1 5 10

<210> 371
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 371

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Ala
1 5 10

<210> 372
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 372

Phe Glu Trp Thr Gly Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 373
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 373

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 374
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postitions 5 and 10 is any amino acid
<400> 374

Phe Glu Trp Thr Xaa Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 375
<211> 14
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 13 is any amino acid
<400> 375

Phe Glu Val Phe Phe Pro Glu Cys Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 376
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 11 is any amino acid
<400> 376

Phe Glu Trp Thr Pro Ala Ile Tyr Trp Gln Xaa Tyr
1 5 10

<210> 377
<211> 13
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 12 is any amino acid
<400> 377

Phe Glu Trp Thr Pro Ser Ala Arg Trp Tyr Gln Xaa Tyr
1 5 10

<210> 378
<211> 13
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 12 is any amino acid
<400> 378

Phe Glu Trp Thr Ser Ala Arg Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 379
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 379

Phe Glu Trp Thr Pro Asn Tyr Trp Gln Xaa Tyr
1 5 10

<210> 380
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 380

Phe Glu Trp Thr Pro Val Tyr Trp Gln Xaa Tyr
1 5 10

<210> 381
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 381

Phe Glu Trp Thr Val Pro Tyr Trp Gln Xaa Tyr
1 5 10

<210> 382
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 11 is any amino acid
<400> 382

Phe Glu Trp Thr Pro Gly Val Val Tyr Gln Xaa Tyr
1 5 10

<210> 383
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 11 is any amino acid
<400> 383

Phe Glu Val Phe Phe Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 384
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 384

Glu Val Phe Phe Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 385
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 385

Tyr Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 386
<211> 11

<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 386

Phe Glu Trp Val Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 387
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 387

Phe Glu Val Phe Phe Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 388
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 388

Phe Glu Val Phe Phe Pro Ser Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 389
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 389

Phe Glu Trp Thr Pro Asn Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 390
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 5 is any amino acid
<400> 390

Ser His Leu Tyr Xaa Gln Pro Tyr Ser Val Gln Met
1 5 10

<210> 391
<211> 13
<212> PRT
<213> Homo sapiens
<220>

<223> Xaa at postition 5 is any amino acid
<400> 391

Thr Leu Val Tyr Xaa Leu Asp Pro Tyr Ser Leu Gln Thr
1 5 10

<210> 392
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 5 is any amino acid
<400> 392

Arg Gly Asp Tyr Xaa Gln Pro Tyr Ser Val Gln Ser
1 5 10

<210> 393
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 5 is any amino acid
<400> 393

Asn Met Val Tyr Xaa Gln Pro Tyr Ser Ile Gln Thr
1 5 10

<210> 394
<211> 9
<212> PRT
<213> Homo sapiens
<400> 394

Val Tyr Trp Gln Pro Tyr Ser Val Gln
1 5

<210> 395
<211> 9
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 3 is any amino acid
<400> 395

Val Tyr Xaa Gln Pro Tyr Ser Val Gln
1 5

<210> 396
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 7 is any amino acid
<400> 396

Thr Phe Val Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10

<210> 397
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 397

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa
1 5 10

<210> 398
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 11 is any amino acid
<400> 398

Xaa Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa
1 5 10

<210> 399
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 399

Phe Glu Trp Thr Pro Gly Tyr Gln Xaa Tyr
1 5 10

<210> 400
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 400

Phe Glu Trp Thr Pro Gly Tyr Gln Xaa Tyr
1 5 10

<210> 401
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 401

Phe Glu Trp Thr Pro Gly Tyr Gln Xaa Tyr
1 5 10

<210> 402

<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 402

Phe Glu Trp Thr Pro Gly Tyr Gln Xaa Tyr
1 5 10

<210> 403
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 403

Phe Glu Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 404
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 404

Phe Glu Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 405
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 405

Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 406
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 406

Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 407
<211> 9
<212> PRT
<213> Homo sapiens

<400> 407

Val Tyr Trp Gln Pro Tyr Ser Val Gln
1 5

<210> 408
<211> 12
<212> PRT
<213> Homo sapiens
<400> 408

Arg Leu Val Tyr Trp Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 409
<211> 11
<212> PRT
<213> Homo sapiens
<400> 409

Arg Leu Val Tyr Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 410
<211> 12
<212> PRT
<213> Homo sapiens
<400> 410

Arg Leu Asp Tyr Trp Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 411
<211> 12
<212> PRT
<213> Homo sapiens
<400> 411

Arg Leu Val Trp Phe Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 412
<211> 12
<212> PRT
<213> Homo sapiens
<400> 412

Arg Leu Val Tyr Trp Gln Pro Tyr Ser Ile Gln Arg
1 5 10

<210> 413
<211> 11
<212> PRT
<213> Homo sapiens
<400> 413

Asp Asn Ser Ser Trp Tyr Asp Ser Phe Leu Leu

1 5 10

<210> 414
<211> 11
<212> PRT
<213> Homo sapiens
<400> 414

Asp Asn Thr Ala Trp Tyr Glu Ser Phe Leu Ala
1 5 10

<210> 415
<211> 11
<212> PRT
<213> Homo sapiens
<400> 415

Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu
1 5 10

<210> 416
<211> 17
<212> PRT
<213> Homo sapiens
<400> 416

Pro Ala Arg Glu Asp Asn Thr Ala Trp Tyr Asp Ser Phe Leu Ile Trp
1 5 10 15

Cys

<210> 417
<211> 17
<212> PRT
<213> Homo sapiens
<400> 417

Thr Ser Glu Tyr Asp Asn Thr Thr Trp Tyr Glu Lys Phe Leu Ala Ser
1 5 10 15

Gln

<210> 418
<211> 17
<212> PRT
<213> Homo sapiens
<400> 418

Ser Gln Ile Pro Asp Asn Thr Ala Trp Tyr Gln Ser Phe Leu Leu His
1 5 10 15

Gly

<210> 419
<211> 17

<212> PRT
<213> Homo sapiens
<400> 419

Ser Pro Phe Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Thr
1 5 10 15

Tyr

<210> 420
<211> 17
<212> PRT
<213> Homo sapiens
<400> 420

Glu Gln Ile Tyr Asp Asn Thr Ala Trp Tyr Asp His Phe Leu Leu Ser
1 5 10 15

Tyr

<210> 421
<211> 17
<212> PRT
<213> Homo sapiens
<400> 421

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

Tyr

<210> 422
<211> 17
<212> PRT
<213> Homo sapiens
<400> 422

Thr Tyr Thr Tyr Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Met Ser
1 5 10 15

Tyr

<210> 423
<211> 17
<212> PRT
<213> Homo sapiens
<400> 423

Thr Met Thr Gln Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Ser
1 5 10 15

Tyr

<210> 424
<211> 17
<212> PRT
<213> Homo sapiens
<400> 424

Thr Ile Asp Asn Thr Ala Trp Tyr Ala Asn Leu Val Gln Thr Tyr Pro
1 5 10 15

Gln

<210> 425
<211> 17
<212> PRT
<213> Homo sapiens
<400> 425

Thr Ile Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Ala Gln Tyr Pro
1 5 10 15

Asp

<210> 426
<211> 17
<212> PRT
<213> Homo sapiens
<400> 426

His Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Thr Tyr Thr
1 5 10 15

Pro

<210> 427
<211> 17
<212> PRT
<213> Homo sapiens
<400> 427

Ser Gln Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Ser Tyr Lys
1 5 10 15

Ala

<210> 428
<211> 17
<212> PRT
<213> Homo sapiens
<400> 428

Gln Ile Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Leu Gln Tyr Asn
1 5 10 15

Ala

<210> 429
<211> 17
<212> PRT
<213> Homo sapiens
<400> 429

Asn Gln Asp Asn Thr Ala Trp Tyr Glu Ser Phe Leu Leu Gln Tyr Asn
1 5 10 15

Thr

<210> 430
<211> 17
<212> PRT
<213> Homo sapiens
<400> 430

Thr Ile Asp Asn Thr Ala Trp Tyr Glu Asn Phe Leu Leu Asn His Asn
1 5 10 15

Leu

<210> 431
<211> 17
<212> PRT
<213> Homo sapiens
<400> 431

His Tyr Asp Asn Thr Ala Trp Tyr Glu Arg Phe Leu Gln Gln Gly Trp
1 5 10 15

His

<210> 432
<211> 21
<212> PRT
<213> Homo sapiens
<400> 432

Glu Thr Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 433
<211> 21
<212> PRT
<213> Homo sapiens
<400> 433

Tyr Ile Pro Phe Thr Trp Glu Glu Ser Asn Ala Tyr Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 434
<211> 21
<212> PRT
<213> Homo sapiens
<400> 434

Asp Gly Tyr Asp Arg Trp Arg Gln Ser Gly Glu Arg Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 435
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 5 is any amino acid
<400> 435

Tyr Ile Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10

<210> 436
<211> 21
<212> PRT
<213> Homo sapiens
<400> 436

Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 437
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 437

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 438
<211> 17
<212> PRT
<213> Homo sapiens
<400> 438

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro Tyr Ala Leu Pro Leu Ser
1 5 10 15

Asp

<210> 439
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 439

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 440
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 440

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 441
<211> 12
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 11 is any amino acid
<400> 441

Phe Glu Val Val Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 442
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 442

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
1 5 10

<210> 443
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 443

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 444
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 444

Phe Glu Trp Thr Pro Tyr Trp Gln Xaa Tyr
1 5 10

<210> 445
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 445

Phe Glu Trp Thr Pro Trp Tyr Gln Xaa Tyr
1 5 10

<210> 446
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 9 is any amino acid
<400> 446

Phe Glu Trp Thr Pro Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 447
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 447

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 448
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 448

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 449
<211> 15

<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 449

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr Ala Leu Pro Leu
1 5 10 15

<210> 450
<211> 21
<212> PRT
<213> Homo sapiens
<400> 450

Thr Ala Asn Val Ser Ser Phe Glu Trp Thr Pro Gly Tyr Trp Gln Pro
1 5 10 15

Tyr Ala Leu Pro Leu
20

<210> 451
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 451

Phe Glu Trp Thr Pro Gly Tyr Trp Gln Xaa Tyr
1 5 10

<210> 452
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 452

Phe Glu Trp Thr Pro Gly Trp Tyr Gln Xaa Tyr
1 5 10

<210> 453
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 453

Phe Glu Trp Thr Pro Gly Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 454
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> Xaa at postition 10 is any amino acid
<400> 454

