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(54) Title: MODIFIED FC MOLECULES

(57) Abstract: Disclosed is a process for preparing a pharmacologically active compound, in which at least one internal conjugation site of an Fc domain sequence is selected that is amenable to conjugation of an additional functional moiety by a defined conjugation chemistry through the side chain of an amino acid residue at the conjugation site. An appropriate amino acid residue for conjugation may be present in a native Fc domain at the conjugation site or may be added by insertion (i.e., between amino acids in the native Fc domain) or by replacement (i.e., removing amino acids and substituting different amino acids). In the latter case, the number of amino acids added need not correspond to the number of amino acids removed from the previously existing Fc domain. This technology may be used to produce useful compositions of matter and pharmaceutical compositions containing them. A DNA encoding the inventive composition of matter, an expression vector containing the DNA, and a host cell containing the expression vector are also disclosed.

WO 2007/022070 A2

MODIFIED FC MOLECULES

This application claims the benefit of U. S. Nonprovisional Application, serial number not yet available, filed August 10, 2006, which claims the benefit of U. S. Provisional Application No. 60/707,842, filed August 12, 2005, both of which are hereby incorporated by reference.

This application incorporates by reference all subject matter contained on the diskette, which is identified by the name of the file, A-1037USSeqList081006.ST25.txt created on August 10, 2006, the size of which file is 229 KB.

Throughout this application various publications are referenced within parentheses or brackets. The disclosures of these publications in their entireties are hereby incorporated by reference in this application in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

1. Field of Art

The present invention relates to the biochemical arts, particularly to conjugates with immunoglobulin Fc domains.

2. Discussion of Related Art

The immunoglobulin Fc domain has found widespread use as a carrier protein for a variety of therapeutic and diagnostic molecules. Antibodies comprise two functionally independent parts, a variable domain known as "Fab", which binds antigen, and a constant domain known as "Fc", which links to such effector functions as complement activation and attack by phagocytic cells. An Fc has a long serum half-life, whereas a Fab is short-lived. (Capon et al. (1989), Nature 337: 525-31). When constructed together with a therapeutic protein or peptide, an Fc domain can provide longer half-life, or can incorporate such functions as Fc receptor binding, protein A binding, complement fixation and perhaps even placental transfer. Id.

Numerous fusions of proteins and peptides have been engineered at either the amino- or carboxy-termini. Also, a variety of enzymes and synthetic reporter molecules have been chemically conjugated to the side chains of non-terminal amino acids as well as the derivatized carbohydrate moieties of the Fc domain. Further, several polymers, such as polyethylene glycol (PEG) have been conjugated to the Fc domain for the purpose of improved half-life *in vivo* and reduced immunogenicity.

The success of the drug Enbrel® (etanercept) brought to fruition the promise of therapeutic agents modified with the constant domain of an antibody. Table 1 summarizes several examples of the use of Fc fusion proteins known in the art.

Table 1. Fc fusion with therapeutic proteins

Form of Fc	Fusion partner	Therapeutic implications	Reference
IgG1	N-terminus of CD30-L	Hodgkin's disease; anaplastic lymphoma; T-cell leukemia	U.S. Patent No. 5,480,981
Murine Fcγ2a	IL-10	anti-inflammatory; transplant rejection	Zheng et al. (1995), J. Immunol. 154: 5590-600
IgG1	TNF receptor	septic shock	Fisher et al. (1996), N. Engl. J. Med. 334: 1697-1702; Van Zee, K. et al. (1996), J. Immunol. 156: 2221-30
IgG, IgA, IgM, or IgE (excluding the first domain)	TNF receptor	inflammation, autoimmune disorders	U.S. Pat. No. 5,808,029, issued September 15, 1998
IgG1	CD4 receptor	AIDS	Capon et al. (1989), Nature 337: 525-31
IgG1, IgG3	N-terminus of IL-2	anti-cancer, antiviral	Harvill et al. (1995), Immunotech. 1: 95-105
IgG1	C-terminus of OPG	osteoarthritis; bone density	WO 97/23614, published July 3, 1997
IgG1	N-terminus of leptin	Anti-obesity	WO 98/28427, filed December 11, 1997
Human Ig C□1	CTLA-4	autoimmune disorders	Linsley (1991), J. Exp. Med. 174:561-9

A more recent development is fusion of randomly generated peptides with the Fc domain. See U.S. Pat. No. 6,660,843, issued December 9, 2003 to Feige et al. (incorporated by reference in its entirety). Such molecules have come to be known as "peptibodies." They include one or more peptides linked to the N-terminus, C-terminus, amino acid side chains, or to more than one of these sites. Peptibody technology enables design of therapeutic agents that incorporate peptides that target one or more ligands or receptors, tumor-homing peptides, membrane-transporting peptides, and the like. Peptibody technology has proven useful in design of a number of such molecules, including linear and disulfide-constrained peptides, "tandem peptide multimers" (i.e., more than one peptide on a single chain of an Fc domain) . See, for example, U.S. Pat. No. 6,660,843; U.S. Pat. App. No. 2003/0195156 A1, published Oct. 16, 2003 (corresponding to WO 02/092620, published Nov. 21, 2002); U.S. Pat. App. No. 2003/0176352, published Sept. 18, 2003 (corresponding to WO 03/031589, published April 17, 2003); U.S. Ser. No. 09/422,838, filed October 22, 1999 (corresponding to WO 00/24770, published May 4, 2000); U.S. Pat. App. No. 2003/0229023, published December 11, 2003; WO 03/057134, published July 17, 2003; U.S. Pat. App. No. 2003/0236193, published December 25, 2003 (corresponding to PCT/US04/010989, filed April 8, 2004); U.S. Ser. No. 10/666,480, filed September 18, 2003 (corresponding to WO 04/026329, published April 1, 2004), U.S. Patent App. No. 2006/0140934, published June 29, 2006 (corresponding to WO 2006/036834, published April 4, 2006), each of which is hereby incorporated by reference in its entirety. The art would benefit from further technology enabling such rational design of polypeptide therapeutic agents.

