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(54) Title: MAMMALIAN CH1 DELETED MIMETIBODIES, COMPOSITIONS, METHODS AND USES

(57) Abstract: The present invention relates to at least one novel human CH1-deleted mimetibody or specified portion or variant, including isolated nucleic acids that encode at least one CH1-deleted mimetibody or specified portion or variant, CH1-deleted 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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**MAMMALIAN CH1 DELETED MIMETIBODIES,
COMPOSITIONS, METHODS AND USES**

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

5 The present invention relates to mammalian CH1-deleted mimetibodies, specified portions and variants specific for biologically active proteins, fragment or ligands, CH1-deleted mimetibody encoding and complementary nucleic acids, host cells, and methods of making and using thereof, including therapeutic formulations, administration and devices.

10 **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
15 activity, or reducing unwanted side effects. One such modification is the use of immunoglobulin fragments fused to receptor proteins, such as entercept. 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
20 proteins, which overcome one more of these and other problems known in the art.

SUMMARY OF THE INVENTION

 The present invention provides isolated human CH1-deleted mimetibodies, including modified immunoglobulins, cleavage products and other specified portions and variants thereof, as well as CH1-
25 deleted 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 isolated CH1-deleted mimetibody or specified portion or variant as described herein and/or as known in the art. The CH1 deleted mimetibody can
30 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 directly linked with at least one partial V region, directly linked with an optional linker sequence, directly linked to at least one therapeutic

peptide, optionally further directly linked with at least a portion of at least one variable antibody sequence. In a preferred embodiment a pair of a CH3-CH2-hinge-partial J sequence-linker-therapeutic peptide with an option N-terminal antibody sequence, the pair optionally linked by association or covalent linkage, such as, but not limited to, a Cys-Cys disulfide bond. In one embodiment, a CH1
5 deleted mimetibody comprises formula (I):

$$(V1(n)\text{-Pep}(n)\text{-Flex}(n)\text{-V2}(n)\text{-pHinge}(n)\text{-CH2}(n)\text{-CH3}(n))(m),$$

where V1 is at least one portion of an N-terminus of an immunoglobulin variable region, Pep is at least one bioactive peptide, Flex is polypeptide that provides structural flexibility by allowing the mimetibody to have alternative orientations and binding properties, V2 is at least one portion of a C-
10 terminus of an immunoglobulin variable region, pHinge 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 an integer between 1 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.

15 Thus, a CH1-deleted mimetibody of the present invention mimics at least a portion of an antibody or immunoglobulin 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 CH1-deleted mimetibody of the present invention can vary as described herein in combination with what is
20 known in the art.

At least one CH1-deleted mimetibody or specified portion or variant of the invention mimics the binding of the Pep 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 CH1-deleted mimetibody or specified
25 portion or variant as described herein and/or as known in the art, wherein the CH1-deleted 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 Pep portion of formula I. A CH1-deleted 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.

30 In one aspect, the present invention provides at least one isolated mammalian CH1-deleted mimetibody, comprising at least one Pep(n) region comprising at least a biologically 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 mammalian CH1-deleted
35 mimetibody, wherein the CH1-deleted 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: 1-1109, or optionally with one or more substitutions, deletions or insertions as described herein or as known in the art.

The at least one CH1-deleted 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 CH1-deleted mimetibody nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such CH1-deleted mimetibody nucleic acids, vectors and/or host cells.

Also provided is an isolated nucleic acid encoding at least one isolated mammalian CH1-deleted 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 CH1-deleted mimetibody, comprising translating the CH1-deleted mimetibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the CH1-deleted mimetibody is expressed in detectable or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated CH1-deleted mimetibody or specified portion or variant encoding nucleic acid and/or CH1-deleted 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 mammalian CH1-deleted 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 antineoplastic, 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 anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, 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-idiotypic antibody to at least one CH1-deleted mimetibody of the present invention. The anti-idiotypic 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 complementarity determining 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 CH1-deleted mimetibody of the present invention. A CH1-deleted 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-idiotypic antibody or fragment that specifically binds at least one CH1 deleted 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 CH1-deleted mimetibody anti-idiotypic antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said CH1-deleted mimetibody anti-idiotypic 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-idiotypic antibody nucleic acids, vectors and/or host cells.

The present invention also provides at least one method for expressing at least one CH1-deleted mimetibody or specified portion or variant, or CH1-deleted mimetibody anti-idiotypic 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 CH1-deleted mimetibody or specified portion or variant, or anti-idiotypic antibody is expressed in detectable and/or recoverable amounts.

The present invention further provides at least one CH1-deleted 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 disorder, 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 ophthalmologic disorder, a pediatric disorder, a poisoning disorder, a psychiatric disorder, a renal disorder, a pulmonary disorder, or any other known disorder. (See., e.g.,
5 The Merck Manual, 17th ed. , Merck Research Laboratories, Merck and Co., Whitehouse Station, NJ (1999), entirely incorporated 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 CH1-deleted mimetibody, specified portion
10 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.

15 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 CH1-deleted mimetibody or specified portion or variant, according to the present invention.

The present invention also provides at least one composition comprising (a) an isolated CH1-deleted mimetibody encoding nucleic acid and/or CH1-deleted mimetibody as described herein; and (b)
20 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 CH1-deleted mimetibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one
25 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 CH1-deleted mimetibody, according to the present invention.

30 The present invention further provides at least one CH1-deleted 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
35 for diagnosing of at least one CH1-deleted 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 mammalian CH1-deleted 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 administering 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 antineoplastic, 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 anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, 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 mammalian CH1-deleted mimetibody of the invention, wherein the device is suitable to contacting or administering the at least one CH1-deleted 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 mammalian CH1-deleted 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 mammalian CH1-deleted 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 CH1-deleted mimetibody. Further provided in the present invention is at least one CH1-deleted mimetibody produced by the above method.

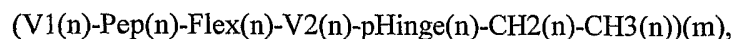
The present invention further provides any invention described herein.

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 CH1-deleted mimetibody. Such mimetibodies or specified portions or variants of the present invention comprise specific CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant as described herein and/or as known in the art. The CH1 deleted 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 directly linked with at least one partial V region, directly linked with an optional linker sequence, directly linked to at least one therapeutic peptide, optionally further directly linked with at least a portion of at least one variable antibody sequence.

In a preferred embodiment a CH1 deleted mimetibody comprises formula (I):



where V1 is at least one portion of an N-terminus of an immunoglobulin variable region, Pep is at least one bioactive peptide, Flex is polypeptide that provides structural flexibility by allowing the mimetibody to have alternative orientations and binding properties, V2 is at least one portion of a C-terminus of an immunoglobulin variable region, pHinge 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 an integer between 1 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. Thus, a CH1-deleted 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 CH1-deleted mimetibody of the present invention can vary as described herein in combination with what is known in the art.

As used herein, a "CH1-deleted mimetibody," "CH1-deleted mimetibody portion," or "CH1-deleted mimetibody fragment" and/or "CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 regions of the variable heavy or light chain; the 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, 25, 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

5 The isolated nucleic acids of the present invention can be used for production of at least one CH1-deleted 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
10 infectious, malignant, and/or neurologic disorder or disease, an anemia; an immune/autoimmune; and/or an cancerous/infectious, 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 CH1-deleted mimetibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation,
15 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 administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

20 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.

25 The following references are entirely incorporated herein by reference: Ausubel, et al., ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., NY, NY (1987-2002); 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 (1994-2002); Colligan et al., *Current Protocols*
30 *in Protein Science*, John Wiley & Sons, NY, NY, (1997-2002).

Mimetibodies of the Present Invention

The CH1 deleted mimetibody can 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 directly linked with at least one partial V region, directly linked with an optional linker sequence, directly linked to at

least one therapeutic peptide, optionally further directly linked with at least a portion of at least one variable antibody sequence. In a preferred embodiment of a pair of a CH3-CH2-hinge-partial J sequence-linker-therapeutic peptide with an option N-terminal antibody sequence, the pair can be linked by association or covalent linkage, such as, but not limited to, a Cys-Cys disulfide bond. Thus, a CH1-deleted 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 CH1-deleted mimetibody of the present invention can vary as described herein in combination with what is known in the art.

In particular, mimetibodies comprise at least one ligand binding region (LBR) that corresponds to at least one portion of at least one complementarity determining region (CDR, e.g., CDR1, CDR2 or CDR3 of HC or LC variable region) of at least one antibody or fragment or portion thereof where at least one ligand protein is inserted into or replaces at least a portion of at least one CDR of the antibody or portion thereof. Such 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 decreased off rate, a selected or more suitable subset of activities, less immunogenicity, 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 CH1-deleted 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.

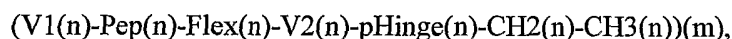
As used herein, the term "human mimetibody" refers to an antibody in which substantially every part of the protein (e.g., LBR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H)) is expected to be substantially non-immunogenic, with only minor sequence changes or variations.

Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans

relative to non-modified human antibodies, or mimetibodies of the present invention. Thus, a human antibody and corresponding CH1-deleted mimetibody of the present invention is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody and CH1-deleted mimetibody can be produced by a non-human animal or cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes, and for a CH1-deleted mimetibody, wherein at least one Ig CDR is replaced by an LBR of at least one ligand protein or fragment.

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 a CH1 deleted mimetibody comprises formula (I):



where V1 is at least one portion of an N-terminus of an immunoglobulin variable region, Pep is at least one bioactive peptide, Flex is polypeptide that provides structural flexibility by allowing the mimetibody to have alternative orientations and binding properties, V2 is at least one portion of a C-terminus of an immunoglobulin variable region, pHinge 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 an integer between 1 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.