Phe Glu Trp Thr Pro Ala Tyr Trp Gln Xaa Tyr
1 5 10

<210> 455
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 455

Phe Glu Trp Thr Pro Ala Trp Tyr Gln Xaa Tyr
1 5 10

<210> 456
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postition 10 is any amino acid
<400> 456

Phe Glu Trp Thr Pro Ala Tyr Tyr Gln Xaa Tyr
1 5 10

<210> 457
<211> 13
<212> PRT
<213> Homo sapiens
<400> 457

Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
1 5 10

<210> 458
<211> 14
<212> PRT
<213> Homo sapiens
<400> 458

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Lys Ala
1 5 10

<210> 459
<211> 14
<212> PRT
<213> Homo sapiens
<400> 459

Ile Glu Gly Pro Thr Leu Arg Glu Trp Leu Ala Ala Arg Ala
1 5 10

<210> 460

<211> 14
<212> PRT
<213> Homo sapiens
<400> 460

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
1 5 10

<210> 461
<211> 14
<212> PRT
<213> Homo sapiens
<400> 461

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Lys Ala
1 5 10

<210> 462
<211> 14
<212> PRT
<213> Homo sapiens
<400> 462

Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala
1 5 10

<210> 463
<211> 14
<212> PRT
<213> Homo sapiens
<400> 463

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
1 5 10

<210> 464
<211> 14
<212> PRT
<213> Homo sapiens
<400> 464

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
1 5 10

<210> 465
<211> 14
<212> PRT
<213> Homo sapiens
<400> 465

Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala
1 5 10

<210> 466
<211> 14
<212> PRT
<213> Homo sapiens

<400> 466

Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala
1 5 10

<210> 467
<211> 14
<212> PRT
<213> Homo sapiens
<400> 467

Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
1 5 10

<210> 468
<211> 9
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postitions 6, 7, and 8 is any amino acid
<400> 468

Val Arg Asp Gln Ile Xaa Xaa Xaa Leu
1 5

<210> 469
<211> 6
<212> PRT
<213> Homo sapiens
<400> 469

Thr Leu Arg Glu Trp Leu
1 5

<210> 470
<211> 10
<212> PRT
<213> Homo sapiens
<400> 470

Gly Arg Val Arg Asp Gln Val Ala Gly Trp
1 5 10

<210> 471
<211> 10
<212> PRT
<213> Homo sapiens
<400> 471

Gly Arg Val Lys Asp Gln Ile Ala Gln Leu
1 5 10

<210> 472
<211> 10
<212> PRT
<213> Homo sapiens
<400> 472

Gly Val Arg Asp Gln Val Ser Trp Ala Leu
1 5 10

<210> 473
<211> 10
<212> PRT
<213> Homo sapiens
<400> 473

Glu Ser Val Arg Glu Gln Val Met Lys Tyr
1 5 10

<210> 474
<211> 10
<212> PRT
<213> Homo sapiens
<400> 474

Ser Val Arg Ser Gln Ile Ser Ala Ser Leu
1 5 10

<210> 475
<211> 10
<212> PRT
<213> Homo sapiens
<400> 475

Gly Val Arg Glu Thr Val Tyr Arg His Met
1 5 10

<210> 476
<211> 11
<212> PRT
<213> Homo sapiens
<400> 476

Gly Val Arg Glu Val Ile Val Met His Met Leu
1 5 10

<210> 477
<211> 11
<212> PRT
<213> Homo sapiens
<400> 477

Gly Arg Val Arg Asp Gln Ile Trp Ala Ala Leu
1 5 10

<210> 478
<211> 11
<212> PRT
<213> Homo sapiens
<400> 478

Ala Gly Val Arg Asp Gln Ile Leu Ile Trp Leu
1 5 10

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Gly Arg Val Arg Asp Gln Ile Met Leu Ser Leu
1 5 10

<210> 480
<211> 11
<212> PRT
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<223> Xaa at postitions 8, 9, and 10 is any amino acid
<400> 480

Gly Arg Val Arg Asp Gln Ile Xaa Xaa Xaa Leu
1 5 10

<210> 481
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<213> Homo sapiens
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Cys Thr Leu Arg Gln Trp Leu Gln Gly Cys
1 5 10

<210> 482
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<213> Homo sapiens
<400> 482

Cys Thr Leu Gln Glu Phe Leu Glu Gly Cys
1 5 10

<210> 483
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<213> Homo sapiens
<400> 483

Cys Thr Arg Thr Glu Trp Leu His Gly Cys
1 5 10

<210> 484
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<213> Homo sapiens
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Cys Thr Leu Arg Glu Trp Leu His Gly Gly Phe Cys
1 5 10

<210> 485
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<213> Homo sapiens
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Cys Thr Leu Arg Glu Trp Val Phe Ala Gly Leu Cys
1 5 10

<210> 486
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Cys Thr Leu Arg Gln Trp Leu Ile Leu Leu Gly Met Cys
1 5 10

<210> 487
<211> 14
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<213> Homo sapiens
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Cys Thr Leu Ala Glu Phe Leu Ala Ser Gly Val Glu Gln Cys
1 5 10

<210> 488
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<212> PRT
<213> Homo sapiens
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Cys Ser Leu Gln Glu Phe Leu Ser His Gly Gly Tyr Val Cys
1 5 10

<210> 489
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<213> Homo sapiens
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Cys Thr Leu Arg Glu Phe Leu Asp Pro Thr Thr Ala Val Cys
1 5 10

<210> 490
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<213> Homo sapiens
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Cys Thr Leu Lys Glu Trp Leu Val Ser His Glu Val Trp Cys
1 5 10

<210> 491
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<212> PRT
<213> Homo sapiens
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1 5 10

<210> 492
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<223> Xaa at postitions 8, 9, and 10 is any amino acid
<400> 492

Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Cys
1 5 10

<210> 493
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<223> Xaa at postitions 8, 9, 10, and 11 is any amino acid
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Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Cys
1 5 10

<210> 494
<211> 13
<212> PRT
<213> Homo sapiens
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<223> Xaa at postitions 8, 9, 10, 11, and 12 is any amino acid
<400> 494

Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Xaa Cys
1 5 10

<210> 495
<211> 14
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<213> Homo sapiens
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<223> Xaa at postitions 8, 9, 10, 11, 12, and 13 is any amino acid
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Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Xaa Xaa Cys
1 5 10

<210> 496
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<213> Homo sapiens
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Arg Glu Gly Pro Thr Leu Arg Gln Trp Met
1 5 10

<210> 497
<211> 10
<212> PRT
<213> Homo sapiens
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Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala
1 5 10

<210> 498
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<212> PRT
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<400> 498

Glu Arg Gly Pro Phe Trp Ala Lys Ala Cys
1 5 10

<210> 499
<211> 10
<212> PRT
<213> Homo sapiens
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Arg Glu Gly Pro Arg Cys Val Met Trp Met
1 5 10

<210> 500
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<212> PRT
<213> Homo sapiens
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Cys Gly Thr Glu Gly Pro Thr Leu Ser Thr Trp Leu Asp Cys
1 5 10

<210> 501
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<213> Homo sapiens
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Cys Glu Gln Asp Gly Pro Thr Leu Leu Glu Trp Leu Lys Cys
1 5 10

<210> 502
<211> 14
<212> PRT
<213> Homo sapiens
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Cys Glu Leu Val Gly Pro Ser Leu Met Ser Trp Leu Thr Cys
1 5 10

<210> 503
<211> 14
<212> PRT
<213> Homo sapiens
<400> 503

Cys Leu Thr Gly Pro Phe Val Thr Gln Trp Leu Tyr Glu Cys
1 5 10

<210> 504
<211> 14
<212> PRT
<213> Homo sapiens
<400> 504

Cys Arg Ala Gly Pro Thr Leu Leu Glu Trp Leu Thr Leu Cys
1 5 10

<210> 505
<211> 14
<212> PRT
<213> Homo sapiens
<400> 505

Cys Ala Asp Gly Pro Thr Leu Arg Glu Trp Ile Ser Phe Cys
1 5 10

<210> 506
<211> 13
<212> PRT
<213> Homo sapiens
<220>
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<400> 506

Cys Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Cys
1 5 10

<210> 507
<211> 14
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2, 12 and 13 is any amino acid
<400> 507

Cys Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Xaa Cys
1 5 10

<210> 508
<211> 14
<212> PRT
<213> Homo sapiens
<220>

<223> Xaa at positions 2, 3, and 13 is any amino acid
<400> 508

Cys Xaa Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Cys
1 5 10

<210> 509
<211> 15
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<220>
<223> Xaa at positions 2, 3, 13, and 14 is any amino acid
<400> 509

Cys Xaa Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Xaa Cys
1 5 10 15

<210> 510
<211> 13
<212> PRT
<213> Homo sapiens
<220>
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<400> 510

Cys Xaa Glu Gly Pro Thr Leu Arg Glu Trp Leu Xaa Cys
1 5 10

<210> 511
<211> 16
<212> PRT
<213> Homo sapiens
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Gly Gly Cys Thr Leu Arg Glu Trp Leu His Gly Gly Phe Cys Gly Gly
1 5 10 15

<210> 512
<211> 18
<212> PRT
<213> Homo sapiens
<400> 512

Gly Gly Cys Ala Asp Gly Pro Thr Leu Arg Glu Trp Ile Ser Phe Cys
1 5 10 15

Gly Gly

<210> 513
<211> 19
<212> PRT
<213> Homo sapiens
<400> 513

Gly Asn Ala Asp Gly Pro Thr Leu Arg Gln Trp Leu Glu Gly Arg Arg
1 5 10 15

Pro Lys Asn

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<211> 19
<212> PRT
<213> Homo sapiens
<400> 514

Leu Ala Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu His Gly Asn Gly
1 5 10 15