Conventional approaches for chemical conjugation to the immunoglobulin Fc domain include random coupling to naturally occurring primary amines such as lysine and the amino-terminus or carboxylic acids such as glutamic acid, aspartic acid and the carboxy terminus. Alternatively, semi-selective site-specific coupling may be achieved through N-terminal conjugation under appropriate conditions, or derivatized carbohydrates as found on Fc proteins isolated from eukaryotic sources, or by partial reduction and coupling of native cysteine residues. (E.g., Kim et al., A pharmaceutical composition comprising an immunoglobulin Fc region as a carrier, WO 2005/047337). While each of these approaches has been applied successfully, they typically suffer from varying degrees of conjugate heterogeneity, relatively low yields and sometimes, significant losses in functional activity are also observed. The art would benefit from a process for selective, site-specific conjugation to the immunoglobulin Fc domain without significant loss in functional activity.

SUMMARY OF THE INVENTION

The present invention concerns compositions of matter and a process for making them. The inventive composition of matter, which is a pharmacologically active compound, comprises a monomeric or multimeric Fc domain having at least one additional functional moiety that is covalently bound (or conjugated), either directly or through a linker, to one or more specifically selected conjugation site(s) in the Fc domain through the side chain of an amino acid residue at the conjugation site(s). Such an internal conjugation site may be already present in a native Fc domain sequence or can be added by insertion (i.e., between amino acids in the native Fc domain) or by replacement (i.e., removing amino acid residue(s) and substituting different canonical and/or non-canonical amino acid residue(s)) in the native Fc domain sequence in order to create or "engineer" the conjugation site. In the latter case, the number of amino acid residues added need not correspond to the number of amino acid residues removed from the previously existing Fc domain sequence.

This inventive process of preparing a pharmacologically active compound comprising an Fc domain includes:

a. selecting at least one internal conjugation site of an Fc domain sequence, said conjugation site being amenable to conjugation of an additional moiety by a defined coupling chemistry through the side chain of an amino acid residue at the conjugation site; and

b. conjugating a predetermined functional moiety to the selected conjugation site by employing the defined conjugation chemistry.

In some embodiments, the functional moiety is a half-life extending moiety and/or a pharmacologically active moiety, which can be, for example, a polypeptide, a peptide, a peptidomimetic, or a non-peptide organic moiety. In other embodiments the additional functional moiety is a moiety detectably labeled with a radioisotope, an enzyme (e.g., a peroxidase or a kinase), a biotinyl moiety, a fluorophore, or a chromophore. Alternatively, the additional functional moiety is an immobilized substrate, such as but not limited to, a plate surface, a bead, a particle, a microparticle, a nanoparticle, a chip, a liposome, a matrix, or the like, provided that in a chain of additional functional moieties, the immobilized substrate is the additional moiety most distal from the Fc domain, and there can be no more than one immobilized substrate in the chain.

The inventive process can be employed to modify an Fc domain that is already linked through an N- or C-terminus or side chain to a polypeptide (e.g., a soluble fragment of TNF-R2, as in etanercept) or to a peptide (e.g., as described in U.S. Pat. App. Nos. 2003/0195156 A1, 2003/0176352, 2003/0229023, and 2003/0236193; WO 00/24770; WO 04/026329). The process described throughout can also be employed to modify an Fc domain that is part of an antibody (e.g., adalimumab, epratuzumab, infliximab, Herceptin®, and the like). In this way, different molecules can be produced that have additional functionalities, such as a binding domain to a different epitope, an additional binding domain to the precursor molecule's existing epitope, or an additional half-life extending moiety.

The compounds of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or any other methods of preparing peptides and fusion proteins with reference to the disclosure of this specification.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them by methods known for other proteinacious molecules and administering an effective amount to a patient, such as a human (or other mammal) in need thereof. Other related aspects are also included in the current invention.

Numerous additional aspects and advantages of the present invention will become apparent upon consideration of the figures and detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a preferred subset (highlighted) of amino acid residue positions for modification as conjugation site(s) from the superset of solvent-exposed surface residues (see Table 2) in a human IgG1 Fc domain sequence (SEQ ID NO:600). Underlined residues are not present in crystal structure 1FC1, and many of these residues are good candidates for modification (e.g., insertion or substitution of amino acid residues) for creation of a conjugation site in accordance with the present invention, particularly the following amino acid residues from the aminoterminal fragment (first eighteen amino acid residues): DKTHTC…C..A..E…GG, i.e., through a side chain in the subsequence at positions 1 through 6 of SEQ ID NO:600, at position 9 of SEQ ID NO:600, at position 11 of SEQ ID NO:600, at position 13 of SEQ ID NO:600, at position 16 of SEQ ID NO:600, at position 17 of SEQ ID NO:600, and the following amino acids from the carboxy terminal fragment: .GK, i.e., a non-terminal site at position 226 of SEQ ID NO:600, or position 227 of SEQ ID NO:600.

Figure 2 shows (SEQ ID NO:599), the sequence of human IgG1 Fc monomer with predicted loop region sequences in boldface; the N-terminal methionine is added for expression from E. coli and is not otherwise present in the native IgG1 sequence (reference sequence SEQ ID NO:600). Amino acid residues useful as preferred sites for insertion or substitution of amino acid residues for creation of a conjugation site in accordance with the present invention are underlined.

Figure 3 shows (SEQ ID NO:599), the sequence of human IgG1 Fc monomer with predicted loop region sequences in boldface. Amino acid residue positions useful as conjugation sites in accordance with the present invention also include the underlined. Preferred surface exposed conjugation sites selected from Figure 1 are indicated by highlighting here.

Figure 4 shows proposed cysteine mutation sites mapped to Fc structure. The amino acid residues identified by arrows are designated positions relative to reference sequence SEQ ID NO:599, as follows:

A: Ser 196, which is the most solvent-exposed and is in a rigid helix.

B: Gln 143, which is a deep polar pocket and is from the same strand as Cys 148.

C: Leu 139, which is an Fc-loop region, and is near the C-terminus in a polar pocket.

D: Ser 145, which is from the same strand as cys 148 and is in a polar pocket on a β-sheet surface in a cleft between subunits.