In a preferred embodiment, at least one CH1-deleted 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 CH1-deleted 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-terminal variable regions can be used for V1 and V2, hinge regions for pHinge, 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 CH1-deleted mimetibody or portion or variant comprising a particular variable region or a variable region comprising a particular sequence (e.g., at least one Pep 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody of the present invention can optionally bind at least one protein ligand with high affinity. For example, at least one CH1-deleted 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) $\times 10^{-10}$ M, 10^{-11} , 10^{-12} , 10^{-13} or any range or value therein.

The affinity or avidity of a CH1-deleted mimetibody for at least one protein ligand can be determined experimentally using any suitable method, e.g., as used for determining 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 CH1-deleted 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 CH1-deleted 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 SEQID NOS:1-1009 as well as at least one portion of an antibody, wherein the above sequences are inserted as the Pep sequence of Formula (I) to provide a CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-

deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant can include, but are not limited to, those encoding the amino acid sequence of a CH1-deleted mimetibody fragment, by itself; the coding sequence for the entire CH1-deleted mimetibody or a portion thereof; the coding sequence for a CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant comprising a CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant of the present invention to facilitate purification. Such regions can be removed prior to final preparation of a CH1-deleted 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, polyadenylation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenylation 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 CH1-deleted mimetibody or specified portion or variant Thereof

A CH1-deleted 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, (1997-2002), 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant thereof.

Preferably, the CH1-deleted 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.
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.

Factor	Principal Source	Primary Activity	Comments
NGF		Promotes neurite outgrowth and neural cell survival.	Several related proteins first identified as proto-oncogenes; trkA (<i>trackA</i>), trkB, trkC.
Erythropoietin (Epo)	Kidney.	Promotes proliferation and differentiation of erythrocytes.	Also considered a 'blood protein,' and a colony stimulating factor.
Transforming Growth Factor α (TGF- α)	Common in transformed cells, found in macrophages and keratinocytes.	Potent keratinocyte growth factor.	Related to EGF.
Transforming Growth Factor β (TGF- β)	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 Morphogenic 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, FSH α , and FSH β), Human Chorionic Gonadotrophins (HCG, HCG α , HCG β), uFSH (urofollitropin), Gonatropin releasing hormone (GRH), Growth Hormone (GH), leuteinizing hormones (LH, LH α , LH β), somatostatin, prolactin, thyrotropin (TSH, TSH α , TSH β), thyrotropin releasing hormone (TRH), parathyroid hormones, estrogens, progesterones, testosterone, 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 IL-1-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.
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.

Cytokine	Principal Source	Primary Activity
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	synergistic 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.
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.

Cytokine	Principal Source	Primary Activity
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
5 (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);
- 5 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. 6,030,808; 6,030,780; Darnell et al., 277 Science 1630-1635 (1997)); Tumor Necrosis
- 10 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
- 15 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.

- 20 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
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); <i>see also</i> 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).

Protein	Principle Activity	Reference
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.	<i>See generally</i> , 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 XIa or the factor VIIa/tissue factor/phospholipid complex. Cleavage at one site yields the intermediate IXa, subsequently converted to fully active form IXa β by cleavage at another site. Factor IXa β 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., 2 nd ed. J.P. Lippincott Co., Philadelphia) 1987; Fujikawa et al., 45 METHODS IN ENZYMOLOGY 74 (1974).
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.	<i>See</i> Davie et al., 48 ADV. ENZYMOL 277 (1979); Jackson, 49 ANN. REV. BIOCHEM. 765 (1980); <i>see also</i> 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).

Protein	Principle Activity	Reference
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 α_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 glutamyl-peptide γ-glutamyl transferase factor XIIIa (fibrinolytic, 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 McDonough, 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 α-helical regions of the Aa, Bb and g chains having protease- (plasmin-) sensitive sites. Another major plasmin sensitive site is in hydrophilic preturbance of α-chain from C-terminal node. Controlled plasmin degradation converts Fbg into fragments D and E.	FURLAN, <i>Fibrinogen</i>, 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 ₂ I 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 ₂ I and cardiolipin have been implicated in the anti-phospholipid related immune disorders LAC and SLE.	<i>See, e.g.</i> , Lozier et al., 81 PNAS 2640-44 (1984); Kato & Enjyo 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 α_2 -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.	<i>See</i> Robbins, 45 METHODS IN ENZYMOLOGY 257 (1976); COLLEN, 243-258 BLOOD COAG. (Zwaal et al., eds., New York, Elsevier, 1986); <i>see also</i> 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.	<i>See</i> Plasminogen.
Plasmin	<i>See</i> 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 <i>in vitro</i> . Regulation of plasmin <i>in vivo</i> occurs mainly through interaction with α_2 -antiplasmin, and to a lesser extent, α_2 -macroglobulin.	<i>See</i> 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 ENZYMOLOGY 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 carboxylglutamic 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).
b-Thromboglobulin	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).

Protein	Principle Activity	Reference
Thrombopoietin	Human TPO (Thrombopoietin, Mpl-ligand, MGDF) stimulates the proliferation and maturation of megakaryocytes and promotes increased circulating levels of platelets <i>in vivo</i> . 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, Haptoglobin, Myoglobin, 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).

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
(disulfide-linked dimer)	stimulation of hematopoiesis ("G-CSF-mimetic")	Paukovits et al., 364 HOPPE-SEYLER'S Z. PHYSIOL. CHEM. 30311 (1984); Laerungal., 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 thyrique (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).
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).

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
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 al., 10 TRENDS GENET. 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.
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).

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
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, gigantism, 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).
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.

Binding partner/ Protein of interest (form of peptide)	Pharmacological activity	Reference
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 (β 2GPI) 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 hematopoiesis ("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 thyrique (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. Natl. 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, gigantism, 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 (β 2GPI) 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 known derivatives thereof may be present, or any known 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 –NH₂. 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 (Z₅, Z₆, ... Z₄₀) 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. X_4 , X_5 , X_6 , and X_7 are as defined in U.S. Pat. No. 5,773,569, which is hereby entirely incorporated by reference, except that: for integrin-binding peptides, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , and X_8 (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
5	GGTYSCHFGPLTWVCKPQGGSSK	14
	GGTYSCHFGPLTWVCKPQGGSSK-Δ-GGTYSCHFGPLTWVCKPQGGSSK	
	GGTYSCHFGPLTWVCKPQGGSS -Δ-ε-amine)	
	\	
	K	
10	/	
	GGTYSCHFGPLTWVCKPQGGSS-Δ- (α-amine)	15
	GGTYSCHFGPLTWVCKPQGGSSK(-Δ-biotin)	16
	CX ₄ X ₅ GPX ₆ TWX ₇ C	17
	GGTYSCHGPLTWVCKPQGG	18
15	VGNYMAHMGPI TWVCRPGG	19
	GGPHHVYACRMGPLTWIC	20
	GGTYSCHFGPLTWVCKPQ	21
	GGLYACHMGPM TWVCQPLRG	22
	TIAQYICYMGPETWECRPSKA	23
20	YSCHFGPLTWVCK	24
	YCHFGPLTWVC	25
	X ₃ X ₄ X ₅ GPX ₆ TWX ₇ X ₈	26
	YX ₂ X ₃ X ₄ X ₅ GPX ₆ TWX ₇ X ₈	27
	X ₁ YX ₂ X ₃ X ₄ X ₅ GPX ₆ X ₇ X ₈ X ₉ X ₁₀ X ₁₁	28
25	X ₁ YX ₂ CX ₄ X ₅ GPX ₆ TWX ₇ CX ₉ X ₁₀ X ₁₁	29
	GGLYLCRFGPVTWDCGYKGG	30
	GGTYSCHFGPLTWVCKPQGG	31
	GGDYHCRMGPLTWVCKPLGG	32
	VGNYMCHFGPI TWVCRPGGG	33
30	GGVYACRMGPITWVC SPLGG	34
	VGNYMAHMGPI TWVCRPGG	35
	GGTYSCHFGPLTWVCKPQ	36
	GGLYACHMGPM TWVCQPLRG	37
	TIAQYICYMGPETWECRPSKA	38

YSCHFGPLTWVCK	39
YCHFGPLTWVC	40
SCHFGPLTWVCK	41
(AX ₂) _n X ₃ X ₄ X ₅ GPX ₆ TWX ₇ X ₈	42

5 **Table 6-IL-1 antagonist peptide sequences**

	SEQUENCE/STRUCTURE	SEQ ID NO:
	Z ₁₁ Z ₇ Z ₈ ZQZ ₅ YZ ₆ Z ₉ Z ₁₀	43
	XXQZ ₅ YZ ₆ XX	44
10	Z ₇ XQZ ₅ YZ ₆ XX	45
	Z ₇ Z ₈ ZQZ ₅ YZ ₆ Z ₉ Z ₁₀	46
	Z ₁₁ Z ₇ Z ₈ ZQZ ₅ YZ ₆ Z ₉ Z 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 ₇ Z ₈ ZQZ ₅ YZ ₆ Z ₉ Z ₁₀ L	48
	Z ₂₃ NZ ₂₄ Z ₃₉ Z ₂₅ Z ₂₆ Z ₂₇ Z ₂₈ Z ₂₉ Z ₃₀ Z ₄₀	49
15	TANVSSFEWTPYYWQPYPALPL	50
	SWTDYGYWQPYPALPISGL	51
	ETPFTWEESNAYYWQPYPALPL	52
	ENTYSPNWADSMYWQPYPALPL	53
	SVGEDHNFWTSEYWQPYPALPL	54
20	DGYDRWRQSGERYWQPYPALPL	55
	FEWTPGYWQPYP	56
	FEWTPGYWQHY	57
	FEWTPGWYQJY	58
	AcFEWTPGWYQJY	59
25	FEVffPGW _p YQJY	60
	FAWTPGYWQJY	61
	FEWAPGYWQJY	62
	FEWVPGYWQJY	63
	FEWTPGYWQJY	64
30	AcFEWTPGYWQJY	65
	FEWTPaWYQJY	66
	FEWTPSarWYQJY	67
	FEWTPGYYQPYP	68
	FEWTPGWWQPYP	69