Arg Asp Thr

<210> 515
<211> 19
<212> PRT
<213> Homo sapiens
<400> 515

His Gly Arg Val Gly Pro Thr Leu Arg Glu Trp Lys Thr Gln Val Ala
1 5 10 15

Thr Lys Lys

<210> 516
<211> 18
<212> PRT
<213> Homo sapiens
<400> 516

Thr Ile Lys Gly Pro Thr Leu Arg Gln Trp Leu Lys Ser Arg Glu His
1 5 10 15

Thr Ser

<210> 517
<211> 18
<212> PRT
<213> Homo sapiens
<400> 517

Ile Ser Asp Gly Pro Thr Leu Lys Glu Trp Leu Ser Val Thr Arg Gly
1 5 10 15

Ala Ser

<210> 518
<211> 18
<212> PRT
<213> Homo sapiens
<400> 518

Ser Ile Glu Gly Pro Thr Leu Arg Glu Trp Leu Thr Ser Arg Thr Pro

1 5 10 15

His Ser

<210> 519
<211> 5
<212> PRT
<213> Homo sapiens
<400> 519

Glu Glu Asp Cys Lys
1 5

<210> 520
<211> 5
<212> PRT
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Glu Glu Asp Cys Lys
1 5

<210> 521
<211> 5
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<213> Homo sapiens
<400> 521

Glu Glu Asp Cys Lys
1 5

<210> 522
<211> 5
<212> PRT
<213> Homo sapiens
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<223> Xaa at position 4 is any amino acid
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Glu Glu Asp Xaa Lys
1 5

<210> 523
<211> 5
<212> PRT
<213> Homo sapiens
<400> 523

Glu Glu Asp Cys Lys
1 5

<210> 524
<211> 5
<212> PRT
<213> Homo sapiens
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<223> Xaa at position 4 is any amino acid
<400> 524

Glu Glu Asp Xaa Lys
1 5

<210> 525
<211> 11
<212> PRT
<213> Homo sapiens
<400> 525

Tyr Cys Phe Thr Ala Ser Glu Asn His Cys Tyr
1 5 10

<210> 526
<211> 11
<212> PRT
<213> Homo sapiens
<400> 526

Tyr Cys Phe Thr Asn Ser Glu Asn His Cys Tyr
1 5 10

<210> 527
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<212> PRT
<213> Homo sapiens
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Tyr Cys Phe Thr Arg Ser Glu Asn His Cys Tyr
1 5 10

<210> 528
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<212> PRT
<213> Homo sapiens
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Phe Cys Ala Ser Glu Asn His Cys Tyr
1 5

<210> 529
<211> 9
<212> PRT
<213> Homo sapiens
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Tyr Cys Ala Ser Glu Asn His Cys Tyr
1 5

<210> 530
<211> 9
<212> PRT
<213> Homo sapiens
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Phe Cys Asn Ser Glu Asn His Cys Tyr

1 5

<210> 531
<211> 9
<212> PRT
<213> Homo sapiens
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Phe Cys Asn Ser Glu Asn Arg Cys Tyr
1 5

<210> 532
<211> 10
<212> PRT
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Phe Cys Asn Ser Val Glu Asn Arg Cys Tyr
1 5 10

<210> 533
<211> 11
<212> PRT
<213> Homo sapiens
<400> 533

Tyr Cys Ser Gln Ser Val Ser Asn Asp Cys Phe
1 5 10

<210> 534
<211> 9
<212> PRT
<213> Homo sapiens
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Phe Cys Val Ser Asn Asp Arg Cys Tyr
1 5

<210> 535
<211> 11
<212> PRT
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Tyr Cys Arg Lys Glu Leu Gly Gln Val Cys Tyr
1 5 10

<210> 536
<211> 9
<212> PRT
<213> Homo sapiens
<400> 536

Tyr Cys Lys Glu Pro Gly Gln Cys Tyr
1 5

<210> 537
<211> 9
<212> PRT
<213> Homo sapiens
<400> 537

Tyr Cys Arg Lys Glu Met Gly Cys Tyr
1 5

<210> 538
<211> 9
<212> PRT
<213> Homo sapiens
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Phe Cys Arg Lys Glu Met Gly Cys Tyr
1 5

<210> 539
<211> 9
<212> PRT
<213> Homo sapiens
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Tyr Cys Trp Ser Gln Asn Leu Cys Tyr
1 5

<210> 540
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<212> PRT
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Tyr Cys Glu Leu Ser Gln Tyr Leu Cys Tyr
1 5 10

<210> 541
<211> 9
<212> PRT
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Tyr Cys Trp Ser Gln Asn Tyr Cys Tyr
1 5

<210> 542
<211> 9
<212> PRT
<213> Homo sapiens
<400> 542

Tyr Cys Trp Ser Gln Tyr Leu Cys Tyr
1 5

<210> 543
<211> 15
<212> PRT

<213> Homo sapiens
<400> 543

Asp Phe Leu Pro His Tyr Lys Asn Thr Ser Leu Gly His Arg Pro
1 5 10 15

<210> 544
<211> 7
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2 and 7 is any amino acid
<400> 544

Arg Xaa Glu Thr Xaa Trp Xaa
1 5

<210> 545
<211> 7
<212> PRT
<213> Homo sapiens
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<223> Xaa at positions 2 and 5 is any amino acid
<400> 545

Arg Xaa Glu Thr Xaa Trp Xaa
1 5

<210> 546
<211> 5
<212> PRT
<213> Homo sapiens
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<223> Xaa at position 5 is any amino acid
<400> 546

Arg Gly Asp Gly Xaa
1 5

<210> 547
<211> 7
<212> PRT
<213> Homo sapiens
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<223> Xaa at position 6 is any amino acid
<400> 547

Cys Arg Gly Asp Gly Xaa Cys
1 5

<210> 548
<211> 9
<212> PRT
<213> Homo sapiens
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<223> Xaa at positions 2, 3, 7 and 8 is any amino acid
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Cys Xaa Xaa Arg Leu Asp Xaa Xaa Cys
1 5

<210> 549
<211> 9
<212> PRT
<213> Homo sapiens
<400> 549

Cys Ala Arg Arg Leu Asp Ala Pro Cys
1 5

<210> 550
<211> 9
<212> PRT
<213> Homo sapiens
<400> 550

Cys Pro Ser Arg Leu Asp Ser Pro Cys
1 5

<210> 551
<211> 9
<212> PRT
<213> Homo sapiens
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<223> Xaa at positions 1, 2, 3, 7, 8, and 9 is any amino acid
<400> 551

Xaa Xaa Xaa Arg Gly Asp Xaa Xaa Xaa
1 5

<210> 552
<211> 9
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2 and 8 is any amino acid
<400> 552

Cys Xaa Cys Arg Gly Asp Cys Xaa Cys
1 5

<210> 553
<211> 9
<212> PRT
<213> Homo sapiens
<400> 553

Cys Asp Cys Arg Gly Asp Cys Phe Cys
1 5

<210> 554
<211> 9
<212> PRT
<213> Homo sapiens
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Cys Asp Cys Arg Gly Asp Cys Leu Cys
1 5

<210> 555
<211> 9
<212> PRT
<213> Homo sapiens
<400> 555

Cys Leu Cys Arg Gly Asp Cys Ile Cys
1 5

<210> 556
<211> 8
<212> PRT
<213> Homo sapiens
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<223> Xaa at positions 1, 2, 5, 6, 7, and 8 is any amino acid
<400> 556

Xaa Xaa Asp Asp Xaa Xaa Xaa Xaa
1 5

<210> 557
<211> 10
<212> PRT
<213> Homo sapiens
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<223> Xaa at positions 1, 2, 3, and 6, 7, 8, 9, and 10 is any amino acid
<400> 557

Xaa Xaa Xaa Asp Asp Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 558
<211> 7
<212> PRT
<213> Homo sapiens
<400> 558

Cys Trp Asp Asp Gly Trp Leu
1 5

<210> 559
<211> 9
<212> PRT
<213> Homo sapiens
<400> 559

Cys Trp Asp Asp Leu Trp Trp Leu Cys
1 5

<210> 560
<211> 8
<212> PRT
<213> Homo sapiens

<400> 560

Cys Trp Asp Asp Gly Leu Met Cys
1 5

<210> 561
<211> 8
<212> PRT
<213> Homo sapiens
<400> 561

Cys Trp Asp Asp Gly Trp Met Cys
1 5

<210> 562
<211> 9
<212> PRT
<213> Homo sapiens
<400> 562

Cys Ser Trp Asp Asp Gly Trp Leu Cys
1 5

<210> 563
<211> 9
<212> PRT
<213> Homo sapiens
<400> 563

Cys Pro Asp Asp Leu Trp Trp Leu Cys
1 5

<210> 564
<211> 13
<212> PRT
<213> Homo sapiens
<400> 564

Cys Gly Arg Glu Cys Pro Arg Leu Cys Gln Ser Ser Cys
1 5 10

<210> 565
<211> 13
<212> PRT
<213> Homo sapiens
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Cys Asn Gly Arg Cys Val Ser Gly Cys Ala Gly Arg Cys
1 5 10

<210> 566
<211> 8
<212> PRT
<213> Homo sapiens
<400> 566

Cys Leu Ser Gly Ser Leu Ser Cys

1 5

<210> 567
<211> 6
<212> PRT
<213> Homo sapiens
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Asn Gly Arg Ala His Ala
1 5

<210> 568
<211> 5
<212> PRT
<213> Homo sapiens
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Cys Asn Gly Arg Cys
1 5

<210> 569
<211> 9
<212> PRT
<213> Homo sapiens
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Cys Asp Cys Arg Gly Asp Cys Phe Cys
1 5

<210> 570
<211> 7
<212> PRT
<213> Homo sapiens
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Cys Gly Ser Leu Val Arg Cys
1 5

<210> 571
<211> 5
<212> PRT
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Asp Leu Xaa Xaa Leu
1 5

<210> 572
<211> 12
<212> PRT
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<400> 572

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr Thr Leu
1 5 10

<210> 573
<211> 10
<212> PRT
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<400> 573

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr
1 5 10

<210> 574
<211> 9
<212> PRT
<213> Homo sapiens
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Arg Thr Asp Leu Asp Ser Leu Arg Thr
1 5

<210> 575
<211> 8
<212> PRT
<213> Homo sapiens
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Arg Thr Asp Leu Asp Ser Leu Arg
1 5