Figure 5 shows SDS-PAGE gel analysis (4-20% Tris:Glycine polyacrylamide gel for 1.5 hours at 125V, 35 mA, 0.1% SDS) of purified huFc-cysteine analogs described in Example 2. Lanes: 1,8 contained MW markers, lanes 2, 9 contained clone 13300 Fc(Q143C), lanes 3, 10 contained clone 13322 Fc(L139C), lanes 4, 11 contained clone 13323 Fc(S145C) and lanes 5, 12 contained clone 13324 Fc(S196C). Lanes 2-6 were reduced and lanes 9-12 were non-reduced.

Figure 6 shows purity by SEC-HPLC analyses of clone 13324 huFc(S196C) as described in Example 2. Samples (20 μg) were eluted in 100 mM sodium phosphate, 150 mM NaCl, pH 6.9 on a TSK G3000SWxl column, 7.8 mm ID x 30 cm, 5 μm bead size) at 0.5 ml/min.

Figure 7 shows purity and mass determination by LC-MS of clone 13324 huFc(S196C) as described in Example 2. Samples (20 μg) were eluted in 0.1% TFA with a linear 0-90% acetonitrile gradient from a Zorbax 300SB-C18 column, 2.1 mm x 150 cm.

Figure 8A shows non-reduced SDS-PAGE analysis of huFc (S196C) analog PEGylated after varying degrees of TCEP reduction, as described in Example 3. Molar stoichiometries of engineered Cysteine: TCEP were: 1:0 in lane 1, 1:0.5 in lane 3, 1:0.75 in lane 4, 1:1 in lane 5, 1:1.25 in lane 6, 1:1.5 in lane 7, 1:2 in lane 8 and 1:5 in lane 9. MW markers were in lane 2. 2 μg of non-reduced protein were loaded to each lane and run in 4-20% Tris-Glycine polyacrylamide gel with 0.1% SDS at 125 V, 35 mA and 5 W, for 1.5 hours.

Figure 8B shows reduced SDS-PAGE analysis of huFc (S196C) analog PEGylated after varying degrees of TCEP reduction, as described in Example 3. Molar stoichiometries of engineered Cysteine: TCEP were: 1:0 in lane 2, 1:0.5 in lane 3, 1:0.75 in lane 4, 1:1 in lane 5, 1:1.25 in lane 6, 1:1.5 in lane 7, 1:2 in lane 8 and 1:5 in lane 9. MW markers were in lane 1. 2 μg of reduced protein were loaded to each lane and run in 4-20% Tris-Glycine polyacrylamide gel with 0.1% SDS at 125 V, 35 mA and 5 W, for 1.5 hours.

Figure 9 shows SEC-HPLC analyses of of huFc (S196C) analog PEGylated after varying degrees of TCEP reduction, as described in Example 3. 20 μg protein were loaded to TSK 3000SWxl column (7.8 mm x 30 cm, 5 micron) and eluted in 100 mM sodium phosphate, 150 mM NaCl, pH 6.9.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS OF THE INVENTION

Definition of Terms

The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances. As used in the specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences".

When used in connection with an amino acid sequence, the term "comprising" means that a compound may include additional amino acid residues on either or both of the N- or C- termini of the given sequence.

A conjugation site being “amenable to conjugation” means that the side chain of the amino acid residue at the selected conjugation site will react with the additional functional moiety of interest (or with a linker covalently attached to the additional functional moiety), under the defined chemical conditions, resulting in covalent binding of the additional functional moiety (directly or via the linker) to the side chain as a major reaction product.

"Antibody" or "antibody peptide(s)" refer to an intact antibody, or a binding fragment thereof that competes with the intact antibody for specific binding and includes chimeric, humanized, fully human, and bispecific antibodies. In certain embodiments, binding fragments are produced by recombinant DNA techniques. In additional embodiments, binding fragments are produced by enzymatic or chemical cleavage of intact antibodies. Binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, and single-chain antibodies.

The inventive composition comprises a Fc domain having at least one additional functional moiety covalently bound to the Fc domain. The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined herein below. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means. In one embodiment, the Fc domain is a human native Fc domain. In other embodiments, the "Fc domain" can be a Fc variant, an analog, a mutant, a truncation, or a derivative of human Fc or of an alternative mammalian Fc polypeptide.

The term "native Fc" refers to a molecule or sequence comprising the amino acid sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form, at which a peptide may be added or conjugated by being covalently bound, directly or indirectly through a linker, to a loop region of the Fc domain. The original immunoglobulin source of the native Fc is preferably of human origin (although non-human mammalian native Fc is included in "native Fc" and can also be useful in some embodiments), and may be any of the immunoglobulins, although IgG1 and IgG2 are preferred. The native Fc may optionally comprise an amino terminal methionine residue. By way of example, SEQ ID NO:600 is the native human IgG1 sequence (used, in some cases, as a reference sequence herein), and Fc variant SEQ ID NO:599 (also used in some cases as a reference sequence herein) is the same sequence with an amino terminal methionine residue. Native Fcs are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (e.g., IgG, IgA, IgE) or subclass (e.g., IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison et al. (1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

Statements or claims concerning amino acid residue positions cited herein relative to one particular "reference sequence" (i.e., SEQ ID NO:600 or SEQ ID NO:599) apply equally to the corresponding position in the other reference sequence, or in a different native Fc sequence, Fc variant sequence, or other modified Fc domain sequence, in an alignment of the two (i.e., comparing the recited reference sequence and the second Fc domain sequence of interest), e.g., position 2 in SEQ ID NO:599 corresponds to position 1 in SEQ ID NO:600, etc.

The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage receptor, FcRn. International applications WO 97/34631 (published 25 September 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

The term "internal" conjugation site means that conjugation of the at least one additional moiety, or moieties, is non-terminal, i.e., not through the α-amino site or the α-carboxy site of the Fc domain, although there optionally can also be additional moieties conjugated terminally at the N-terminal and/or C-terminal of the Fc domain.