	FEWTPNYWQPY	70
	FEVffPvYWQJY	71
	FEWTPecGYWQJY	72
	FEWTPAibYWQJY	73
5	FEVffSarGYWQJY	74
	FEWTPGYWQPY	75
	FEWTPGYWQHY	76
	FEWTPGWYQJY	77
	AcFEWTPGWYQJY	78
10	FEWTPGW-pY-QJY	79
	FAWTPGYWQJY	80
	FEWAPGYWQJY	81
	FEWVPGYWQJY	82
	FEWTPGYWQJY	83
15	AcFEWTPGYWQJY	84
	FEWTPAWYQJY	85
	FEWTPSarWYQJY	86
	FEWTPGYYQPY	87
	FEWTPGWWQPY	88
20	FEWTPNYWQPY	89
	FEWTPVYWQJY	90
	FEWTPecGYWQJY	91
	FEWTPAibYWQJY	92
	FEWTSarGYWQJY	93
25	FEWTPGYWQPYALPL	94
	NapEWTPGYYQJY	95
	YEWTPGYYQJY	96
	FEWVPGYYQJY	97
	FEWTPSYYQJY	99
30	FEWTPNYYQJY	99
	TKPR	100
	RKSSK	101
	RKQDK	102
	NRKQDK	103
35	RKQDKR	104

	VTKFYF	105
	VTKFY	106
	VTDFY	107
5	SHLYWQPYSVQ	108
	TLVYWQPYSLQT	109
	RGDYWQPYSVQS	110
	VHVVWQPYSVQT	111
	RLVYWQPYSVQT	112
10	SRVWFQPYSLQS	113
	NMVYWQPYSIQT	114
	SVVFWQPYSVQT	115
	TFVYWQPYALPL	116
	TLVYWQPYSIQR	117
15	RLVYWQPYSVQR	118
	SPVFWQPYSIQI	119
	WIEWWQPYSVQS	120
	SLIYWQPYSLQM	121
	TRLYWQPYSVQR	122
20	RCDYWQPYSVQT	123
	MRVFWQPYSVQN	124
	KIVYWQPYSVQT	125
	RHLYWQPYSVQR	126
	ALVWWQPYSEI	127
25	SRVWFQPYSLQS	128
	WEQPYALPLE	129
	QLVWWQPYSVQR	130
	DLRYWQPYSVQV	131
	ELVWWQPYSLQL	132
30	DLVWWQPYSVQW	133
	NGNYWQPYSFQV	134
	ELVYWQPYSIQR	135
	ELMY)AIQPYSVQE	136
	NLLYWQPYSMQD	137
35	GYEWYQPYSVQR	138
		139

	RSVYWPYISVQR	
	LSEQYQPYSVQR	140
	GGGWWQPYSVQR	141
	VGRWYQPYSVQR	142
5	VHVYWPYSVQR	143
	QARWYQPYSVQR	144
	VHVYWPYSVQT	145
	RSVYWPYSVQR	146
	TRVWFQPYSVQR	147
10	GRIWFQPYSVQR	148
	GRVWFQPYSVQR	149
	ARTWYQPYSVQR	150
	ARVWWQPYSVQM	151
	RLMFYQPYSVQR	152
15	ESMWYQPYSVQR	153
	HFGWWQPYSVHM	154
	ARFWWQPYSVQR	155
	RLVYWPYAPIY	156
	RLVYWPYSYQT	157
20	RLVYWPYSLPI	158
	RLVYWPYSVQA	159
	SRVWYQPYAKGL	160
	SRVWYQPYAQGL	161
	SRVWYQPYAMPL	162
25	SRVWYQPYSVQA	163
	SRVWYQPYSLGL	164
	SRVWYQPYAREL	165
	SRVWYQPYSRQP	166
	SRVWYQPYFVQP	167
30	EYEWYQPYALPL	168
	IPEYWQPYALPL	169
	SRIWWQPYALPL	170
	DPLFWQPYALPL	171
	SRQWVQPYALPL	172
35	IRSWWQPYALPL	173
		174

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	RGYWQPYALPL	175
	RLLWVQPYALPL	176
	EYRWFQPYALPL	177
	DAYWVQPYALPL	178
5	WSGYFQPYALPL	179
	NIEFWQPYALPL	180
	TRDWVQPYALPL	181
	DSSWYQPYALPL	182
	IGNWYQPYALPL	183
10	NLRWDQPYALPL	184
	LPEFWQPYALPL	185
	DSYWWQPYALPL	186
	RSQYYQPYALPL	187
	ARFWLQPYALPL	188
15	NSYFWQPYALPL	189
	RFMYWQPYSVQR	190
	AHLFWQPYSVQR	191
	WWQPYALPL	192
	YYQPYALPL	193
20	YFQPYALGL	194
	YWYQPYALPL	195
	RWWQPYATPL	196
	GWYQPYALGF	197
	YWYQPYALGL	198
25	IWYQPYAMPL	199
	SNMQPYQRLS	200
	TFVYWQPYAVGLPAAETACN	201
	TFVYWQPYSVQMTITGKVTM	202
	TFVYWQPYSSHXXVPXGFPL	203
30	TFVYWQPYYGNPQWAIHVRH	204
	TFVYWQPYVLELPEGAVRA	205
	TFVYWQPYVDYVWPIPIAQV	206
	GWYQPYVDGWR	207
	RWEQPYVKDGWS	208
35	EWYQPYALGWAR	209

	GWQPYARGL	210
	LFEQPYAKALGL	211
	GWEQPYARGLAG	212
	AWVQPYATPLDE	213
5	MWYQPYSSQPAE	214
	GWTQPYSQQGEV	215
	DWFQPYSIQSDE	216
	PWQPYARGFG	217
	RPLYWQPYSVQV	218
10	TLIYWQPYSVQI	219
	RFDYWQPYSDQT	220
	WHQFVQPYALPL	221
	EWDSVYWQPYSVQTLLR	223
	WEQNVYWQPYSVQSFAD	224
15	SDVVYWQPYSVQSLEM	225
	YYDGVYWQPYSVQVMPA	226
	SDIWYQPYALPL	227
	QRIWWQPYALPL	228
	SRIWWQPYALPL	229
20	RSLYWQPYALPL	230
	TIIWEQPYALPL	231
	WETWYQPYALPL	232
	SYDWEQPYALPL	233
	SRIWCQPYALPL	234
25	EIMFWQPYALPL	235
	DYVWQQPYALPL	236
	MDLLVQWYQPYALPL	237
	GSKVILWYQPYALPL	238
	RQGANIWYQPYALPL	239
30	GGGDEPWWYQPYALPL	240
	SQLERTWYQPYALPL	241
	ETWVREWWYQPYALPL	242
	KKGSTQWYQPYALPL	243
	LQARMNWYQPYALPL	244
35	EPRSQKWYQPYALPL	245

	VKQKWRWYQPYALPL	246
	LRRHDVWYQPYALPL	247
	RSTASIWYQPYALPL	248
	ESKEDQWYQPYALPL	249
5	EGLTMKWYQPYALPL	250
	EGSREGWYQPYALPL	251
	VIEWWQPYALPL	252
	VWYWEQPYALPL	253
	ASEWWQPYALPL	254
10	FYEWQPYALPL	255
	EGWVWQPYALPL	256
	WGEWLQPYALPL	257
	DYVWEQPYALPL	258
	AHTWWQPYALPL	259
15	FIEWFQPYALPL	260
	WLAWEQPYALPL	261
	VMEWWQPYALPL	262
	ERMWQPYALPL	263
	NXXWXXPYALPL	264
20	WGNWYQPYALPL	265
	TLYWEQPYALPL	266
	VWRWEQPYALPL	267
	LLWTQPYALPL	268
	SRIWXX PYALPL	269
25	SDIWYQPYALPL	270
	WGYYXX PYALPL	271
	TSGWYQPYALPL	272
	VHPYXXPYALPL	273
	EHSYFQPYALPL	274
30	XXIWYQPYALPL	275
	AQLHSQPYALPL	276
	WANWFQPYALPL	277
	SRLYSQPYALPL	278
	GVTFSQPYALPL	279
35	SIVWSQPYALPL	280

	SRDLVQPYALPL	281
	HWGHVYWQPYSVQDDL	282
	SWHSVYWQPYSVQSVPE	283
	WRDSVYWQPYSVQPESA	284
5	TWDAVYWQPYSVQKWLD	285
	TPPWVYWQPYSVQSLDP	286
	YWSSVYWQPYSVQSVHS	287
	YWYQPYALGL	288
	YWYQPYALPL	289
10	EWIQPYATGL	290
	NWEQPYAKPL	291
	AFYQPYALPL	292
	FLYQPYALPL	293
	VCKQPYLEWC	294
15	ETPFTWEESNAYYWQPYALPL	295
	QGWL TWQDSVDMYWQPYALPL	296
	FSEAGYTWPE NTYWQPYALPL	297
	TESPGGLDWAKIYWQPYALPL	298
	DGYDRWRQSGERYWQPYALPL	299
20	TANVSSF EWTPGYWQPYALPL	300
	SVGEDHNF WTSE YWQPYALPL	301
	MNDQTSEVSTFPYWQPYALPL	302
	SWSEAFEQPRNLYWQPYALPL	303
	QYAEPSALNDWGYWQPYALPL	304
25	NGDWATADWSNYYWQPYALPL	305
	THDEHIYWQPYALPL	306
	MLEKTYTTWTPG YWQPYALPL	307
	WSDPLTRDADLYWQPYALPL	308
	SDAFTTQDSQAMYWQPYALPL	309
30	GDDAAWR TDSLTYWQPYALPL	310
	AIIRQLYRWSEMYWQPYALPL	311
	ENTYSPNWADSMYWQPYALPL	312
	MNDQTSEVSTFPYWQPYALPL	313
	SVGEDHNF WTSEYWQPYALPL	314
35	QTPFTWEESNAYYWQPYALPL	315