<210> 576
<211> 12
<212> PRT
<213> Homo sapiens
<400> 576

Gly Asp Leu Asp Leu Leu Lys Leu Arg Leu Thr Leu
1 5 10

<210> 577
<211> 12
<212> PRT
<213> Homo sapiens
<400> 577

Gly Asp Leu His Ser Leu Arg Gln Leu Leu Ser Arg
1 5 10

<210> 578
<211> 12
<212> PRT
<213> Homo sapiens
<400> 578

Arg Asp Asp Leu His Met Leu Arg Leu Gln Leu Trp
1 5 10

<210> 579

<211> 12
<212> PRT
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Ser Ser Asp Leu His Ala Leu Lys Lys Arg Tyr Gly
1 5 10

<210> 580
<211> 12
<212> PRT
<213> Homo sapiens
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Arg Gly Asp Leu Lys Gln Leu Ser Glu Leu Thr Trp
1 5 10

<210> 581
<211> 12
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<400> 581

Arg Gly Asp Leu Ala Ala Leu Ser Ala Pro Pro Val
1 5 10

<210> 582
<211> 12
<212> PRT
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Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 583
<211> 12
<212> PRT
<213> Homo sapiens
<400> 583

Asp Ile Thr Trp Asp Glu Leu Trp Lys Ile Met Asn
1 5 10

<210> 584
<211> 12
<212> PRT
<213> Homo sapiens
<400> 584

Asp Tyr Thr Trp Phe Glu Leu Trp Asp Met Met Gln
1 5 10

<210> 585
<211> 12
<212> PRT
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<400> 585

Gln Ile Thr Trp Ala Gln Leu Trp Asn Met Met Lys
1 5 10

<210> 586
<211> 12
<212> PRT
<213> Homo sapiens
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Asp Met Thr Trp His Asp Leu Trp Thr Leu Met Ser
1 5 10

<210> 587
<211> 12
<212> PRT
<213> Homo sapiens
<400> 587

Asp Tyr Ser Trp His Asp Leu Trp Glu Met Met Ser
1 5 10

<210> 588
<211> 12
<212> PRT
<213> Homo sapiens
<400> 588

Glu Ile Thr Trp Asp Gln Leu Trp Glu Val Met Asn
1 5 10

<210> 589
<211> 12
<212> PRT
<213> Homo sapiens
<400> 589

His Val Ser Trp Glu Gln Leu Trp Asp Ile Met Asn
1 5 10

<210> 590
<211> 12
<212> PRT
<213> Homo sapiens
<400> 590

His Ile Thr Trp Asp Gln Leu Trp Arg Ile Met Thr
1 5 10

<210> 591
<211> 13
<212> PRT
<213> Homo sapiens
<400> 591

Arg Asn Met Ser Trp Leu Glu Leu Trp Glu His Met Lys

1 5 10

<210> 592
<211> 18
<212> PRT
<213> Homo sapiens
<400> 592

Ala Glu Trp Thr Trp Asp Gln Leu Trp His Val Met Asn Pro Ala Glu
1 5 10 15

Ser Gln

<210> 593
<211> 14
<212> PRT
<213> Homo sapiens
<400> 593

His Arg Ala Glu Trp Leu Ala Leu Trp Glu Gln Met Ser Pro
1 5 10

<210> 594
<211> 14
<212> PRT
<213> Homo sapiens
<400> 594

Lys Lys Glu Asp Trp Leu Ala Leu Trp Arg Ile Met Ser Val
1 5 10

<210> 595
<211> 11
<212> PRT
<213> Homo sapiens
<400> 595

Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 596
<211> 12
<212> PRT
<213> Homo sapiens
<400> 596

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 597
<211> 12
<212> PRT
<213> Homo sapiens
<400> 597

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys

1 5 10

<210> 598
<211> 12
<212> PRT
<213> Homo sapiens
<400> 598

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 599
<211> 16
<212> PRT
<213> Homo sapiens
<400> 599

Cys Gln Asn Arg Tyr Thr Asp Leu Val Ala Ile Gln Asn Lys Asn Glu
1 5 10 15

<210> 600
<211> 17
<212> PRT
<213> Homo sapiens
<400> 600

Ala Glu Asn Trp Ala Asp Asn Glu Pro Asn Asn Lys Arg Asn Asn Glu
1 5 10 15

Asp

<210> 601
<211> 19
<212> PRT
<213> Homo sapiens
<400> 601

Arg Lys Asn Asn Lys Thr Trp Thr Trp Val Gly Thr Lys Lys Ala Leu
1 5 10 15

Thr Asn Glu

<210> 602
<211> 13
<212> PRT
<213> Homo sapiens
<400> 602

Lys Lys Ala Leu Thr Asn Glu Ala Glu Asn Trp Ala Asp
1 5 10

<210> 603
<211> 16
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 3 and 15 is any amino acid
<400> 603

Cys Gln Xaa Arg Tyr Thr Asp Leu Val Ala Ile Gln Asn Lys Xaa Glu
1 5 10 15

<210> 604
<211> 19
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 3, 5, 6, 13 and 15 is any amino acid
<400> 604

Arg Lys Xaa Asn Xaa Xaa Trp Thr Trp Val Gly Thr Xaa Lys Xaa Leu
1 5 10 15

Thr Glu Glu

<210> 605
<211> 17
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 13 and 15 is any amino acid
<400> 605

Ala Glu Asn Trp Ala Asp Gly Glu Pro Asn Asn Lys Xaa Asn Xaa Glu
1 5 10 15

Asp

<210> 606
<211> 16
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2, 3, 4, 7, and 15 is any amino acid
<400> 606

Cys Xaa Xaa Xaa Tyr Thr Xaa Leu Val Ala Ile Gln Asn Lys Xaa Glu
1 5 10 15

<210> 607
<211> 19
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at postitions 3-6, 8, 13, 15 and 18 is any amino acid
<400> 607

Arg Lys Xaa Xaa Xaa Xaa Trp Xaa Trp Val Gly Thr Xaa Lys Xaa Leu
1 5 10 15

Thr Xaa Glu

<210> 608

<211> 16
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2, 5, 6, 7, 12, 13 and 14 is any amino acid
<400> 608

Ala Xaa Asn Trp Xaa Xaa Xaa Glu Pro Asn Asn Xaa Xaa Xaa Glu Asp
1 5 10 15

<210> 609
<211> 13
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 1, 3, 6, 9, 12, and 13 is any amino acid
<400> 609

Xaa Lys Xaa Lys Thr Xaa Glu Ala Xaa Asn Trp Xaa Xaa
1 5 10

<210> 610
<211> 33
<212> PRT
<213> Homo sapiens
<400> 610

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
1 5 10 15

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

Gln

<210> 611
<211> 33
<212> PRT
<213> Homo sapiens
<400> 611

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
1 5 10 15

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

Glu

<210> 612
<211> 22
<212> PRT
<213> Homo sapiens
<400> 612

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
1 5 10 15

Thr Leu Leu Ser Ala Val
20

<210> 613
<211> 22
<212> PRT
<213> Homo sapiens
<400> 613

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
1 5 10 15

Thr Leu Leu Ser Ala Val
20

<210> 614
<211> 23
<212> PRT
<213> Homo sapiens
<400> 614

Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe
1 5 10 15

Lys Thr Leu Leu Ser Ala Val
20

<210> 615
<211> 24
<212> PRT
<213> Homo sapiens
<400> 615

Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
1 5 10 15

Phe Lys Thr Leu Leu Ser Ala Val
20

<210> 616
<211> 24
<212> PRT
<213> Homo sapiens
<400> 616

Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
1 5 10 15

Phe Lys Thr Leu Leu Ser Ala Val
20

<210> 617
<211> 11
<212> PRT
<213> Homo sapiens
<400> 617

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser
1 5 10

<210> 618
<211> 26
<212> PRT
<213> Homo sapiens
<400> 618

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu
1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

<210> 619
<211> 26
<212> PRT
<213> Homo sapiens
<400> 619

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu
1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

<210> 620
<211> 26
<212> PRT
<213> Homo sapiens
<400> 620

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu
1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

<210> 621
<211> 22
<212> PRT
<213> Homo sapiens
<400> 621

Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu
1 5 10 15

Ile Ser Trp Ile Lys Arg
20

<210> 622
<211> 19
<212> PRT
<213> Homo sapiens
<400> 622

Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu Ile Ser Trp

1 5 10 15

Ile Lys Arg

<210> 623
<211> 12
<212> PRT
<213> Homo sapiens
<400> 623

Lys Leu Leu Leu Leu Leu Lys Leu Leu Leu Leu Lys
1 5 10

<210> 624
<211> 12
<212> PRT
<213> Homo sapiens
<400> 624

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 625
<211> 12
<212> PRT
<213> Homo sapiens
<400> 625

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 626
<211> 12
<212> PRT
<213> Homo sapiens
<400> 626

Lys Lys Leu Leu Lys Leu Lys Leu Lys Leu Lys Lys
1 5 10

<210> 627
<211> 12
<212> PRT
<213> Homo sapiens
<400> 627

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 628
<211> 12
<212> PRT
<213> Homo sapiens
<400> 628

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys

1 5 10

<210> 629
<211> 6
<212> PRT
<213> Homo sapiens
<400> 629

Lys Leu Leu Leu Leu Lys
1 5

<210> 630
<211> 8
<212> PRT
<213> Homo sapiens
<400> 630

Lys Leu Leu Leu Lys Leu Leu Lys
1 5

<210> 631
<211> 12
<212> PRT
<213> Homo sapiens
<400> 631

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 632
<211> 12
<212> PRT
<213> Homo sapiens
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Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 633
<211> 12
<212> PRT
<213> Homo sapiens
<400> 633

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 634
<211> 12
<212> PRT
<213> Homo sapiens
<400> 634