The term "loop" region or "Fc-loop" region refers to a primary sequence of amino acid residues which connects two regions comprising secondary structure, such as an α-helix or a β-sheet, in the immediate N-terminal and C-terminal directions of primary structure from the loop region. Examples include, but are not limited to, CH2 or CH3 loop regions. One of skill in the art understands that a loop region, while not itself comprising secondary structure, may influence or contribute to secondary or higher order protein structure.

The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more Fc domain polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers, trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently. Exemplary dimers within the scope of this invention are as shown in U.S. Pat. No. 6,660,843, Figure 2, which is hereby incorporated by reference. "Dimers" include homodimers and heterodimers.

The terms "derivatizing" and "derivative" or "derivatized" comprise processes and resulting compounds respectively in which (1) the compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or in vivo; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-terminus is replaced by $-NRR^1$, $NRC(O)R^1$, $-NRC(O)OR^1$, $-NRS(O)_2R^1$, -NHC(O)NHR, a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and R^1 and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by $-C(O)R^2$ or $-NR^3R^4$ wherein R^2, R^3 and R^4 are as defined hereinafter; and (6) compounds in which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

The term "half-life extending moiety refers to a pharmaceutically acceptable moiety, domain, or "vehicle" covalently linked or conjugated to the Fc domain and/or a pharmaceutically active moiety, that prevents or mitigates in vivo proteolytic degradation or other activity-diminishing chemical modification of the pharmaceutically active moiety, increases half-life or other pharmacokinetic properties such as but not limited to increasing the rate of absorption, reduces toxicity, improves solubility, increases biological activity and/or target selectivity of the pharmaceutically active moiety with respect to a target of interest, increases manufacturability, and/or reduces immunogenicity of the pharmaceutically active moiety (e.g., a peptide or non-peptide moiety), compared to an unconjugated form of the pharamaceutically active moiety. Polyethylene glycol (PEG) is an example of a useful half-life extending moiety. Other examples of the half-life extending moiety, in accordance with the invention, include a copolymer of ethylene glycol, a copolymer of propylene glycol, a carboxymethylcellulose, a polyvinyl pyrrolidone, a poly-1,3-dioxolane, a poly-1,3,6-trioxane, an ethylene/maleic anhydride copolymer, a polyaminoacid (e.g., polylysine), a dextran n-vinyl pyrrolidone, a poly n-vinyl pyrrolidone, a propylene glycol homopolymer, a propylene oxide polymer, an ethylene oxide polymer, a polyoxyethylated polyol, a polyvinyl alcohol, a linear or branched glycosylated chain, a polyacetal, a long chain fatty acid, a long chain hydrophobic aliphatic group, an immunoglobulin F_c domain (see, e.g., Feige et al., Modified peptides as therapeutic agents, US Patent No. 6,660,843), an albumin (e.g., human serum albumin; see, e.g., Rosen et al., Albumin fusion proteins, US Patent No. 6,926,898 and US 2005/0054051; Bridon et al., Protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components, US 6,887,470), a transthyretin (TTR; see, e.g., Walker et al., Use of transthyretin peptide/protein fusions to increase the serum half-life of pharmacologically active peptides/proteins, US 2003/0195154 A1; 2003/0191056 A1), or a thyroxine-binding globulin (TBG).

Other embodiments of the useful half-life extending moiety, in accordance with the invention, include peptide ligands or small (non-peptide organic) molecule ligands that have binding affinity for a long half-life serum protein under physiological conditions of temperature, pH, and ionic strength. Examples include an albumin-binding peptide or small molecule ligand, a transthyretin-binding peptide or small molecule ligand, a thyroxine-binding globulin-binding peptide or small molecule ligand, an antibody-binding peptide or small molecule ligand, or another peptide or small molecule that has an affinity for a long half-life serum protein. (See, e.g., Blaney et al., Method and compositions for increasing the serum half-life of pharmacologically active agents by binding to transthyretin-selective ligands, US Patent. No. 5,714,142; Sato et al., Serum albumin binding moieties, US 2003/0069395 A1; Jones et al., Pharmaceutical active conjugates, US Patent No. 6,342,225). A "long half-life serum protein" is one of the hundreds of different proteins dissolved in mammalian blood plasma, including so-called "carrier proteins" (such as albumin, transferrin and haptoglobin), fibrinogen and other blood coagulation factors, complement components, immunoglobulins, enzyme inhibitors, precursors of substances such as angiotensin and bradykinin and many other types of proteins. The invention encompasses the use of any single species of pharmaceutically acceptable half-life extending moiety, such as, but not limited to, those described herein, or the use of a combination of two or more different half-life extending moieties.

The term "polypeptide" refers to molecules of greater than 40 amino acids, whether existing in nature or not, provided that such molecules are not membrane-bound. Exemplary polypeptides include interleukin (IL)-1ra, leptin, soluble tumor necrosis factor (TNF) receptors type 1 and type 2 (sTNF-R1, sTNF-R2), keratinocyte growth factor (KGF), erythropoietin (EPO), thrombopoietin (TPO), granulocyte colony-stimulating factor (G-CSF), darbepoietin, glial cell line-derived neurotrophic factor (GDNF), Fab fragments and the like. "Polypeptide" and "protein" are used interchangeably herein.

The term "peptide" refers to molecules of 2 to 40 amino acid residues in length, with molecules of 3 to 40 amino acid residues or 6 to 40 amino acid residues in length preferred. Exemplary peptides may be randomly generated by any of the methods cited above, carried in a peptide library (e.g., a phage display library), or derived by digestion of proteins. "Peptides" include cyclic peptides.

In further describing peptides or polypeptides herein, a one-letter abbreviation system is frequently applied to designate the identities of the twenty "canonical" amino acid residues generally incorporated into naturally occurring peptides and proteins (Table 1A). Such one-letter abbreviations are entirely interchangeable in meaning with three-letter abbreviations, or non-abbreviated amino acid names. Within the one-letter abbreviation system used herein, an uppercase letter indicates a L-amino acid, and a lower case letter indicates a D-amino acid, unless otherwise noted herein. For example, the abbreviation "R" designates L-arginine and the abbreviation "r" designates D-arginine.