	ENPFTWQESNAYYWQPYALPL	316
	VTPFTWEDSNVF YWQPYALPL	317
	QIPFTWEQSNAYYWQPYALPL	318
	QAPL TWQESAAYYWQPYALPL	319
5	EPTFTWEESKAT YWQPYALPL	320
	TTTLTWEEASNAYYWQPYALPL	321
	ESPLTWEESSALYWQPYALPL	322
	ETPLTWEEASNAYYWQPYALPL	323
	EATFTWAESNAYYWQPYALPL	324
10	EALFTWKESTAYYWQPYALPL	325
	STP-TWEEASNAYYWQPYALPL	326
	ETPFTWEEASNAYYWQPYALPL	327
	KAPFTWEESQAYYWQPYALPL	328
	STSFTWEEASNAYYWQPYALPL	329
15	DSTFTWEEASNAYYWQPYALPL	330
	YIPFTWEEASNAYYWQPYALPL	331
	QTAFTWEEASNAYYWQPYALPL	332
	ETLFTWEEASNAT YWQPYALPL	333
	VSSFTWEEASNAYYWQPYALPL	334
20	QPYALPL	335
	Py-1-NapPYQJYALPL	336
	TANVSSF EWTPG YWQPYALPL	337
	FEWTPGYWQPYALPL	338
	FEWTPGYWQJYALPL	339
25	FEWTPGYYQJYALPL	340
	ETPFTWEEASNAYYWQPYALPL	341
	FTWEEASNAYYWQJYALPL	342
	ADVLYWQPYAPVTLWV	343
	GDVAEYWQPYALPLTSL	344
30	SWTDYGYWQPYALPISGL	345
	FEWTPGYWQPYALPL	346
	FEWTPGYWQJYALPL	347
	FEWTPGWYQPYALPL	348
	FEWTPGWYQJYALPL	349
35	FEWTPGYYQPYALPL	350

	FEWTPGYYQJYALPL	351
	TANVSSFEWTPGYWQPYALPL	352
	SWTDYGYWQPYALPISGL	353
	ETPFTWEESNAWAIQPYALPL	354
5	ENTYSPNWADSMYWQPYALPL	355
	SVGEDHNFWTSEYWQPYALPL	356
	DGYDRWRQSGERYWQPYALPL	357
	FEWTPGYWQPYALPL	358
	FEWTPGYWQPY	359
10	FEWTPGYWQJY	360
	EWTPGYWQPY	361
	FEWTPGWYQJY	362
	AEWTPGYWQJY	363
	FAWTPGYWQJY	364
15	FEATPGYWQJY	365
	FEWAPGYWQJY	366
	FEWTAGYWQJY	367
	FEWTPAYWQJY	368
	FEWTPGAWQJY	369
20	FEWTPGYAQJY	370
	FEWTPGYWQJA	371
	FEWTGGYWQJY	372
	FEWTPGYWQJY	373
	FEWTJGYWQJY	374
25	FEVffPecGYWQJY	375
	FEWTPAibYWQJY	376
	FEWTPSarWYQJY	377
	FEWTSarGYWQJY	378
	FEWTPNYWQJY	379
30	FEWTPVYWQJY	380
	FEWTVPYWQJY	381
	AcFEWTPGVVYQJY	382
	AcFEVffPGYWQJY	383
	INap-EVffPGYYQJY	384
35	YEWTPGYYQJY	385

	FEWVPGYYQJY	386
	FEVffPGYYQJY	387
	FEVffPsYYQJY	388
	FEWTPnYYQJY	389
5	SHLY-Nap-QPYSVQM	390
	TLVY-Nap-LDPYSLQT	391
	RGDY-Nap-QPYSVQS	392
	NMVY-Nap-QPYSIQT	393
	VYWQPYSVQ	394
10	VY-Nap-QPYSVQ	395
	TFVYWQJYALPL	396
	FEWTPGYYQJ-Bpa	397
	XaaFEWTPGYYQJ-Bpa	398
	FEWTPGY-Bpa-QJY	399
15	AeFEWTPGY-Bpa-QJY	400
	FEWTPG-Bpa-YQJY	401
	AcFEWTPG-Bpa-YQJY	402
	AcFE-Bpa-TPGYYQJY	403
	AcFE-Bpa-TPGYYQJY	404
20	Bpa-EWTPGYYQJY	405
	AcBpa-EWTPGYYQJY	406
	VYWQPYSVQ	407
	RLVYWQPYSVQR	408
	RLVY-Nap-QPYSVQR	409
25	RLDYWQPYSVQR	410
	RLVWFQPYSVQR	411
	RLVYWQPYSIQR	412
	DNSSWYDSFLL	413
	DNTAWYESFLA	414
30	DNTAWYENFLL	415
	PAREDNTAWYDSFLIWC	416
	TSEYDNTTWYKFLASQ	417
	SQIPDNTAWYQSFLHGH	418
	SPFIDNTAWYENFLLTY	419
35	EQIYDNTAWYDHFLLSY	420

	TPFIDNTAWYENFLLTY	421
	TYTYDNTAWYERFLMSY	422
	TMTQDNTAWYENFLLSY	423
	TIDNTAWYANLVQTPQ	424
5	TIDNTAWYERFLAQYPD	425
	HIDNTAWYENFLLTYTP	426
	SQDNTAWYENFLLSYKA	427
	QIDNTAWYERFLLQYNA	428
	NQDNTAWYESFLLQYNT	429
10	TIDNTAWYENFLLNHNL	430
	HYDNTAWYERFLQQGWH	431
	ETPFTWEESNAYYWQPYALPL	432
	YIPFTWEESNAYYWQPYALPL	433
	DGYDRWRQSGERYWQPYALPL	434
15	pY-INap-pY-QJYALPL	435
	TANVSSFEWTPGYWQPYALPL	436
	FEWTPGYWQJYALPL	437
	FEWTPGYWQPYALPLSD	438
	FEWTPGYYQJYALPL	439
20	FEWTPGYWQJY	440
	AcFEVVTPGYWQJY	441
	AcFEWTPGWYQJY	442
	AcFEWTPGYYQJY	443
	AcFEWTPaYWQJY	444
25	AcFEWTPaWYQJY	445
	AcFEWTPaYYQJY	446
	FEWTPGYYQJYALPL	447
	FEWTPGYWQJYALPL	448
	FEWTPGWYQJYALPL	449
30	TANVSSFEWTPGYWQPYALPL	450
	AcFEWTPGYWQJY	451
	AcFEWTPGWYQJY	452
	AcFEWTPGYYQJY	453
	AcFEWTPAYWQJY	454
35	AcFEWTPAWYQJY	455

AcFEWTPAYYQJY

456

Table 7-TPO-mimetic peptide sequences

Sequence/structure	SEQ-ID-NO:
EGPTLRQWLAARA	457
IEGPTLRQWLAACA	458
IEGPTLRQWLAARA	459
IEGPTLRQWLAARA-A- IEGPTLRQWLAARA	460
IEGPTLRQWLAACA-A- IEGPTLRQWLAACA	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

Sequence/structure	SEQ-ID-NO:
GRVRDQI(X) ₃ L	480
CTLRQWLQGC	481
CTLQEFLEGC	482
CTRTEWLHGC	483
CTLREWLHGGFC	484
CTLREWVFAGLC	485
CTLRQWLILLGMC	486
CTLAEFASGVEQC	487
CSLQEFSLHGGYVC	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
5	EED α K	520
	pGluED α K	521
	PicSD α K	522
	EEDCK- Δ -EEDCK	523
	EEDXK- Δ -EEDXK	524

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Table 9-TNF-antagonist peptide sequences

	Sequence/structure	SEQ ID NO:
	YCFTASENH CY	525
15	YCFTNSENH CY	526
	YCFTRSENH CY	527
	FCASENH CY	528
	YCASENH CY	529
	FCNSENH CY	530
20	FCNSENRCY	531
	FCNSVENRCY	532
	YCSQSVSND CF	533
	FCVSNDRCY	534
	YCRKELGQVCY	535
25	YCKEPGQCY	536
	YCRKEMGCY	537
	FCRKEMGCY	538
	YCWSQNLCY	539
	YCELSQYLCY	540
30	YCWSQNYCY	541
	YCWSQYLCY	542
	DFLPHYKNTSLGHRP	543

Table 10-Integrin-binding peptide sequences

	Sequence/structure	SEQ ID NO:
	RX ₁ ETX ₂ WX ₃	544
	RX ₁ ETX ₂ WX ₃	545
5	RGDGX	546
	CRGDGXC	547
	CX ₁ X ₂ RLDX ₃ X ₄ C	548
	CARRLDAPC	549
	CPSRLDSPC	550
10	X ₁ X ₂ X ₃ RGDX ₄ X ₅ X ₆	551
	CX ₂ CRGDCX ₅ C	552
	CDCRGDCFC	553
	CDCRGDCLC	554
	CLCRGDCIC	555
15	X ₁ X ₂ DDX ₄ X ₅ X ₇ X ₈	556
	X ₁ X ₂ X ₃ DDX ₄ X ₅ X ₆ X ₇ X ₈	557
	CWDDGWL	558
	CWDDLWWLC	559
	CWDDGLMC	560
20	CWDDGWMC	561
	CSWDDGWLC	562
	CPDDLWWLC	563
	NGR	NR
	GSL	NR
25	RGD	NR
	CGRECPRLCQSSC	564
	CNGRCVSGCAGRC	565
	CLSGSLSC	566
	RGD	NR
30	NGR	NR
	GSL	NR
	NGRAHA	567
	CNGRC	568
	CDCRGDCFC	569
35	CGSLVRC	570