Lys Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Lys
1 5 10

<210> 635

<211> 12
<212> PRT
<213> Homo sapiens
<400> 635

Lys Val Val Val Lys Val Val Val Lys Val Val Lys
1 5 10

<210> 636
<211> 12
<212> PRT
<213> Homo sapiens
<400> 636

Lys Val Val Val Lys Val Lys Val Lys Val Val Lys
1 5 10

<210> 637
<211> 11
<212> PRT
<213> Homo sapiens
<400> 637

Lys Val Val Val Lys Val Lys Val Lys Val Lys
1 5 10

<210> 638
<211> 12
<212> PRT
<213> Homo sapiens
<400> 638

Lys Val Val Val Lys Val Lys Val Lys Val Val Lys
1 5 10

<210> 639
<211> 6
<212> PRT
<213> Homo sapiens
<400> 639

Lys Leu Ile Leu Lys Leu
1 5

<210> 640
<211> 6
<212> PRT
<213> Homo sapiens
<400> 640

Lys Val Leu His Leu Leu
1 5

<210> 641
<211> 6
<212> PRT
<213> Homo sapiens

<400> 641

Leu Lys Leu Arg Leu Leu
1 5

<210> 642
<211> 6
<212> PRT
<213> Homo sapiens
<400> 642

Lys Pro Leu His Leu Leu
1 5

<210> 643
<211> 8
<212> PRT
<213> Homo sapiens
<400> 643

Lys Leu Ile Leu Lys Leu Val Arg
1 5

<210> 644
<211> 8
<212> PRT
<213> Homo sapiens
<400> 644

Lys Val Phe His Leu Leu His Leu
1 5

<210> 645
<211> 8
<212> PRT
<213> Homo sapiens
<400> 645

His Lys Phe Arg Ile Leu Lys Leu
1 5

<210> 646
<211> 8
<212> PRT
<213> Homo sapiens
<400> 646

Lys Pro Phe His Ile Leu His Leu
1 5

<210> 647
<211> 12
<212> PRT
<213> Homo sapiens
<400> 647

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys

1 5 10

<210> 648
<211> 12
<212> PRT
<213> Homo sapiens
<400> 648

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 649
<211> 12
<212> PRT
<213> Homo sapiens
<400> 649

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 650
<211> 12
<212> PRT
<213> Homo sapiens
<400> 650

Lys Ile Pro Ile Lys Ile Lys Ile Lys Ile Pro Lys
1 5 10

<210> 651
<211> 12
<212> PRT
<213> Homo sapiens
<400> 651

Lys Ile Pro Ile Lys Ile Lys Ile Lys Ile Val Lys
1 5 10

<210> 652
<211> 12
<212> PRT
<213> Homo sapiens
<400> 652

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

<210> 653
<211> 12
<212> PRT
<213> Homo sapiens
<400> 653

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

<210> 654
<211> 12
<212> PRT
<213> Homo sapiens
<400> 654

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

<210> 655
<211> 12
<212> PRT
<213> Homo sapiens
<400> 655

Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg
1 5 10

<210> 656
<211> 12
<212> PRT
<213> Homo sapiens
<400> 656

Arg Ile Ile Val Arg Ile Arg Leu Arg Ile Ile Arg
1 5 10

<210> 657
<211> 12
<212> PRT
<213> Homo sapiens
<400> 657

Arg Ile Gly Ile Arg Leu Arg Val Arg Ile Ile Arg
1 5 10

<210> 658
<211> 12
<212> PRT
<213> Homo sapiens
<400> 658

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg
1 5 10

<210> 659
<211> 12
<212> PRT
<213> Homo sapiens
<400> 659

Arg Ile Ala Val Lys Trp Arg Leu Arg Phe Ile Lys
1 5 10

<210> 660
<211> 12
<212> PRT

<213> Homo sapiens
<400> 660

Lys Ile Gly Trp Lys Leu Arg Val Arg Ile Ile Arg
1 5 10

<210> 661
<211> 12
<212> PRT
<213> Homo sapiens
<400> 661

Lys Lys Ile Gly Trp Leu Ile Ile Arg Val Arg Arg
1 5 10

<210> 662
<211> 14
<212> PRT
<213> Homo sapiens
<400> 662

Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg
1 5 10

<210> 663
<211> 14
<212> PRT
<213> Homo sapiens
<400> 663

Arg Ile Ile Val Arg Ile Arg Leu Arg Ile Ile Arg Val Arg
1 5 10

<210> 664
<211> 14
<212> PRT
<213> Homo sapiens
<400> 664

Arg Ile Gly Ile Arg Leu Arg Val Arg Ile Ile Arg Arg Val
1 5 10

<210> 665
<211> 16
<212> PRT
<213> Homo sapiens
<400> 665

Lys Ile Val Ile Arg Ile Arg Ala Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

<210> 666
<211> 16
<212> PRT
<213> Homo sapiens
<400> 666

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 667
<211> 16
<212> PRT
<213> Homo sapiens
<400> 667

Lys Ile Gly Ile Lys Ala Arg Val Arg Ile Ile Arg Val Lys Ile Ile
1 5 10 15

<210> 668
<211> 16
<212> PRT
<213> Homo sapiens
<400> 668

Arg Ile Ile Val His Ile Arg Leu Arg Ile Ile His His Ile Arg Leu
1 5 10 15

<210> 669
<211> 16
<212> PRT
<213> Homo sapiens
<400> 669

His Ile Gly Ile Lys Ala His Val Arg Ile Ile Arg Val His Ile Ile
1 5 10 15

<210> 670
<211> 16
<212> PRT
<213> Homo sapiens
<400> 670

Arg Ile Tyr Val Lys Ile His Leu Arg Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 671
<211> 16
<212> PRT
<213> Homo sapiens
<400> 671

Lys Ile Gly His Lys Ala Arg Val His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 672
<211> 16
<212> PRT
<213> Homo sapiens
<400> 672

Arg Ile Tyr Val Lys Pro His Pro Arg Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 673
<211> 16
<212> PRT
<213> Homo sapiens
<400> 673

Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 674
<211> 19
<212> PRT
<213> Homo sapiens
<400> 674

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

Lys Ile Val

<210> 675
<211> 19
<212> PRT
<213> Homo sapiens
<400> 675

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

Ile Lys Lys

<210> 676
<211> 19
<212> PRT
<213> Homo sapiens
<400> 676

Lys Ile Gly Trp Lys Leu Arg Val Arg Ile Ile Arg Val Lys Ile Gly
1 5 10 15

Arg Leu Arg

<210> 677
<211> 25
<212> PRT
<213> Homo sapiens
<400> 677

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

Lys Ile Val Lys Val Lys Arg Ile Arg
20 25

<210> 678
<211> 26
<212> PRT
<213> Homo sapiens
<400> 678

Arg Phe Ala Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

Ile Lys Lys Ile Arg Lys Arg Val Ile Lys
20 25

<210> 679
<211> 30
<212> PRT
<213> Homo sapiens
<400> 679

Lys Ala Gly Trp Lys Leu Arg Val Arg Ile Ile Arg Val Lys Ile Gly
1 5 10 15

Arg Leu Arg Lys Ile Gly Trp Lys Lys Arg Val Arg Ile Lys
20 25 30

<210> 680
<211> 16
<212> PRT
<213> Homo sapiens
<400> 680

Arg Ile Tyr Val Lys Pro His Pro Arg Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 681
<211> 16
<212> PRT
<213> Homo sapiens
<400> 681

Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 682
<211> 19
<212> PRT
<213> Homo sapiens
<400> 682

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

Lys Ile Val

<210> 683
<211> 19
<212> PRT
<213> Homo sapiens

<400> 683

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

Ile Lys Lys

<210> 684
<211> 16
<212> PRT
<213> Homo sapiens
<400> 684

Arg Ile Tyr Val Ser Lys Ile Ser Ile Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 685
<211> 19
<212> PRT
<213> Homo sapiens
<400> 685

Lys Ile Val Ile Phe Thr Arg Ile Arg Leu Thr Ser Ile Arg Ile Arg
1 5 10 15

Ser Ile Val

<210> 686
<211> 16
<212> PRT
<213> Homo sapiens
<400> 686

Lys Pro Ile His Lys Ala Arg Pro Thr Ile Ile Arg Tyr Lys Met Ile
1 5 10 15

<210> 687
<211> 25
<212> PRT
<213> Homo sapiens
<400> 687

Cys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
1 5 10 15

Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 688
<211> 26
<212> PRT
<213> Homo sapiens
<400> 688

Cys Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro
1 5 10 15

Leu Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 689
<211> 27
<212> PRT
<213> Homo sapiens
<400> 689

Cys Lys Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser
1 5 10 15

Pro Leu Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 690
<211> 16
<212> PRT
<213> Homo sapiens
<400> 690

Cys Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Cys
1 5 10 15

<210> 691
<211> 18
<212> PRT
<213> Homo sapiens
<400> 691

Cys Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile
1 5 10 15

Ile Cys

<210> 692
<211> 28
<212> PRT
<213> Homo sapiens
<400> 692

Cys Arg Phe Ala Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg
1 5 10 15

Leu Ile Lys Lys Ile Arg Lys Arg Val Ile Lys Cys
20 25

<210> 693
<211> 13
<212> PRT
<213> Homo sapiens
<400> 693

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys Cys
1 5 10

<210> 694
<211> 12
<212> PRT
<213> Homo sapiens
<400> 694

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 695
<211> 13
<212> PRT
<213> Homo sapiens
<400> 695

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys Cys
1 5 10

<210> 696
<211> 12
<212> PRT
<213> Homo sapiens
<400> 696

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 697
<211> 28
<212> PRT
<213> Homo sapiens
<400> 697

His Ser Asp Ala Val Phe Tyr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
20 25

<210> 698
<211> 28
<212> PRT
<213> Homo sapiens
<400> 698

His Ser Asp Ala Val Phe Tyr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
20 25

<210> 699
<211> 4
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 1, 2, 3, and 4 is any amino acid

<400> 699

Xaa Xaa Xaa Xaa
1

<210> 700
<211> 5
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 1 and 3 is any amino acid
<400> 700

Xaa Ser Xaa Leu Asn
1 5

<210> 701
<211> 4
<212> PRT
<213> Homo sapiens
<400> 701

Lys Lys Tyr Leu
1

<210> 702
<211> 5
<212> PRT
<213> Homo sapiens
<400> 702

Asn Ser Ile Leu Asn
1 5

<210> 703
<211> 4
<212> PRT
<213> Homo sapiens
<400> 703

Lys Lys Tyr Leu
1

<210> 704
<211> 4
<212> PRT
<213> Homo sapiens
<400> 704

Lys Lys Tyr Ala
1

<210> 705
<211> 6
<212> PRT
<213> Homo sapiens
<400> 705

Ala Val Lys Lys Tyr Leu
1 5

<210> 706
<211> 5
<212> PRT
<213> Homo sapiens
<400> 706

Asn Ser Ile Leu Asn
1 5

<210> 707
<211> 4
<212> PRT
<213> Homo sapiens
<400> 707

Lys Lys Tyr Val
1

<210> 708
<211> 4
<212> PRT
<213> Homo sapiens
<400> 708

Ser Ile Leu Asn
1

<210> 709
<211> 5
<212> PRT
<213> Homo sapiens
<400> 709

Lys Lys Tyr Leu Leu
1 5

<210> 710
<211> 5
<212> PRT
<213> Homo sapiens
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Asn Ser Tyr Leu Asn
1 5