Table 1A. One-letter abbreviations for the canonical amino acids. Three-letter abbreviations are in parentheses.

Alanine (Ala)	A
Glutamine (Gln)	Q
Leucine (Leu)	L
Serine (Ser)	S
Arginine (Arg)	R
Glutamic Acid (Glu)	E
Lysine (Lys)	K
Threonine (Thr)	T
Asparagine (Asn)	N
Glycine (Gly)	G
Methionine (Met)	M
Tryptophan (Trp)	W
Aspartic Acid (Asp)	D
Histidine (His)	H
Phenylalanine (Phe)	F
Tyrosine (Tyr)	Y
Cysteine (Cys)	C

Isoleucine (Ile)	I
Proline (Pro)	P
Valine (Val)	V

An amino acid substitution in an amino acid sequence is typically designated herein with a one-letter abbreviation for the amino acid residue in a particular position, followed by the numerical amino acid position relative to the native peptide or polypeptide sequence of interest, which is then followed by the one-letter symbol for the amino acid residue substituted in. For example, "T30D" symbolizes a substitution of a threonine residue by an aspartate residue at amino acid position 30, relative to a hypothetical native peptide or polypeptide sequence. By way of further example, "R18hR" or "R18Cit" indicates a substitution of an arginine residue by a homoarginine or a citrulline residue, respectively, at amino acid position 18, relative to the hypothetical native peptide or polypeptide. An amino acid position within the amino acid sequence of any particular poly peptide or peptide (or peptide analog) described herein may differ from its position relative to the native sequence, i.e., as determined in an alignment of the N-terminal or C-terminal end of the peptide's amino acid sequence with the N-terminal or C-terminal end, as appropriate, of the native polypeptide or peptide sequence.

The term "non-canonical amino acid residue" refers to amino acid residues in D- or L-form that are not among the 20 canonical amino acids generally incorporated into naturally occurring proteins. Non-canonical amino acids include naturally rare (in peptides or proteins) amino acid residues or unnatural amino acid residues. Example of non-canonical amino acids include, without limitation, β-amino acids, homoamino acids, cyclic amino acids, α-, α-disubstituted amino acids, N-alkyl amino acids, and amino acids with derivatized side chains. Other examples include (in the L-form or D-form): citrulline (Cit), homocitrulline (hCit), *N*-methylcitrulline (NMeCit), *N*-methylhomocitrulline (NMeHoCit), ornithine (Orn or O), *N*-Methylornithine (NMeOrn), sarcosine (Sar), homolysine (hK or Hlys), homoarginine (hR or hArg), homoglutamine (hQ), *N*-methylarginine

(NMeR), *N*-methylleucine (NMeL), *N*-methylhomolysine (NMeHoK), *N*-methylglutamine (NMeQ), norleucine (Nle), norvaline (Nva), 1,2,3,4-tetrahydroisoquinoline (Tic), nitrophenylalanine (nitrophe), aminophenylalanine (aminophe), benzylphenyalanine (benzylphe), γ-carboxyglutamic acid (γ-carboxyglu), hydroxyproline (hydroxypro), *p*-carboxyl-phenylalanine (Cpa), α-aminoadipic acid (Aad), acetylarginine (acetylarg), α, β-diaminopropionoic acid (Dpr), α, γ-diaminobutyric acid (Dab), diaminopropionic acid (Dap), β-(1-Naphthyl)-alanine (1Na1), β-(2-Naphthyl)-alanine (2Na1), cyclohexylalanine (Cha), 4-methyl-phenylalanine (MePhe), β, β-diphenyl-alanine (BiPhA), aminobutyric acid (Abu), 4-phenyl-phenylalanine (4Bip), α-amino-isobutyric acid (Aib), beta-alanine, beta-aminopropionic acid, piperidinic acid, aminocaprioic acid, aminoheptanoic acid, aminopimelic acid, desmosine, diaminopimelic acid, N-ethylglycine, N-ethylaspargine, hyroxylysine, allo-hydroxylysine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, ω-methylarginine, and other similar amino acids, and derivatized forms of any of these as described herein.

Nomenclature and Symbolism for Amino Acids and Peptides by the UPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) have been published in the following documents: Biochem. J., 1984, 219, 345-373; Eur. J. Biochem., 1984, 138, 9-37; 1985, 152, 1; 1993, 213, 2; Internat. J. Pept. Prot. Res., 1984, 24, following p 84; J. Biol. Chem., 1985, 260,14-42; Pure Appl. Chem., 1984, 56, 595-624; Amino Acids and Peptides, 1985, 16, 387-410; Biochemical Nomenclature and Related Documents, 2nd edition, Portland Press, 1992, pages 39-69.The term “protease” is synonymous with “peptidase”. Proteases comprise two groups of enzymes: the endopeptidases which cleave peptide bonds at points within the protein, and the exopeptidases, which remove one or more amino acids from either N- or C-terminus respectively. The term “proteinase” is also used as a synonym for endopeptidase. The four mechanistic classes of proteinases are: serine proteinases, cysteine proteinases, aspartic proteinases, and metallo-proteinases. In addition to these four mechanistic classes, there is a section of the enzyme nomenclature which is allocated for proteases of unidentified catalytic mechanism. This indicates that the catalytic mechanism has not been identified.

Cleavage subsite nomenclature is commonly adopted from a scheme created by Schechter and Berger (Schechter I. & Berger A., On the size of the active site in proteases. I. Papain, Biochemical and Biophysical Research Communication, 27:157 (1967); Schechter I. & Berger A., On the active site of proteases. 3. Mapping the active site of papain; specific inhibitor peptides of papain, Biochemical and Biophysical Research Communication, 32:898 (1968)). According to this model, amino acid residues in a substrate undergoing cleavage are designated P1,P2, P3, P4 etc. in the N-terminal direction from the cleaved bond. Likewise, the residues in the C-terminal direction are designated P1', P2', P3', P4'. etc.