	DLXXL	571
	RTDLDSLRTYTL	572
	RTDLDSLRTY	573
	RTDLDSLRT	574
5	RTDLDSLRL	575
	GDLDLLKLRLTL	576
	GDLHSLRQLLSR	577
	RDDLHMLRLQLW	578
	SSDLHALKKRYG	579
10	RGDLKQLSELTW	580
	RGDLAALSAPPV	581

Table 11-Selectin antagonist peptide sequences

15	Sequence/structure	SEQ ID NO:
	DITWDQLWDLMK	582
	DITWDELWKIMN	583
	DYTWFEWDMMQ	584
	QITWAQLWNMMK	585
20	DMTWHDLWTLMS	586
	DYSWHDLWEMMS	587
	EITWDQLWEVMN	588
	HVSWEQLWDIMN	589
	HITWDQLWRIMT	590
25	RNMSWLELWEHMK	591
	AEWTWDQLWHVMNPAESQ	592
	HRAEWLALWEQMSP	593
	KKEDWLALWRIMSV	594
	ITWDQLWDLMK	595
30	DITWDQLWDLMK	596
	DITWDQLWDLMK	597
	DITWDQLWDLMK	598
	CQNRYTDLVAIQNKNE	599
	AENWADNEPNNKRNNED	600
35	RKNNKTWTWVGTKKALTNE	601

	KKALTNEAENWAD	602
	CQXRYTDLVAIQNKXE	603
	RKXNXXWTWVGTXKXLTEE	604
	AENWADGEPNNKXNXED	605
5	CXXXYTXLVAIQNKXE	606
	RKXXXXWXWVGTXKXLTXE	607
	AXNWXXXEPNNXXXED	608
	XKXKTXEAXNWXX	609

10 **Table 12-Antipathogenic peptide sequences**

Sequence/structure

SEQ ID NO:

	GFFALIPKIISSPLFKTLLSAVGSALSSSGGQQ	610
	GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE	611
15	GFFALIPKIISSPLFKTLLSAV	612
	GFFALIPKIISSPLFKTLLSAV	613
	KGFFALIPKIISSPLFKTLLSAV	614
	KKGFFALIPKIISSPLFKTLLSAV	615
	KKGFFALIPKIISSPLFKTLLSAV	616
20	GFFALIPKIIS	617
	GIGAVLKVLTTGLPALISWIKRKRQQ	618
	GIGAVLKVLTTGLPALISWIKRKRQQ	619
	GIGAVLKVLTTGLPALISWIKRKRQQ	620
	GIGAVLKVLTTGLPALISWIKR	621
25	AVLKVLTTGLPALISWIKR	622
	KLLLLLKLLLLK	623
	KLLLKLLKLLK	624
	KLLKLLKLLK	625
	KKLLKLLKLLK	626
30	KLLKLLKLLK	627
	KLLKLLKLLK	628
	KLLLLK	629
	KLLKLLK	630
	KLLKLLKLLK	631
35	KLLKLLKLLK	632

	KLLLKLKLKLLK	633
	KAAAKAAAKAAK	634
	KVVVKVVVKVVK	635
	KVVVKVKVKVVK	636
5	KVVVKVKVKVK	637
	KVVVKVKVKVVK	638
	KLILKL	639
	KVLHLL	640
	LKLRL	641
10	KPLHLL	642
	KLILKLVR	643
	KVFHLLHL	644
	HKFRILKL	645
	KPFHILHL	646
15	KIiIKIKIKIK	647
	KIiIKIKIKIK	648
	KIiIKIKIKIK	649
	KIPKIKIKIPK	650
	KIPKIKIKIVK	651
20	RIIRIRIRIR	652
	RIiIRIRIRIR	653
	RI[IRIRIRIR	654
	RIVIRIRIRLIR	655
	RIIVRIRLRIR	656
25	RIGIRLRVRIIR	657
	KIVIRIRIRLIR	658
	RIAVKWRLRFIK	659
	KIGWKLVRRIIR	660
	KKIGWLIIRVRR	661
30	RIVIRIRIRLIRIR	662
	RIIVRIRLRRIIRVR	663
	RIGIRLRVRIIRRV	664
	KIVIRIRARLIRIRIR	665
	RIIVKIRLRRIKKIRL	666
35	KIGIKARVRRIIRVKII	667

	RIIVHIRLRRIHHIRL	668
	HIGIKAHVRIRRVHII	669
	RIYVKIHLRYIKKIRL	670
	KIGHKARVHIIRYKII	671
5	RIYVKPHPRYIKKIRL	672
	KPGHKARPHIIRYKII	673
	KIVIRIRIRLIRIRIRKIV	674
	RIIVKIRLRRIKKIRLIKK	675
	KIGWKLRVRIIRVKIGRLR	676
10	KI.VIRIRIRLIRIRIRKIVKVKRIR	677
	RFAVKIRLRRIKKIRLIKKIRKRVIK	678
	KAGWKLRVRIIRVKIGRLRKIGWKKRVRIK	679
	RIYVKPHPRYIKKIRL	680
	KPGHKARPHIIRYKII	681
15	KIVIRIRIRLIRIRIRKIV	682
	RIIVKIRLRRIKKIRLIKK	683
	RIYVSKISYIKKIRL	684
	KIVIFTRIRLTSIRIRSIV	685
	KPIHKARPTIIRYKMI	686
20	cyclicCKGFFALIPKISSPLFKTLLSAVC	687
	CKKGFFALIPKISSPLFKTLLSAVC	688
	CKKKGFFALIPKISSPLFKTLLSAVC	689
	CyclicCRIVIRIRIRLIRIRC	690
	CyclicCKPGHKARPHIIRYKIIIC	691
25	CyclicCRFAVKIRLRRIKKIRLIKKIRKRVIKC	692
	KLLKLLL KLLKC	693
	KLLKLLLKLLK	694
	KLLKLLKLLKC	695
	KLLKLLLKLLK	696

30

Table 13-VIP-mimetic peptide sequences

	Sequence/structure	SEQ ID NO:
	HSDAVFYDNYTR LRKQMAVKKYLN SILN	697
	Me HSDAVFYDNYTR LRKQMAVKKYLN SILN	698
35	X ₁ X ₁ ' X ₁ " X ₂	699

	X ₃ SX ₄ LN	700
	KKYL	701
	NSILN	702
	KKYL	703
5	KKYA	704
	AVKKYL	705
	NSILN	706
	KKYV	707
	SILauN	708
10	KKYLN _{le}	709
	NSYLN	710
	NSIYN	711
	KKYLPPNSILN	712
	LauKKYL	713
15	CapKKYL	714
	KYL	NR
	KKYN _{le}	715
	VKKYL	716
	LNSILN	717
20	YLNSILN	718
	KKYLN	719
	KKYLNS	720
	KKYLNSI	721
	KKYLNSIL	722
25	KKYL	723
	KKYDA	724
	AVKKYL	725
	NSILN	726
	KKYV	727
30	SILauN	728
	NSYLN	729
	NSIYN	730
	KKYLN _{le}	731
	KKYLPPNSILN	732
35	KKYL	733

	KKYDA	734
	AVKKYL	735
	NSILN	736
	IKKYV	737
5	SILauN	738
	LauKKYL	739
	CapKKYL	740
	KYL	NR
	KYL	NR
10	KKYNle	741
	VKKYL	742
	LNSILN	743
	YLNSILN	744
	KKYLNle	745
15	KKYLN	746
	KKYLNLS	747
	KKYLNLSI	748
	KKYLNLSIL	749
	KKKYLD	750
20	cyclicCKKYLK	751
	CKKYLK	752
	KKYA	753
	WWTDTGLW	754
	WWTDDGLW	755
25	WWDTRGLWVWTI	756
	FWGNDGIWLESG	757
	DWDQFGLWRGAA	758
	RWDDNGLWVVVL	759
	SGMWSHYGIWMG	760
30	GGRWDQAGLWVA	761
	KLWSEQGIWMGE	762
	CWSMHGLWLC	763
	GCWDNTGIWVPC	764
	DWDTRGLWVY	765
35	SLWDENGAWI	766

	KWDDRGLWMH	767
	QAWNERGLWT	768
	QWDTRGLWVA	769
	WNVHGIWQE	770
5	SWDTRGLWVE	771
	DWDTRGLWVA	772
	SWGRDGLWIE	773
	EWTDNGLWAL	774
	SWDEKGLWSA	775
10	SWDSSGLWMD	776

Table 14-Mdm/hdm antagonist peptide sequences

	Sequence/structure	SEQ ID NO:
	TFSDLW	777
15	QETFSDLWKLLP	778
	QPTFSDLWKLLP	779
	QETFSDYWKLLP	780
	QPTFSDYWKLLP	781
	MPRFMDYWEGLN	782
20	VQNFIDYWTQQF	783
	TGPAFTHYWATF	784
	IDRAPTRDHWFALV	785
	PRPALVFADYWETLY	786
	PAFSRFWSDLSAGAH	787
25	PAFSRFWSKLSAGAH	788
	PXFXDYWXXL	789
	QETFSDLWKLLP	790
	QPTFSDLWKLLP	791
	QETFSDYWKLLP	792
30	QPTFSDYWKLLP	793