<210> 711
<211> 5
<212> PRT
<213> Homo sapiens
<400> 711

Asn Ser Ile Tyr Asn
1 5

<210> 712
<211> 11
<212> PRT
<213> Homo sapiens
<400> 712

Lys Lys Tyr Leu Pro Pro Asn Ser Ile Leu Asn
1 5 10

<210> 713
<211> 5
<212> PRT
<213> Homo sapiens
<400> 713

Leu Lys Lys Tyr Leu
1 5

<210> 714
<211> 4
<212> PRT
<213> Homo sapiens
<400> 714

Lys Lys Tyr Leu
1

<210> 715
<211> 4
<212> PRT
<213> Homo sapiens
<400> 715

Lys Lys Tyr Leu
1

<210> 716
<211> 5
<212> PRT
<213> Homo sapiens
<400> 716

Val Lys Lys Tyr Leu
1 5

<210> 717
<211> 6
<212> PRT
<213> Homo sapiens
<400> 717

Leu Asn Ser Ile Leu Asn
1 5

<210> 718

<211> 7
<212> PRT
<213> Homo sapiens
<400> 718

Tyr Leu Asn Ser Ile Leu Asn
1 5

<210> 719
<211> 5
<212> PRT
<213> Homo sapiens
<400> 719

Lys Lys Tyr Leu Asn
1 5

<210> 720
<211> 6
<212> PRT
<213> Homo sapiens
<400> 720

Lys Lys Tyr Leu Asn Ser
1 5

<210> 721
<211> 7
<212> PRT
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<400> 721

Lys Lys Tyr Leu Asn Ser Ile
1 5

<210> 722
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<212> PRT
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Lys Lys Tyr Leu Asn Ser Ile Leu
1 5

<210> 723
<211> 4
<212> PRT
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Lys Lys Tyr Leu
1

<210> 724
<211> 5
<212> PRT
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<400> 724

Lys Lys Tyr Asp Ala
1 5

<210> 725
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<213> Homo sapiens
<400> 725

Ala Val Lys Lys Tyr Leu
1 5

<210> 726
<211> 5
<212> PRT
<213> Homo sapiens
<400> 726

Asn Ser Ile Leu Asn
1 5

<210> 727
<211> 4
<212> PRT
<213> Homo sapiens
<400> 727

Lys Lys Tyr Val
1

<210> 728
<211> 4
<212> PRT
<213> Homo sapiens
<400> 728

Ser Ile Leu Asn
1

<210> 729
<211> 5
<212> PRT
<213> Homo sapiens
<400> 729

Asn Ser Tyr Leu Asn
1 5

<210> 730
<211> 5
<212> PRT
<213> Homo sapiens
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Asn Ser Ile Tyr Asn

1 5

<210> 731
<211> 5
<212> PRT
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<400> 731

Lys Lys Tyr Leu Leu
1 5

<210> 732
<211> 11
<212> PRT
<213> Homo sapiens
<400> 732

Lys Lys Tyr Leu Pro Pro Asn Ser Ile Leu Asn
1 5 10

<210> 733
<211> 4
<212> PRT
<213> Homo sapiens
<400> 733

Lys Lys Tyr Leu
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Val Gln Asn Phe Ile Asp Tyr Trp Thr Gln Gln Phe
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Thr Gly Pro Ala Phe Thr His Tyr Trp Ala Thr Phe
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Ile Asp Arg Ala Pro Thr Phe Arg Asp His Trp Phe Ala Leu Val
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Pro Arg Pro Ala Leu Val Phe Ala Asp Tyr Trp Glu Thr Leu Tyr
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Pro Ala Phe Ser Arg Phe Trp Ser Asp Leu Ser Ala Gly Ala His
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Pro Ala Phe Ser Arg Phe Trp Ser Lys Leu Ser Ala Gly Ala His
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Gln Pro Thr Phe Ser Asp Tyr Trp Lys Leu Leu Pro
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1 5 10

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Ser Cys Trp Arg Trp Gly Lys Tyr Gln Ile Cys Gly Ser
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Ser Cys Val Ser Trp Gly Ala Leu Lys Leu Cys Gly Ser
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Ser Cys Ile Arg Trp Gly Gln Asn Thr Phe Cys Gly Ser
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Ser Cys Trp Gln Trp Gly Asn Leu Lys Ile Cys Gly Ser
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Ser Cys Val Arg Trp Gly Gln Leu Ser Ile Cys Gly Ser
1 5 10

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Thr Met Leu Ala Lys
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Arg Arg Trp Lys Lys Asn Phe Ile Ala Val Ser Ala Ala Asn Arg Phe
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Lys Lys

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Arg Lys Trp Gln Lys Thr Gly His Ala Val Arg Ala Ile Gly Arg Leu
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Ser Ser

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Ile Asn Leu Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
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Val Ala

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Leu Lys Lys Leu Leu Lys Leu Leu Lys Lys Leu Leu Lys Leu
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Leu Lys Trp Lys Lys Leu Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys
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Leu Leu

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Ala Glu Trp Pro Ser Leu Thr Glu Ile Lys Thr Leu Ser His Phe Ser
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Val

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Ala Glu Trp Pro Ser Pro Thr Arg Val Ile Ser Thr Thr Tyr Phe Gly
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Ser

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Ala Glu Leu Ala His Trp Pro Pro Val Lys Thr Val Leu Arg Ser Phe
1 5 10 15

Thr

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Asn

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Ala Glu Trp Pro Ser Leu Thr Glu Ile Lys
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Arg

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Arg Trp Leu Ser Ser Arg Pro Leu Pro Pro Leu Pro Leu Pro Pro Arg
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Thr

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Gly Ser Gly Ser Tyr Asp Thr Leu Ala Leu Pro Ser Leu Pro Leu His
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Pro Met Ser Ser
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Gly Ser Gly Ser Tyr Asp Thr Arg Ala Leu Pro Ser Leu Pro Leu His
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Pro Met Ser Ser
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Gly Ser Gly Ser Ser Gly Val Thr Met Tyr Pro Lys Leu Pro Pro His
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Trp Ser Met Ala
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Gly Ser Gly Ser Ser Gly Val Arg Met Tyr Pro Lys Leu Pro Pro His
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Trp Ser Met Ala
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Gly Ser Gly Ser Ser Ser Met Arg Met Val Pro Thr Ile Pro Gly Ser
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Ala Lys His Gly
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Arg Asn Arg Gln Lys Thr
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Arg Asn Arg Gln
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Arg Asn Arg Gln Lys
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Asn Arg Gln Lys Thr
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Arg Gln Lys Thr
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Arg Pro Leu Pro Pro Leu Pro
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Arg Glu Leu Pro Pro Leu Pro
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Ser Pro Leu Pro Pro Leu Pro
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Gly Pro Leu Pro Pro Leu Pro
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Arg Pro Leu Pro Ile Pro Pro
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Arg Pro Leu Pro Ile Pro Pro
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Arg Arg Leu Pro Pro Thr Pro
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Arg Arg Leu Pro Pro Thr Pro
1 5

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Arg Gln Leu Pro Pro Thr Pro
1 5

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Arg Pro Leu Pro Ser Arg Pro
1 5

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Arg Pro Leu Pro Thr Arg Pro
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Ser Arg Leu Pro Pro Leu Pro
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Arg Ala Leu Pro Ser Pro Pro
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Arg Arg Leu Pro Arg Thr Pro
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Arg Pro Val Pro Pro Ile Thr
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Ile Leu Ala Pro Pro Val Pro
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Arg Pro Leu Pro Met Leu Pro
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Arg Pro Leu Pro Ile Leu Pro
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Arg Pro Leu Pro Ser Leu Pro
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Arg Pro Leu Pro Met Ile Pro
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Arg Pro Leu Pro Leu Ile Pro
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Arg Pro Leu Pro Pro Thr Pro
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Arg Ser Leu Pro Pro Leu Pro
1 5

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Arg Pro Gln Pro Pro Pro Pro
1 5

<210> 852
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Arg Gln Leu Pro Ile Pro Pro
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Xaa Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Xaa Pro
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Xaa Xaa Xaa Arg Pro Leu Pro Pro Ile Pro Xaa Xaa
1 5 10

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Xaa Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Xaa Xaa
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Arg Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Xaa Pro
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<210> 857

<211> 12
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Arg Xaa Xaa Arg Pro Leu Pro Pro Leu Pro Pro Pro
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Pro Pro Pro Tyr Pro Pro Pro Pro Ile Pro Xaa Xaa
1 5 10

<210> 859
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Pro Pro Pro Tyr Pro Pro Pro Pro Val Pro Xaa Xaa
1 5 10

<210> 860
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<212> PRT
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<223> Xaa at positions 2, 3, and 8 is any amino acid
<400> 860

Leu Xaa Xaa Arg Pro Leu Pro Xaa Thr Pro
1 5 10

<210> 861
<211> 10
<212> PRT
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<223> Xaa at positions 1, 2, 3 and 8 is any amino acid
<400> 861

Xaa Xaa Xaa Arg Pro Leu Pro Xaa Leu Pro
1 5 10

<210> 862
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<212> PRT
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<220>
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<400> 862

Pro Pro Xaa Xaa Xaa Pro Pro Pro Xaa Pro
1 5 10

<210> 863
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Xaa Pro Pro Xaa Pro Xaa Lys Pro Xaa Trp Leu
1 5 10

<210> 864
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<400> 864

Arg Pro Xaa Xaa Pro Xaa Arg Xaa Ser Xaa Pro
1 5 10

<210> 865
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<212> PRT
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Pro Pro Val Pro Pro Arg Pro Xaa Xaa Thr Leu
1 5 10

<210> 866
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<212> PRT
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<400> 866

Xaa Pro Xaa Leu Pro Xaa Lys
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Xaa Xaa Asp Xaa Pro Leu Pro Xaa Leu Pro
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<211> 12
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<213> Homo sapiens
<220>
<223> Xaa at postitions 1-2, 10, 12 is any amino acid
<400> 868