The skilled artisan is aware of a variety of tools for identifying protease binding or protease cleavage sites of interest. For example, the PeptideCutter software tool is available through the ExPASy (Expert Protein Analysis System) proteomics server of the Swiss Institute of Bioinformatics (SIB; www.expasy.org/tools/peptidecutter). PeptideCutter searches a protein sequence from the SWISS-PROT and/or TrEMBL databases or a user-entered protein sequence for protease cleavage sites. Single proteases and chemicals, a selection or the whole list of proteases and chemicals can be used. Different forms of output of the results are available: tables of cleavage sites either grouped alphabetically according to enzyme names or sequentially according to the amino acid number. A third option for output is a map of cleavage sites. The sequence and the cleavage sites mapped onto it are grouped in blocks, the size of which can be chosen by the user. Other tools are also known for determining protease cleavage sites. (E.g., Turk, B. et al., Determination of protease cleavage site motifs using mixture-based oriented peptide libraries, Nature Biotechnology, 19:661-667 (2001); Barrett A. et al., Handbook of proteolytic enzymes, Academic Press (1998)).

The serine proteinases include the chymotrypsin family, which includes mammalian protease enzymes such as chymotrypsin, trypsin or elastase or kallikrein. The serine proteinases exhibit different substrate specificities, which are related to amino acid substitutions in the various enzyme subsites interacting with the substrate residues. Some enzymes have an extended interaction site with the substrate whereas others have a specificity restricted to the P1 substrate residue.

Trypsin preferentially cleaves at R or K in position P1. A statistical study carried out by Keil (1992) described the negative influences of residues surrounding the Arg- and Lys- bonds (i.e. the positions P2 and P1', respectively) during trypsin cleavage. (Keil, B., Specificity of proteolysis, Springer-Verlag Berlin-Heidelberg-NewYork, 335 (1992)). A proline residue in position P1' normally exerts a strong negative influence on trypsin cleavage. Similarly, the positioning of R and K in P1' results in an inhibition, as well as negatively charged residues in positions P2 and P1'.

Chymotrypsin preferentially cleaves at a W, Y or F in position P1 (high specificity) and to a lesser extent at L, M or H residue in position P1. (Keil, 1992). Exceptions to these rules are the following: When W is found in position P1, the cleavage is blocked when M or P are found in position P1' at the same time. Furthermore, a proline residue in position P1' nearly fully blocks the cleavage independent of the amino acids found in position P1. When an M residue is found in position P1, the cleavage is blocked by the presence of a Y residue in position P1'. Finally, when H is located in position P1, the presence of a D, M or W residue also blocks the cleavage.

Membrane metallo-endopeptidase (NEP; neutral endopeptidase, kidney-brush-border neutral proteinase, enkephalinase, EC 3.4.24.11) cleaves peptides at the amino side of hydrophobic amino acid residues. (Connelly, JC et al., Neutral Endopeptidase 24.11 in Human Neutrophils: Cleavage of Chemotactic Peptide, PNAS, 82(24):8737-8741 (1985)).

Thrombin preferentially cleaves at an R residue in position P1. (Keil, 1992). The natural substrate of thrombin is fibrinogen. Optimum cleavage sites are when an R residue is in position P1 and Gly is in position P2 and position P1'. Likewise, when hydrophobic amino acid residues are found in position P4 and position P3, a proline residue in position P2, an R residue in position P1, and non-acidic amino acid residues in position P1' and position P2'. A very important residue for its natural substrate fibrinogen is a D residue in P10.

Caspases are a family of cysteine proteases bearing an active site with a conserved amino acid sequence and which cleave peptides specifically following D residues. (Earnshaw WC et al., Mammalian caspases: Structure, activation, substrates, and functions during apoptosis, Annual Review of Biochemistry, 68:383-424 (1999)).

The Arg-C proteinase preferentially cleaves at an R residue in position P1. The cleavage behavior seems to be only moderately affected by residues in position P1'. (Keil, 1992). The Asp-N endopeptidase cleaves specifically bonds with a D residue in position P1'. (Keil, 1992).

The foregoing is merely exemplary and by no means an exhaustive treatment of knowledge available to the skilled artisan concerning protease binding and/or cleavage sites that the skilled artisan may be interested in eliminating in practicing the invention.

The term "randomized" as used to refer to peptide sequences refers to random sequences (e.g., selected by phage display methods) and sequences in which one or more residues of a naturally occurring molecule is replaced by an amino acid residue not appearing in that position in the naturally occurring molecule. Exemplary methods for identifying peptide sequences include phage display, E. coli display, ribosome display, yeast-based screening, RNA-peptide screening, chemical screening, rational design, protein structural analysis, and the like.

A peptidomimetic can include a small peptide-like chain that contains one or more amide bond isosteres and can contain both natural and unnatural amino acids. Such peptide-like peptidomimetics typically arise from modification of an existing polypeptide or peptide in order to alter the molecule's properties. For example, they may arise from modifications to change the molecule's stability or biological activity. These modifications involve changes to the peptide that will not occur naturally (such as incorporation of unnatural amino acids). Alternatively, peptidomimetics include non-peptide small molecules having peptide-like biochemical or pharmacological activity and/or chemical structure, such as, but not limited to, steric structure. An example of such a peptidomimetic compound is BIBN 4096 BS.

The term "pharmacologically active" means that a substance so described is determined to have activity that affects a medical parameter (e.g., blood pressure, blood cell count, cholesterol level) or disease state (e.g., cancer, autoimmune disorders, neurological disorders, chronic pain). Thus, pharmacologically active peptides or polypeptides comprise agonistic or mimetic and antagonistic peptides as defined below.