Table 15-Calmodulin antagonist peptide sequences

	Sequence/structure	SEQ ID NO:
35	SCVKWKGKKEFCGS	794

	SCWKYWGKECGS	795
	SCYEWGKLRWCGS	796
	SCLRWGKWSNCGS	797
	SCWRWGKYQICGS	798
5	SCVSWGALKLCGS	799
	SCIRWGQNTFCGS	800
	SCWQWGNLKICGS	801
	SCVRWGQLSICGS	802
	LKKFNARRKLKGAILTTMLAK	803
10	RRWKKNFIAVSAANRFKK	804
	RKWQKTGHAVRAIGRLSS	805
	INLKALAALAKKIL	806
	KIWSILAPLGTTLVKLVA	807
	LKKLLKLLKKLLKL	808
15	LKWKLLKLLKKLLKKLL	809
	AEWPSLTEIKTLSHFSV	810
	AEWPSPTRVISTTYFGS	811
	AELAHWPPVKTVLRSFT	812
	AEGSWLQLLNLMKQMN	813
20	AEWPSLTEIK	814

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

	Sequence/structure	SEQ ID NO:
25	SGSGVLKRPLPILPVTR	815
	RWLSSRPLPPLPLPPRT	816
	GSGSYDTLALPSLPLHPMSS	817
	GSGSYDTRALPSLPLHPMSS	818
	GSGSSGVTMYPKLPPHWSMA	819
30	GSGSSGVRMYPKLPPHWSMA	820
	GSGSSSMRMVPTIPGSAKHG	821
	RNR	NR
	QT	NR
	RQK	NR
35	NRQ	NR

	RQK	NR
	RNRQKT	822
	RNRQ	823
	RNRQK	824
5	NRQKT	825
	RQKT	826

Table 17-SH3 antagonist peptide sequences

10	Sequence/structure	SEQ ID NO:
	RPLPPLP	827
	RELPLP	828
	SPLPPLP	829
	GPLPPLP	830
15	RPLPIPP	831
	RPLPIPP	832
	RRLPPTP	834
	RQLPPTP	835
	RPLPSRP	836
20	RPLPTRP	837
	SRLPPLP	838
	RALPSPP	839
	RRLPRTT	840
	RPVPPIT	841
25	ILAPPVP	842
	RPLPMLP	843
	RPLPILP	844
	RPLPSLP	845
	RPLPSLP	846
30	RPLPMIP	847
	RPLPLIP	848
	RPLPPTP	849
	RSLPPLP	850
	RPQPPPP	851
35	RQLPIPP	852

	XXXRPLPPLPXP	853
	XXXRPLPIPXX	854
	XXXRPLPPLPXX	855
	RXXRPLPPLPXP	856
5	RXXRPLPPLPPP	857
	PPPYPPPIIPXX	858
	PPPYPPPPVPXX	859
	LXXRPLPXTP	860
	ΨXXRPLPXL	861
10	PPXΘXPPPΨP	862
	+PPΨPXKPXWL	863
	RPXΨPΨR+SXP	864
	PPVPPRPXXTL	865
	ΨPΨLPΨK	866
15	+ΘDXPLPXL	867

Table 18-Somatostatin or cortistatin mimetic peptide sequences

	Sequence/structure	SEQID NO:
20	X ¹ X 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
25	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
30	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
5	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
10	Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	893

Table 19-UKR antagonist peptide sequences

	Sequence/structure	SEQID NO:
15	AEPMPHSLNFSQYLWYT	894
	AEHTYSSLWDTYSPLAF	895
	AELDLWMRHYPLSFSNR	896
	AESSLWTRYAWPSMPSY	897
	AEWHPGLSFGSYLWSKT	898
20	AEPALLNWSFFFNPGLH	899
	AEWSFYNLHLPEPQTIF	900
	AEPLDLWSLYSLPPLAM	901
	AEPTLWQLYQFPLRLSG	902
	AEISFSELMWLRSTPAF	903
25	AELSEADLWTTWFGMGS	904
	AESSLWRIFSPSALMMS	905
	AESLPTLTSILWGKESV	906
	AETLFMDLWHDKHILLT	907
	AEILNFPLWHEPLWSTE	908
30	AESQTGTLNTLFWNTLR	909
	AEPVYQYELDSYLRSY	910
	AELDLSTFYDIQYLLRT	911
	AEFFKLGPNGYVYLHSA	912
	FKLXXXGYVYL	913
35	AESTYHHLSLGYMYTLN	914

YHXLXXGYMYT

915

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

	Sequence/structure	SEQ ID NO:
	Xaa-Yaa-Arg	NR
5	Arg-Yaa-Xaa	NR
	Xaa-Arg-Yaa	NR
	Yaa-Arg-Xaa	NR
	Ala-Arg	NR
	Arg-Arg	NR
10	Asn-Arg	NR
	Asp-Arg	NR
	Cys-Arg	NR
	Gln-Arg	NR
	Glu-Arg	NR
15	Gly-Arg	NR
	His-Arg	NR
	Ile-Arg	NR
	Leu-Arg	NR
	Lys-Arg	NR
20	Met-Arg	NR
	Phe-Arg	NR
	Ser-Arg	NR
	Thr-Arg	NR
	Trp-Arg	NR
25	Tyr-Arg	NR
	Val-Arg	NR
	Ala-Glu-Arg	NR
	Arg-Glu-Arg	NR
	Asn-Glu-Arg	NR
30	Asp-Glu-Arg	NR
	Cys-Glu-Arg	NR
	Gln-Glu-Arg	NR
	Glu-Glu-Arg	NR
	Gly-Glu-Arg	NR
35	His-Glu-Arg	NR

	Ile-Glu-Arg	NR
	Leu-Glu-Arg	NR
	Lys-Glu-Arg	NR
	Met-Glu-Arg	NR
5	Phe-Glu-Arg	NR
	Pro-Glu-Arg	NR
	Ser-Glu-Arg	NR
	Thr-Glu-Arg	NR
	Trp-Glu-Arg	NR
10	Tyr-Glu-Arg	NR
	Val-Glu-Arg	NR
	Arg-Ala	NR
	Arg-Asp	NR
	Arg-Cys	NR
15	Arg-Gln	NR
	Arg-Glu	NR
	Arg-Gly	NR
	Arg-His	NR
	Arg-Ile	NR
20	Arg-Leu	NR
	Arg-Lys	NR
	Arg-Met	NR
	Arg-Phe	NR
	Arg-Pro	NR
25	Arg-Ser	NR
	Arg-Thr	NR
	Arg-Trp	NR
	Arg-Tyr	NR
	Arg-Val	NR
30	Arg-Glu-Ala	NR
	Arg-Glu-Asn	NR
	Arg-Glu-Asp	NR
	Arg-Glu-Cys	NR
	Arg-Glu-Gln	NR
35	Arg-Glu-Glu	NR

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	Arg-Glu-Gly	NR
	Arg-Glu-His	NR
	Arg-Glu-Ile	NR
	Arg-Glu-Leu	NR
5	Arg-Glu-Lys	NR
	Arg-Glu-Met	NR
	Arg-Glu-Phe	NR
	Arg-Glu-Pro	NR
	Arg-Glu-Ser	NR
10	Arg-Glu-Thr	NR
	Arg-Glu-Trp	NR
	Arg-Glu-Tyr	NR
	Arg-Glu-Val	NR
	Ala-Arg-Glu	NR
15	Arg-Arg-Glu	NR
	Asn-Arg-Glu	NR
	Asp-Arg-Glu	NR
	Cys-Arg-Glu	NR
	Gln-Arg-Glu	NR
20	Glu-Arg-Glu	NR
	Gly-Arg-Glu	NR
	His-Arg-Glu	NR
	Ile-Arg-Glu	NR
	Leu-Arg-Glu	NR
25	Lys-Arg-Glu	NR
	Met-Arg-Glu	NR
	Phe-Arg-Glu	NR
	Pro-Arg-Glu	NR
	Ser-Arg-Glu	NR
30	Thr-Arg-Glu	NR
	Trp-Arg-Glu	NR
	Tyr-Arg-Glu	NR
	Val-Arg-Glu	NR
	Glu-Arg-Ala	NR
35	Glu-Arg-Arg	NR

	Glu-Arg-Asn	NR
	Glu-Arg-Asp	NR
	Glu-Arg-Cys	NR
	Glu-Arg-Gln	NR
5	Glu-Arg-Gly	NR
	Glu-Arg-His	NR
	Glu-Arg-Ile	NR
	Glu-Arg-Leu	NR
	Glu-Arg-Lys	NR
10	Glu-Arg-Met	NR
	Glu-Arg-Phe	NR
	Glu-Arg-Pro	NR
	Glu-Arg-Ser	NR
	Glu-Arg-Thr	NR
15	Glu-Arg-Trp	NR
	Glu-Arg-Tyr	NR
	Glu-Arg-Val	NR

Table 21-Additional Exemplary Pharmacologically Active Peptides

20

	Sequence/Structure	SEQ ID NO:	Activity
	VEPNCDIHVMWEWECFERL	916	VEGF-antagonist
	GERWCFDGPLTWVCGEES	917	VEGF-antagonist
25	RGWVEICVADDNGMCVTEAQ	918	VEGF-antagonist
	GWDECDVARMWEWECFAGV	919	VEGF- antagonist
	GERWCFDGPRAWVCGWEI	920	VEGF- antagonist
	EELWCFDGPRAWVCGYVK	921	VEGF- antagonist
	RGWVEICAADDYGRCLTEAQ	922	VEGF- antagonist
30	RGWVEICESDVWGRCL	923	VEGF- antagonist
	RGWVEICESDVWGRCL	924	VEGF- antagonist
	GGNECDIARMWEWECFERL	925	VEGF- antagonist
	RGWVEICAADDYGRCL	926	VEGF-antagonist
	CTTHWGFTLC	927	MMP inhibitor
35	CLRSGXGC	928	MMP inhibitor