Xaa Xaa Asn Phe Phe Trp Lys Thr Phe Xaa Ser Xaa
1 5 10

<210> 869
<211> 17
<212> PRT
<213> Homo sapiens
<400> 869

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15
Lys

<210> 870
<211> 15
<212> PRT
<213> Homo sapiens
<400> 870

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10 15

<210> 871
<211> 13
<212> PRT
<213> Homo sapiens
<400> 871

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10

<210> 872
<211> 16
<212> PRT
<213> Homo sapiens
<400> 872

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15

<210> 873
<211> 14
<212> PRT
<213> Homo sapiens
<400> 873

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 874
<211> 12
<212> PRT
<213> Homo sapiens
<400> 874

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 875
<211> 16
<212> PRT
<213> Homo sapiens
<400> 875

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15

<210> 876
<211> 15
<212> PRT
<213> Homo sapiens
<400> 876

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10 15

<210> 877
<211> 13
<212> PRT
<213> Homo sapiens
<400> 877

Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10

<210> 878
<211> 16
<212> PRT
<213> Homo sapiens
<400> 878

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15

<210> 879
<211> 14
<212> PRT
<213> Homo sapiens
<400> 879

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 880
<211> 12
<212> PRT
<213> Homo sapiens

<400> 880

Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 881
<211> 17
<212> PRT
<213> Homo sapiens
<400> 881

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

Lys

<210> 882
<211> 15
<212> PRT
<213> Homo sapiens
<400> 882

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10 15

<210> 883
<211> 13
<212> PRT
<213> Homo sapiens
<400> 883

Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10

<210> 884
<211> 16
<212> PRT
<213> Homo sapiens
<400> 884

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

<210> 885
<211> 14
<212> PRT
<213> Homo sapiens
<400> 885

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10

<210> 886

<211> 12
<212> PRT
<213> Homo sapiens
<400> 886

Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10

<210> 887
<211> 17
<212> PRT
<213> Homo sapiens
<400> 887

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

Lys

<210> 888
<211> 15
<212> PRT
<213> Homo sapiens
<400> 888

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10 15

<210> 889
<211> 13
<212> PRT
<213> Homo sapiens
<400> 889

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10

<210> 890
<211> 16
<212> PRT
<213> Homo sapiens
<400> 890

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

<210> 891
<211> 14
<212> PRT
<213> Homo sapiens
<400> 891

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys

1 5 10

<210> 892
<211> 12
<212> PRT
<213> Homo sapiens
<400> 892

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10

<210> 893
<211> 17
<212> PRT
<213> Homo sapiens
<400> 893

Ala Glu Pro Met Pro His Ser Leu Asn Phe Ser Gln Tyr Leu Trp Tyr
1 5 10 15

Thr

<210> 894
<211> 17
<212> PRT
<213> Homo sapiens
<400> 894

Ala Glu His Thr Tyr Ser Ser Leu Trp Asp Thr Tyr Ser Pro Leu Ala
1 5 10 15

Phe

<210> 895
<211> 17
<212> PRT
<213> Homo sapiens
<400> 895

Ala Glu Leu Asp Leu Trp Met Arg His Tyr Pro Leu Ser Phe Ser Asn
1 5 10 15

Arg

<210> 896
<211> 17
<212> PRT
<213> Homo sapiens
<400> 896

Ala Glu Ser Ser Leu Trp Thr Arg Tyr Ala Trp Pro Ser Met Pro Ser
1 5 10 15

Tyr

<210> 897
<211> 17
<212> PRT
<213> Homo sapiens
<400> 897

Ala Glu Trp His Pro Gly Leu Ser Phe Gly Ser Tyr Leu Trp Ser Lys
1 5 10 15

Thr

<210> 898
<211> 17
<212> PRT
<213> Homo sapiens
<400> 898

Ala Glu Pro Ala Leu Leu Asn Trp Ser Phe Phe Phe Asn Pro Gly Leu
1 5 10 15

His

<210> 899
<211> 17
<212> PRT
<213> Homo sapiens
<400> 899

Ala Glu Trp Ser Phe Tyr Asn Leu His Leu Pro Glu Pro Gln Thr Ile
1 5 10 15

Phe

<210> 900
<211> 17
<212> PRT
<213> Homo sapiens
<400> 900
Ala Glu Trp Ser Phe Tyr Asn Leu His Leu Pro Glu Pro Gln Thr Ile
1 5 10 15

Phe

<210> 901
<211> 17
<212> PRT
<213> Homo sapiens
<400> 901

Ala Glu Pro Leu Asp Leu Trp Ser Leu Tyr Ser Leu Pro Pro Leu Ala
1 5 10 15

Met

<210> 902
<211> 17
<212> PRT

<213> Homo sapiens
<400> 902

Ala Glu Pro Thr Leu Trp Gln Leu Tyr Gln Phe Pro Leu Arg Leu Ser
1 5 10 15

Gly

<210> 903
<211> 17
<212> PRT
<213> Homo sapiens
<400> 903

Ala Glu Ile Ser Phe Ser Glu Leu Met Trp Leu Arg Ser Thr Pro Ala
1 5 10 15

Phe

<210> 904
<211> 17
<212> PRT
<213> Homo sapiens
<400> 904

Ala Glu Leu Ser Glu Ala Asp Leu Trp Thr Thr Trp Phe Gly Met Gly
1 5 10 15

Ser

<210> 905
<211> 17
<212> PRT
<213> Homo sapiens
<400> 905

Ala Glu Ser Ser Leu Trp Arg Ile Phe Ser Pro Ser Ala Leu Met Met
1 5 10 15

Ser

<210> 906
<211> 17
<212> PRT
<213> Homo sapiens
<400> 906

Ala Glu Ser Leu Pro Thr Leu Thr Ser Ile Leu Trp Gly Lys Glu Ser
1 5 10 15

Val

<210> 907

<211> 17
<212> PRT
<213> Homo sapiens
<400> 907

Ala Glu Thr Leu Phe Met Asp Leu Trp His Asp Lys His Ile Leu Leu
1 5 10 15

Thr

<210> 908
<211> 17
<212> PRT
<213> Homo sapiens
<400> 908

Ala Glu Ile Leu Asn Phe Pro Leu Trp His Glu Pro Leu Trp Ser Thr
1 5 10 15

Glu

<210> 909
<211> 17
<212> PRT
<213> Homo sapiens
<400> 909

Ala Glu Ser Gln Thr Gly Thr Leu Asn Thr Leu Phe Trp Asn Thr Leu
1 5 10 15

Arg

<210> 910
<211> 17
<212> PRT
<213> Homo sapiens
<400> 910

Ala Glu Pro Val Tyr Gln Tyr Glu Leu Asp Ser Tyr Leu Arg Ser Tyr
1 5 10 15

Tyr

<210> 911
<211> 17
<212> PRT
<213> Homo sapiens
<400> 911

Ala Glu Leu Asp Leu Ser Thr Phe Tyr Asp Ile Gln Tyr Leu Leu Arg
1 5 10 15

Thr

<210> 912
<211> 17
<212> PRT
<213> Homo sapiens
<400> 912

Ala Glu Phe Phe Lys Leu Gly Pro Asn Gly Tyr Val Tyr Leu His Ser
1 5 10 15

Ala

<210> 913
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 4, 5, and 6 is any amino acid
<400> 913

Phe Lys Leu Xaa Xaa Xaa Gly Tyr Val Tyr Leu
1 5 10

<210> 914
<211> 17
<212> PRT
<213> Homo sapiens
<400> 914

Ala Glu Ser Thr Tyr His His Leu Ser Leu Gly Tyr Met Tyr Thr Leu
1 5 10 15

Asn

<210> 915
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 3, 5, and 6 is any amino acid
<400> 915

Tyr His Xaa Leu Xaa Xaa Gly Tyr Met Tyr Thr
1 5 10

<210> 916
<211> 19
<212> PRT
<213> Homo sapiens
<400> 916

Val Glu Pro Asn Cys Asp Ile His Val Met Trp Glu Trp Glu Cys Phe
1 5 10 15

Glu Arg Leu

<210> 917
<211> 18
<212> PRT
<213> Homo sapiens
<400> 917

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

Glu Ser

<210> 918
<211> 20
<212> PRT
<213> Homo sapiens
<400> 918

Arg Gly Trp Val Glu Ile Cys Val Ala Asp Asp Asn Gly Met Cys Val
1 5 10 15

Thr Glu Ala Gln
20

<210> 919
<211> 19
<212> PRT
<213> Homo sapiens
<400> 919

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

Ala Gly Val

<210> 920
<211> 18
<212> PRT
<213> Homo sapiens
<400> 920

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

Glu Ile

<210> 921
<211> 18
<212> PRT
<213> Homo sapiens
<400> 921

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

Val Lys

<210> 922
<211> 20
<212> PRT
<213> Homo sapiens
<400> 922

Arg Gly Trp Val Glu Ile Cys Ala Ala Asp Asp Tyr Gly Arg Cys Leu
1 5 10 15

Thr Glu Ala Gln
20

<210> 923
<211> 16
<212> PRT
<213> Homo sapiens
<400> 923

Arg Gly Trp Val Glu Ile Cys Glu Ser Asp Val Trp Gly Arg Cys Leu
1 5 10 15

<210> 924
<211> 16
<212> PRT
<213> Homo sapiens
<400> 924

Arg Gly Trp Val Glu Ile Cys Glu Ser Asp Val Trp Gly Arg Cys Leu
1 5 10 15

<210> 925
<211> 19
<212> PRT
<213> Homo sapiens
<400> 925

Gly Gly Asn Glu Cys Asp Ile Ala Arg Met Trp Glu Trp Glu Cys Phe
1 5 10 15

Glu Arg Leu

<210> 926
<211> 16
<212> PRT
<213> Homo sapiens
<400> 926

Arg Gly Trp Val Glu Ile Cys Ala Ala Asp Asp Tyr Gly Arg Cys Leu
1 5 10 15

<210> 927
<211> 10
<212> PRT
<213> Homo sapiens

<400> 927

Cys Thr Thr His Trp Gly Phe Thr Leu Cys
1 5 10

<210> 928
<211> 8
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at position 6 is any amino acid
<400> 928