The terms "-mimetic peptide" and "-agonist peptide" refer, respectively, to a peptide or polypeptide having biological activity comparable to a protein (e.g., EPO, TPO, G-CSF) of interest or to a peptide or polypeptide that interacts as an agonist with a particular protein of interest. These terms further include peptides or polypeptides that indirectly mimic the activity of a protein of interest, such as by potentiating the effects of the natural ligand of the protein of interest; see, for example, the EPO-mimetic peptides listed in Table 5 hereof and in U.S. Pat. No. 6,660,843, which is hereby incorporated by reference. Thus, the term "EPO-mimetic peptide" comprises any peptides or polypeptides that can be identified or derived as described in Wrighton et al. (1996), Science 273: 458-63, Naranda et al. (1999), Proc. Natl. Acad. Sci. USA 96: 7569-74, or any other reference in Table 5 identified as having EPO-mimetic subject matter. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides or polypeptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "-antagonist peptide" or "inhibitor peptide" refers to a peptide that blocks or in some way interferes with the biological activity of the associated protein of interest, or has biological activity comparable to a known antagonist or inhibitor of the associated protein of interest. Thus, the term "BAFF-antagonist peptide" comprises peptides that can be identified or derived as described in U.S. Pat. Appln. No. 2003/0195156 A1, which is incorporated herein by reference and those peptides appearing in Table 10. Those of ordinary skill in the art appreciate that the foregoing reference enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

In the inventive composition of composition matter, the monomeric or multimeric Fc domain has at least one additional functional moiety that is covalently bound (or conjugated) to one or more "specifically selected" conjugation site(s) in the Fc domain. The term "specifically selected" with respect to conjugation site means that the major product or derivative of the conjugation chemistry (or chemical reaction) employed is through the side chain of an amino acid residue at the specifically selected conjugation site in the Fc domain. Minor reaction products can also result from the conjugation reaction, but these can be purified out, if desired or appropriate. "Toxin peptides" include peptides and polypeptides having the same amino acid sequence of a naturally occurring pharmacologically active peptide or polypeptide that can be isolated from a venom, and also include modified peptide analogs of such naturally occurring molecules. (See, e.g., Kalman et al., ShK-Dap22, a potent Kv1.3-specific immunosuppressive polypeptide, J. Biol. Chem. 273(49):32697-707 (1998); Kem et al., US Patent No. 6,077,680; Mouhat et al., OsK1 derivatives, WO 2006/002850 A2; Chandy et al., Analogs of SHK toxin and their uses in selective inhibition of Kv1.3 potassium channels, WO 2006/042151). Snakes, scorpions, spiders, bees, snails and sea anemone are a few examples of organisms that produce venom that can serve as a rich source of small bioactive toxin peptides or "toxins" that potently and selectively target ion channels and receptors.

The toxin peptides are usually between about 20 and about 80 amino acids in length, contain 2-5 disulfide linkages and form a very compact structure. Toxin peptides (e.g., from the venom of scorpions, sea anemones and cone snails) have been isolated and characterized for their impact on ion channels. Such peptides appear to have evolved from a relatively small number of structural frameworks that are particularly well suited to addressing the critical issues of potency and stability. The majority of scorpion and Conus toxin peptides, for example, contain 10-40 amino acids and up to five disulfide bonds, forming extremely compact and constrained structure (microproteins) often resistant to proteolysis. The conotoxin and scorpion toxin peptides can be divided into a number of superfamilies based on their disulfide connections and peptide folds. The solution structure of many of these has been determined by NMR spectroscopy, illustrating their compact structure and verifying conservation of their family fold. (E.g., Tudor et al., Ionisation behaviour and solution properties of the potassium-channel blocker ShK toxin, Eur. J. Biochem. 251(1-2):133-41(1998); Pennington et al., Role of disulfide bonds in the structure and potassium channel blocking activity of ShK toxin, Biochem. 38(44): 14549-58 (1999); Jaravine et al., Three-dimensional structure of toxin OSK1 from Orthochirus scrobiculosus scorpion venom, Biochem. 36(6):1223-32 (1997); del Rio-Portillo et al.; NMR solution structure of Cn12, a novel peptide from the Mexican scorpion Centruroides noxius with a typical beta-toxin sequence but with alpha-like physiological activity, Eur. J. Biochem. 271(12): 2504-16 (2004); Prochnicka-Chalufour et al., Solution structure of discrepin, a new K+-channel blocking peptide from the alpha-KTx15 subfamily, Biochem. 45(6):1795-1804 (2006)). Examples of pharmacologically active toxin peptides for which the practice of the present invention can be useful include, but are not limited to ShK, OSK1, charybdotoxin (ChTx), kaliotoxin1 KTX1), or maurotoxin, or toxin peptide analogs of any of these, modified from the native sequences at one or more amino acid residues. Other examples are known in the art, or can be found in U.S. Patent Application No. 11/406,454 (titled: Toxin Peptide Therapeutic Agents), filed on April 17, 2006, which is incorporated by reference in its entirety.

The term “TPO-mimetic peptide” comprises peptides that can be identified or derived as described in Cwirla et al. (1997), Science 276: 1696-9 , U.S. Pat. Nos. 5,869,451 and 5,932,946, which are incorporated by reference; U.S. Pat. App. No. 2003/0176352, published Sept. 18, 2003, which is incorporated by reference; WO 03/031589, published April 17, 2003; WO 00/24770, published May 4, 2000; and any peptides appearing in Table 6. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "ang-2-binding peptide" comprises peptides that can be identified or derived as described in U.S. Pat. App. No. 2003/0229023, published Dec. 11, 2003; WO 03/057134, published 7/17/03; U.S. 2003/0236193, published Dec. 25, 2003 (each of which is incorporated herein by reference); and any peptides appearing in Table 7. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "NGF-binding peptide" comprises peptides that can be identified or derived as described in WO 04/026329, published April 1, 2004 and any peptides identified in Table 8. Those of ordinary skill in the art appreciate that this reference enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

The term "myostatin-binding peptide" comprises peptides that can be identified or derived as described in U.S. Ser. No. 10/742,379, filed December 19, 2003, which is incorporated herein by reference, and peptides appearing in Table 9. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed therein by following the disclosed procedures with different peptide libraries.

"PEGylated peptide" is meant a peptide or protein having a polyethylene glycol (PEG) moiety covalently bound to an amino acid residue of the peptide itself or to a peptidyl or non-peptidyl linker (including but not limited to aromatic linkers) that is covalently bound to a residue of the peptide.