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	CXXHWGFXXC	929	MMP inhibitor
	CXPXC	930	MMP inhibitor
	CRRHWGFEEC	931	MMP inhibitor
	STTHWGF TLS	932	MMP inhibitor
5	CSLHWGFWWC	933	CTLA4-mimetic
	GFVCSGIFAVGVGRC	934	CTLA4-mimetic
	APGVRLGCAVLGRYC	935	CTLA4-mimetic
	LLGRMK	936	Antiviral (HBV)
	ICVVQDWGHHRCTAGHMANLTSHASAI	937	C3b antagonist
10	ICVVQDWGHHRCT	938	C3b antagonist
	CVVQDWGHHAC	939	C3b antagonist
	STGGFDDVYDWARGVSSALTTTLVATR	940	Vinculin-binding
	STGGFDDVYDWARRVSSALTTTLVATR	941	Vinculin-binding
	SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	942	Vinculin-binding
15	SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	943	Vinculin-binding
	SSPSLYTQFLVNYESAATRIQDLLIASRPSR	944	Vinculin-binding
	SUGMIDILLGAILQRAADATRTSIPIPSLQNSIR	945	Vinculin-binding
	DVYTKKELIECARRVSEK	946	Vinculin-binding
	EKGSYYPGSGIAQFHIDYNNVS	947	C4BP-binding
20	SGIAQFHIDYNNVSSAEGWHVN	948	C41BP-binding
	LVTVEKGSYYPGSGIAQFHIDYNNVSSAEGWHVN	949	4BP-binding
	SGIAQFHIDYNNVS	950	C4BP-binding
	LLGRMK	951	anti-HBV
	ALLGRMKG	952	anti-HBV
25	LDPAFIR	953	anti-HBV
	CXXRGDC	954	Inhibition of platelet aggregation
	RPLPPLP	955	Src antagonist
	PPVPPR	956	Src antagonist
	XFXDXWXXLXX	957	Anti-cancer
30	KACRRLFGPVDSEQLSRDCD	958	pl 6-mimetic
	RERWNFDFTETPLEGDFAW	959	pl 6-mimetic
	KRRQTSMTDFYHSKRRLIFS	960	pl 6-mimetic
	TSMTDFYHSKRRLIFSKRKP	961	pl 6-mimetic
	RRLIF	962	p16-mimetic
35	KRRQTSATDFYHSKRRLIFSRQIKIWFQNRMRMKWKK	963	p16-mimetic

	KRRLLFSKRQIKIWFQNRRMKWKK	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
5	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
10	NTLKTPRV	969	I32GPI Ab binding
	NTLKTPRVGGC	970	02GPI Ab binding
	KDKATF	971	02GPI Ab binding
	KDKATFGCHD	972	P2GPI Ab binding
	KDKATFGCHDGC	973	02GPI Ab binding
15	TLRVYK	974	02GPI Ab binding
	ATLRVYKG	975	02GPI Ab binding
	CATLRVYKGG	976	132GPI Ab binding
	INLKALAALAKKIL	977	Membrane transporting
	GWT	NR	Membrane transporting
20	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

25 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

30 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

35 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 CH1-deleted 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 "CH1-deleted mimetibody activity" refers to a CH1-deleted 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 CH1-deleted 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 CH1-deleted 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, wherein at least one of the LBRs is replaced by at least one LBR as described herein. In one embodiment, the human CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant thereof comprises an IgG1 heavy chain and an IgG1 light chain.

At least one CH1-deleted 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 LBR of at least one CH1-deleted mimetibody, specified portion or variant of the present 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.

Generally, the CH1-deleted mimetibody or ligand-binding fragment of the present invention can comprise a ligand binding region (LBR) (e.g., LBR1, LBR2 and LBR3) or variant provided in at least one heavy chain variable region and at least one ligand binding region (LBR1, LBR2 and LBR3) or variant provided in at least one light chain variable region. As a non-limiting example, the CH1-deleted mimetibody or ligand-binding portion or variant can comprise at least one of the heavy chain

LBR3, and/or a light chain LBR3. In a particular embodiment, the CH1-deleted mimetibody or ligand-binding fragment can have an ligand-binding region that comprises at least a portion of at least one heavy chain LBR (i.e., LBR1, LBR2 and/or LBR3) having the amino acid sequence of the corresponding LBRs 1, 2 and/or 3. In another particular embodiment, the CH1-deleted mimetibody or ligand-binding portion or variant can have an ligand-binding region that comprises at least a portion of at least one light chain LBR (i.e., LBR1, LBR2 and/or LBR3) having the amino acid sequence of the corresponding LBRs 1, 2 and/or 3. Such mimetibodies can be prepared by joining together the various portions (e.g., LBRs, framework) of the CH1-deleted mimetibody using known techniques, by preparing and expressing at least one (i.e., one or more) nucleic acid molecules that encode the CH1-deleted mimetibody, using known techniques of recombinant DNA technology or by using any other suitable method, such as chemical synthesis.

The CH1-deleted mimetibody can comprise at least one of a 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 CH1-deleted 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 and LBRs 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 or LBRs 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):

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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	Phenylalanine	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 CH1-deleted 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.

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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 CH1-deleted mimetibody LBR, 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.

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Amino acids in a CH1-deleted 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 CH1-deleted 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 the Pep 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 activities or functions of said CH1-deleted mimetibody.

A CH1-deleted mimetibody or specified portion or variant can further optionally comprise at least one functional portion of at least one polypeptide as Pep portion of Formula (I), at least one of 90-100% of SEQID NOS:1-1109. A CH1-deleted mimetibody can further optionally comprise an amino acid sequence for the Pep portion of Formula (I), selected from one or more of SEQID NOS:1-1109.

In one embodiment, the Pep amino acid sequence of an immunoglobulin chain, or portion thereof (e.g., comprising at least one specified variable region, LBR) 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 pyrrolidone, 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 CH1-deleted mimetibody or specified portion or variant. Each organic moiety that is bonded to a CH1-deleted 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 CH1-deleted 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 pyrrolidone. Preferably, the hydrophilic polymer that modifies the CH1-deleted mimetibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example, PEG₂₅₀₀, PEG₅₀₀₀, PEG₇₅₀₀, PEG₉₀₀₀, PEG₁₀₀₀₀, PEG₁₂₅₀₀, PEG₁₅₀₀₀, 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 (C₁₂, laurate), n-tetradecanoate (C₁₄, myristate), n-octadecanoate (C₁₈, stearate), n-eicosanoate (C₂₀, arachidate), n-docosanoate (C₂₂, behenate), n-triacontanoate (C₃₀), n-tetracontanoate (C₄₀), *cis*- Δ^9 -octadecanoate (C₁₈, oleate), all *cis*- $\Delta^{5,8,11,14}$ -eicosatetraenoate (C₂₀, 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, acryloyl, 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 C₁-C₁₂ 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, -(CH₂)₃-, -NH-(CH₂)₆-NH-, -(CH₂)₂-NH- and -CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-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 CH1-deleted mimetibody or ligand-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the CH1-deleted 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 CH1-deleted mimetibody or ligand-binding fragment. The reduced CH1-deleted mimetibody or ligand-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified CH1-deleted mimetibody of the invention. Modified human mimetibodies and ligand-binding fragments comprising an organic moiety that is bonded to specific sites of a CH1-deleted 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).

CH1-DELETED MIMETIBODY COMPOSITIONS

The present invention also provides at least one CH1-deleted 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 antineoplastic, 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; Pharmacotherapy 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, antituberculosics 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 antifatulents, 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
 5 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.
 10 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
 15 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,
 20 pyrimethamine, pyrimethamine with sulfadoxine. The at least one antituberculous 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
 25 amoxicillin/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
 30 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, cephalixin hydrochloride, cephalixin monohydrate, cephradine, loracarbef. The
 35 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 succinate, 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 amlodipine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, isosorbide mononitrate, nadolol, nifedipine 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 hydrochloride, lisinopril, losartan potassium, methyldopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil,
- 5 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,
- 10 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*.)
- 15 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
- 20 sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opioid 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
- 25 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,
- 30 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, ethosuximide, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate,
- 35 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, fluphenazine 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, benzotropine 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., parasympathomimetic) 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, 5 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 10 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, 15 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, dextromethorphan hydrobromide, diphenhydramine hydrochloride, guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant, 20 budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetate, 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, 25 magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enzymes 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 attapulgit, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincture (camphorated). The at least one laxative can be at least one selected from 30 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, 35 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, ranitidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook*.)

The at least one corticosteroids 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 norethindrone, norethindrone, norethindrone acetate, norgestrel, progesterone. The at least one gonadotropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucagon 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, desmopressin 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 gluconate, 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, thiotepe. 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, 5 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, *Haemophilus b* conjugate vaccines, 10 hepatitis A vaccine (inactivated), hepatitis 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 15 (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 20 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 (intravenous), hepatitis B immune globulin (human), immune globulin intramuscular, immune globulin intravenous, rabies 25 immune globulin (human), respiratory syncytial virus immune globulin intravenous (human), Rh₀(D) immune globulin (human), Rh₀(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, 30 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 from bacitracin, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, 35 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 acetylcholine 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, hydrocortisone 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 caloric 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*.)

CH1 deleted 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 CH1 deleted 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, entercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, 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 erythropoietin (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 limited 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 difficile*, *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.