Cys Leu Arg Ser Gly Xaa Gly Cys
1 5

<210> 929
<211> 10
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2, 3, 8 and 9 is any amino acid
<400> 929

Cys Xaa Xaa His Trp Gly Phe Xaa Xaa Cys
1 5 10

<210> 930
<211> 5
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2 and 4 is any amino acid
<400> 930

Cys Xaa Pro Xaa Cys
1 5

<210> 931
<211> 10
<212> PRT
<213> Homo sapiens
<400> 931

Cys Arg Arg His Trp Gly Phe Glu Phe Cys
1 5 10

<210> 932
<211> 10
<212> PRT
<213> Homo sapiens
<400> 932

Ser Thr Thr His Trp Gly Phe Thr Leu Ser
1 5 10

<210> 933

<211> 10
<212> PRT
<213> Homo sapiens
<400> 933

Cys Ser Leu His Trp Gly Phe Trp Trp Cys
1 5 10

<210> 934
<211> 15
<212> PRT
<213> Homo sapiens
<400> 934

Gly Phe Val Cys Ser Gly Ile Phe Ala Val Gly Val Gly Arg Cys
1 5 10 15

<210> 935
<211> 15
<212> PRT
<213> Homo sapiens
<400> 935

Ala Pro Gly Val Arg Leu Gly Cys Ala Val Leu Gly Arg Tyr Cys
1 5 10 15

<210> 936
<211> 6
<212> PRT
<213> Homo sapiens
<400> 936

Leu Leu Gly Arg Met Lys
1 5

<210> 937
<211> 27
<212> PRT
<213> Homo sapiens
<400> 937

Ile Cys Val Val Gln Asp Trp Gly His His Arg Cys Thr Ala Gly His
1 5 10 15

Met Ala Asn Leu Thr Ser His Ala Ser Ala Ile
20 25

<210> 938
<211> 13
<212> PRT
<213> Homo sapiens
<400> 938

Ile Cys Val Val Gln Asp Trp Gly His His Arg Cys Thr
1 5 10

<210> 939
<211> 11
<212> PRT
<213> Homo sapiens
<400> 939

Cys Val Val Gln Asp Trp Gly His His Ala Cys
1 5 10

<210> 940
<211> 27
<212> PRT
<213> Homo sapiens
<400> 940

Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Gly Val Ser
1 5 10 15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
20 25

<210> 941
<211> 27
<212> PRT
<213> Homo sapiens
<400> 941

Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Arg Val Ser
1 5 10 15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
20 25

<210> 942
<211> 30
<212> PRT
<213> Homo sapiens
<400> 942

Ser Arg Gly Val Asn Phe Ser Glu Trp Leu Tyr Asp Met Ser Ala Ala
1 5 10 15

Met Lys Glu Ala Ser Asn Val Phe Pro Ser Arg Arg Ser Arg
20 25 30

<210> 943
<211> 30
<212> PRT
<213> Homo sapiens
<400> 943

Ser Ser Gln Asn Trp Asp Met Glu Ala Gly Val Glu Asp Leu Thr Ala
1 5 10 15

Ala Met Leu Gly Leu Leu Ser Thr Ile His Ser Ser Ser Arg
20 25 30

<210> 944
<211> 31
<212> PRT
<213> Homo sapiens
<400> 944

Ser Ser Pro Ser Leu Tyr Thr Gln Phe Leu Val Asn Tyr Glu Ser Ala
1 5 10 15

Ala Thr Arg Ile Gln Asp Leu Leu Ile Ala Ser Arg Pro Ser Arg
20 25 30

<210> 945
<211> 31
<212> PRT
<213> Homo sapiens
<400> 945

Ser Ser Thr Gly Trp Val Asp Leu Leu Gly Ala Leu Gln Arg Ala Ala
1 5 10 15

Asp Ala Thr Arg Thr Ser Ile Pro Pro Ser Leu Gln Asn Ser Arg
20 25 30

<210> 946
<211> 18
<212> PRT
<213> Homo sapiens
<400> 946

Asp Val Tyr Thr Lys Lys Glu Leu Ile Glu Cys Ala Arg Arg Val Ser
1 5 10 15

Glu Lys

<210> 947
<211> 22
<212> PRT
<213> Homo sapiens
<400> 947

Glu Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala Gln Phe His Ile
1 5 10 15

Asp Tyr Asn Asn Val Ser
20

<210> 948
<211> 22
<212> PRT
<213> Homo sapiens
<400> 948

Ser Gly Ile Ala Gln Phe His Ile Asp Tyr Asn Asn Val Ser Ser Ala
1 5 10 15

Glu Gly Trp His Val Asn
20

<210> 949
<211> 34
<212> PRT
<213> Homo sapiens
<400> 949

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

Gln Phe His Ile Asp Tyr Asn Asn Val Ser Ser Ala Glu Gly Trp His
20 25 30

Val Asn

<210> 950
<211> 14
<212> PRT
<213> Homo sapiens
<400> 950

Ser Gly Ile Ala Gln Phe His Ile Asp Tyr Asn Asn Val Ser
1 5 10

<210> 951
<211> 6
<212> PRT
<213> Homo sapiens
<400> 951

Leu Leu Gly Arg Met Lys
1 5

<210> 952
<211> 8
<212> PRT
<213> Homo sapiens
<400> 952

Ala Leu Leu Gly Arg Met Lys Gly
1 5

<210> 953
<211> 7
<212> PRT
<213> Homo sapiens
<400> 953

Leu Asp Pro Ala Phe Ile Arg
1 5

<210> 954
<211> 7
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 2 and 3 is any amino acid
<400> 954

Cys Xaa Xaa Arg Gly Asp Cys
1 5

<210> 955
<211> 7
<212> PRT
<213> Homo sapiens
<400> 955

Arg Pro Leu Pro Pro Leu Pro
1 5

<210> 956
<211> 6
<212> PRT
<213> Homo sapiens
<400> 956

Pro Pro Val Pro Pro Arg
1 5

<210> 957
<211> 11
<212> PRT
<213> Homo sapiens
<220>
<223> Xaa at positions 1, 3, 5, 7, 8, 10 and 11 is any amino acid
<400> 957

Xaa Phe Xaa Asp Xaa Trp Xaa Xaa Leu Xaa Xaa
1 5 10

<210> 958
<211> 20
<212> PRT
<213> Homo sapiens
<400> 958

Lys Ala Cys Arg Arg Leu Phe Gly Pro Val Asp Ser Glu Gln Leu Ser
1 5 10 15

Arg Asp Cys Asp
20

<210> 959
<211> 20
<212> PRT
<213> Homo sapiens

<400> 959

Arg Glu Arg Trp Asn Phe Asp Phe Val Thr Glu Thr Pro Leu Glu Gly
1 5 10 15

Asp Phe Ala Trp
20

<210> 960
<211> 20
<212> PRT
<213> Homo sapiens
<400> 960

Lys Arg Arg Gln Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg
1 5 10 15

Leu Ile Phe Ser
20

<210> 961
<211> 20
<212> PRT
<213> Homo sapiens
<400> 961

Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg Leu Ile Phe Ser
1 5 10 15

Lys Arg Lys Pro
20

<210> 962
<211> 5
<212> PRT
<213> Homo sapiens
<400> 962

Arg Arg Leu Ile Phe
1 5

<210> 963
<211> 36
<212> PRT
<213> Homo sapiens
<400> 963

Lys Arg Arg Gln Thr Ser Ala Thr Asp Phe Tyr His Ser Lys Arg Arg
1 5 10 15

Leu Ile Phe Ser Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met
20 25 30

Lys Trp Lys Lys
35

<210> 964
<211> 24
<212> PRT
<213> Homo sapiens
<400> 964

Lys Arg Arg Leu Ile Phe Ser Lys Arg Gln Ile Lys Ile Trp Phe Gln
1 5 10 15

Asn Arg Arg Met Lys Trp Lys Lys
20

<210> 965
<211> 25
<212> PRT
<213> Homo sapiens
<400> 965

Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe
1 5 10 15

Val Met Thr Ala Ala Ser Cys Phe Gln
20 25

<210> 966
<211> 27
<212> PRT
<213> Homo sapiens
<400> 966

Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly
1 5 10 15

Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val
20 25

<210> 967
<211> 15
<212> PRT
<213> Homo sapiens
<400> 967

Trp His Trp Arg His Arg Ile Pro Leu Gln Leu Ala Ala Gly Arg
1 5 10 15

<210> 968
<211> 6
<212> PRT
<213> Homo sapiens
<400> 968

Leu Lys Thr Pro Arg Val
1 5

<210> 969
<211> 8
<212> PRT
<213> Homo sapiens

<400> 969

Asn Thr Leu Lys Thr Pro Arg Val
1 5

<210> 970
<211> 11
<212> PRT
<213> Homo sapiens
<400> 970

Asn Thr Leu Lys Thr Pro Arg Val Gly Gly Cys
1 5 10

<210> 971
<211> 6
<212> PRT
<213> Homo sapiens
<400> 971

Lys Asp Lys Ala Thr Phe
1 5

<210> 972
<211> 10
<212> PRT
<213> Homo sapiens
<400> 972

Lys Asp Lys Ala Thr Phe Gly Cys His Asp
1 5 10

<210> 973
<211> 12
<212> PRT
<213> Homo sapiens
<400> 973

Lys Asp Lys Ala Thr Phe Gly Cys His Asp Gly Cys
1 5 10

<210> 974
<211> 6
<212> PRT
<213> Homo sapiens
<400> 974

Thr Leu Arg Val Tyr Lys
1 5

<210> 975
<211> 8
<212> PRT
<213> Homo sapiens
<400> 975

Ala Thr Leu Arg Val Tyr Lys Gly

1 5

<210> 976
<211> 10
<212> PRT
<213> Homo sapiens
<400> 976

Cys Ala Thr Leu Arg Val Tyr Lys Gly Gly
1 5 10

<210> 977
<211> 14
<212> PRT
<213> Homo sapiens
<400> 977

Ile Asn Leu Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
1 5 10

<210> 978
<211> 12
<212> PRT
<213> Homo sapiens
<400> 978

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly
1 5 10

<210> 979
<211> 27
<212> PRT
<213> Homo sapiens
<400> 979

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25