CH1-deleted 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 CH1-deleted 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/CH1-deleted 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.

CH1-deleted 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 CH1-deleted 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 CH1-deleted 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. Preferred 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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® polyols, other block copolymers, 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 biological 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 CH1-deleted mimetibody or specified portion or variant in the invention can be prepared by a process that comprises mixing at least one CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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.

5 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 CH1-deleted 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
10 thus provides a more convenient treatment regimen than currently available.

 At least one CH1-deleted 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
15 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
20 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, multiple myeloma, AIDS-associated anemia, concomitant treatment for patients with or without autologous blood donation
25 awaiting elective surgery, preoperative 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-
30 728, 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 al., Blood. 1978;52:1196-1210; Sawyer et al., Blood. 1989;74:103-109; Winearls et al., Lancet.
35 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 incorporated 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 CH1-deleted 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/infectious 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/epididymitis, 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), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant 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

5 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, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core

10 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

15 panencephalitis, Hallerorden-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

20 composition or pharmaceutical composition comprising at least one CH1-deleted 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

25 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 arteriosclerotic 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,

30 regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, 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, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta

and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, 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 erythropoietin (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," "TNF α antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNF α activity *in vitro*, *in situ* and/or preferably *in vivo*. For example, a suitable TNF human antibody of the present invention can bind TNF α and includes anti-TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNF α . 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 TNF α 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 TNF α in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNF α , the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} \text{M}^{-1}$. 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, (1992-2002); Kozbor *et al.*, *Immunol. Today*, 4:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, New York (1987-2002); 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 TNF α 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 TNF α 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 TNF α with high affinity and possess low immunogenicity). A functional equivalent of TNF receptor molecule also includes
5 modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF α 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
10 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 (1987-2002).

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
15 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 CH1-deleted mimetibody or specified portion or variant to a cell,
20 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 CH1-deleted 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.
25 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 CH1-deleted mimetibody composition that total, on average, a range from at least about 0.01 to 500 milligrams of at least one CH1-deleted mimetibody or specified portion or variant
30 /kilogram of patient per dose, and preferably from at least about 0.1 to 100 milligrams CH1-deleted 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 μ g/ml serum concentration per single or multiple administration. 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.

5 Preferred doses can optionally include 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 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.

15 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.

25 As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 aqueous 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 semisynthetic 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 CH1-deleted mimetibody or specified portion or variant by parenteral, subcutaneous, intramuscular, intravenous, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. Protein, CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 propellant 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 AERxTM 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant Compositions as a Spray

A spray including CH1-deleted mimetibody or specified portion or variant composition protein can be produced by forcing a suspension or solution of at least one CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant composition protein suitable for use with a sprayer typically include CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant composition

proteins include albumin, protamine, or the like. Typical carbohydrates useful in formulating CH1-deleted mimetibody or specified portion or variant composition proteins include sucrose, mannitol, lactose, trehalose, glucose, or the like. The CH1-deleted mimetibody or specified portion or variant composition protein formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant compositions by a Nebulizer

CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant composition protein either directly or through a coupling fluid, creating an aerosol including the CH1-deleted mimetibody or specified portion or variant composition protein. Advantageously, particles of CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant suitable for use with a nebulizer, either jet or ultrasonic, typically include CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant composition proteins include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one CH1-deleted mimetibody or specified portion or variant include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one CH1-deleted 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 CH1-deleted 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 CH1-deleted mimetibody or specified portion or variant protein can also be included in the formulation.

Administration of CH1-deleted mimetibody or specified portion or variant compositions By A Metered Dose Inhaler

In a metered dose inhaler (MDI), a propellant, at least one CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 (hydrofluoroalkane-134a), HFA-227 (hydrofluoroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one CH1-deleted 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 CH1-deleted 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 CH1-deleted 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, pregelatinized 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.

5 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
10 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. 5,587,753 are used to deliver biologically active agents orally are known in the art.

Transdermal Formulations and Administration

For transdermal administration, the at least one CH1-deleted mimetibody or specified portion
15 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,
20 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
25 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
30 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
35 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
5 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).

10 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 CH1-deleted mimetibody in Mammalian Cells

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the CH1-deleted 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, HTLV, HIV 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 pIRESneo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clontech 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 CH1-deleted 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 CH1-deleted 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 CH1-deleted 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 HTLV. 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 CH1-deleted mimetibody or specified portion or variant is used, e.g., as presented in SEQID NOS: 13, 14, 15, 16, 17, 18, corresponding to HC and LC variable regions of a CH1-deleted 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
5 also used in this construct (e.g., as provided in vector p1351).

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
10 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
15 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
20 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
25 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
30 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).

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 of NfusCG1 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 NfusCG1 were analyzed. Mutations that would decrease the predicted immunogenicity of one or more peptides are evaluated for *in vivo* effect on immunogenicity.

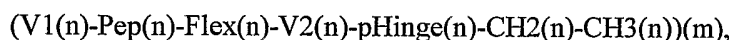
Advantages: The novel construct, NfusCG1 described above offers an alternative way of displaying bioactive peptides. In addition, proposed modifications are expected to, in combination and in addition to the novel features of mimetibodies of the present invention, enhance their utility.

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

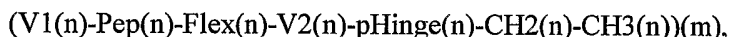
WHAT IS CLAIMED IS:

1 . At least one CH1 deleted mimetibody nucleic acid, comprising at least one polynucleotide encoding a polypeptide according to Formula (I):



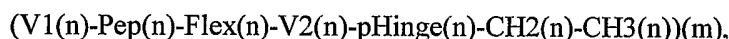
5 where V1 is at least one portion of an N-terminus of an immunoglobulin variable region, Pep is at least one bioactive peptide, Flex is polypeptide that provides structural flexibility by allowing the mimetibody to have alternative orientations and binding properties, V2 is at least one portion of a C-terminus of an immunoglobulin variable region, pHinge 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
10 least a portion of an immunoglobulin CH3 constant region, n and m can be an integer between 1 and 10.

2 . At least one CH1 deleted mimetibody polypeptide, comprising a polypeptide according to Formula (I):



15 where V1 is at least one portion of an N-terminus of an immunoglobulin variable region, Pep is at least one bioactive peptide selected from SEQ ID NOS:43-518, Flex is polypeptide that provides structural flexibility by allowing the mimetibody to have alternative orientations and binding properties, V2 is at least one portion of a C-terminus of an immunoglobulin variable region, pHinge is at least a portion of an immunoglobulin variable hinge region, CH2 is at least a portion of an immunoglobulin CH2
20 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, n and m can be an integer between 1 and 10.

3 . At least one CH1 deleted mimetibody polypeptide, comprising a polypeptide according to Formula (I):



25 where V1 is at least one portion of an N-terminus of an immunoglobulin variable region, Pep is at least one bioactive peptide selected from SEQ ID NOS:519-1110, Flex is polypeptide that provides structural flexibility by allowing the mimetibody to have alternative orientations and binding properties, V2 is at least one portion of a C-terminus of an immunoglobulin variable region, pHinge is at least a portion of an immunoglobulin variable hinge region, CH2 is at least a portion of an
30 immunoglobulin CH2 constant region, CH3 is at least a portion of an immunoglobulin CH3 constant region, n and m can be an integer between 1 and 10.

4 . A(n) CH1 deleted mimetibody nucleic acid or CH1 deleted mimetibody polypeptide according to any of claims 1-3, wherein said polypeptide has at least one activity of at least one Pep polypeptide.

35 5 . A CH1 deleted mimetibody antibody, comprising a monoclonal or

polyclonal antibody, fusion protein, or fragment thereof, that specifically binds at least one CH1 deleted mimetibody polypeptide according to any of claims 1-3.

6 . A CH1 deleted mimetibody nucleic acid encoding at least one CH1 deleted mimetibody polypeptide or CH1 deleted mimetibody antibody according to any of claim 1-5.

5 7 . A CH1 deleted mimetibody vector comprising at least one isolated nucleic acid according to claim 6.

8 . A CH1 deleted mimetibody host cell comprising an isolated nucleic acid according to claim 7.

10 9 . A CH1 deleted 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.

15 10 . A method for producing at least one CH1 deleted mimetibody polypeptide or CH1 deleted mimetibody antibody, comprising translating a nucleic acid according to claim 6 under conditions in vitro, in vivo or in situ, such that the CH1 deleted mimetibody or antibody is expressed in detectable or recoverable amounts.

11 . A composition comprising at least one CH1 deleted mimetibody nucleic acid, CH1 deleted mimetibody polypeptide, or CH1 deleted mimetibody antibody according to any of claims 1-5.

20 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-
25 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 antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

30 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 15 . A method for diagnosing or treating a CH1 deleted mimetibody ligand related condition in a cell, tissue, organ or animal, comprising

35 (a) contacting or administering a composition comprising an effective amount of at least one

CH1 deleted mimetibody nucleic acid, polypeptide or antibody according to any of claims 1-5, 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 CH1 deleted mimetibody antibody; 0.000001-500 mg of said CH1 deleted mimetibody; or 0.0001-100 μ g of said CH1 deleted 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 antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

19 . A device, comprising at least one isolated CH1 deleted mimetibody polypeptide, antibody or nucleic acid according to any of claims 1-5, wherein said device is suitable for contacting or administering said at least one of said CH1 deleted 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 CH1 deleted mimetibody polypeptide, antibody or nucleic acid according to any of claims 1-5.

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 CH1 deleted mimetibody polypeptide, antibody or nucleic acid according to any of claims 1-5, 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 CH1 deleted mimetibody polypeptide, antibody or nucleic acid, produced by a method according to claim 22.