By "polyethylene glycol" or "PEG" is meant a polyalkylene glycol compound or a derivative thereof, with or without coupling agents or derivatization with coupling or activating moieties (e.g., with aldehyde, hydroxysuccinimidyl, hydrazide, thiol, triflate, tresylate, azirdine, oxirane, orthopyridyl disulphide, vinylsulfone, iodoacetamide or a maleimide moiety). In accordance with the present invention, useful PEG includes substantially linear, straight chain PEG, branched PEG, or dendritic PEG. (See, e.g., Merrill, US Patent No. 5,171,264; Harris et al., Multiarmed, monofunctional, polymer for coupling to molecules and surfaces, US Patent No. 5,932,462; Shen, N-maleimidyl polymer derivatives, US Patent No. 6,602,498).

Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. By "physiologically acceptable salts" is meant any salts that are known or later discovered to be pharmaceutically acceptable. Some examples are: acetate; trifluoroacetate; hydrohalides, such as hydrochloride and hydrobromide; sulfate; citrate; maleate; tartrate; glycolate; gluconate; succinate; mesylate; besylate; and oxalate salts.

General Methodology

The present invention relates to a process for preparing a pharmacologically active compound involving selecting at least one internal conjugation site of an Fc domain sequence. The conjugation site must be amenable to conjugation of an additional functional moiety by a defined conjugation chemistry through the side chain of an amino acid residue at the conjugation site. Achieving highly selective, site-specific conjugation to Fc, in accordance with the present invention, requires consideration of a diverse variety of design criteria. First, the conjugation partner, i.e., the additional functional moiety (or moieties) of interest, and a preferred conjugation or coupling chemistry must be defined or predetermined. fFunctional moieties such as, but not limited to, proteins, peptides, polymers or other non-peptide organic moieties (e.g., "small molecules"), can be conjugated or coupled to the selected conjugation site through an assortment of different conjugation chemistries known in the art. For example, a maleimide-activated conjugation partner targeting an accessible cysteine thiol on the Fc domain is one embodiment, but numerous conjugation or coupling chemistries targeting the side chains of either canonical or non-canonical , e.g., unnatural amino acids in the Fc domain sequence, can be employed in accordance with the present invention.

Chemistries for the chemoselective conjugation, in accordance with the present invention, to specifically derivatized peptides, polymers, small molecules, or other agents to engineer proteins displaying novel and specifically reactive side chain functionality include: copper(I)-catalyzed azide–alkyne [3+2] dipolar cycloadditions, Staudinger ligation, other acyl transfers processes (S→N; X→N), oximations, hydrazone bonding formation and other suitable organic chemistry reactions such as cross-couplings using water-soluble palladium catalysts. (E.g., Bong et al., Chemoselective Pd(0)-catalyzed peptide coupling in water, Organic Letters 3(16):2509-11 (2001); Dibowski et al., Bioconjugation of peptides by palladium-catalyzed C-C cross-coupling in water, Angew. Chem. Int. Ed. 37(4):476-78 (1998); DeVasher et al., Aqueous-phase, palladium-catalyzed cross-coupling of aryl bromides under mild conditions, using water-soluble, sterically demanding alkylphosphines, J. Org. Chem. 69:7919-27 (2004); Shaugnessy et al., J.Org. Chem, 2003, 68, 6767-6774; Prescher, JA and Bertozzi CR, Chemistry in living system, Nature Chemical Biology 1(1); 13-21 (2005)). Some useful conjugation chemistries are illustrated in Table 1B below.

Table 1B. Some useful conjugation chemistries. Citations: 17 = Link et al., Presentation and detection of azide functionality in bacterial cell surface proteins, J. Am. Chem. Soc. 126:10598-602 (2004); 19 = Chen et al., Site-specific labeling of cell surface proteins with biophysical probes using biotin ligase, Nat. Methods 2:99-104 (2005); 20 = Zhang et al., A new strategy for the site-specific modification of proteins in vivo, Biochemistry 42:6735-46 (2003); 22 = Mahal et al., Engineering chemical reactivity on cell surfaces through oligosaccharide biosynthesis, Science 276:1125-28 (1997); 25 = Kho et al., A tagging-via-substrate technology for detection and proteomics of farnesylated proteins, Proc. Natl. Acad. Sci. USA 101:12479-484 (2004); 26 = Speers et al., Activity-based protein profiling in vivo using a copper(I)-catalyzed azide-alkyne [3 + 2] cycloaddition, J. Am. Chem Soc. 125:4686-87 (2003); 29 = Speers et al., Profiling enzyme activities in vivo using click chemistry, methods, Chem. Biol. 11:535-46 (2004); 30 = Prescher et al., Chemical remodeling of cell surfaces in living animals, Nature 430:873-77 (2004); 34 = Agard et al., A strain-promoted [3 + 2] azide-alkyne cycloaddition for covalent modification of biomolecules in living systems, J. Am. Chem. Soc. 126:15046-47 (2004).

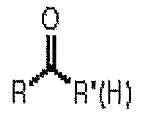
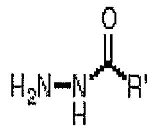
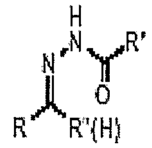
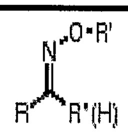
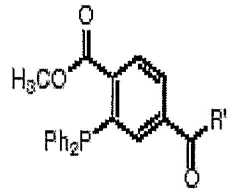
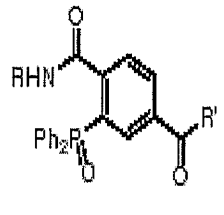
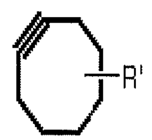
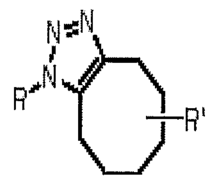
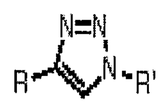
 Ketone/aldehyde			Protein[19,20] Glycan[22]
	H_2N-O-R'		
$R-N_3$ Azide	Staudinger ligation 		Protein[17,20] Glycan[30,31] Lipid[25]
	'Click' chemistry ≡—R', Cu(I), ligand		
	Strain-promoted cycloaddition 		
R—≡ Terminal alkyne	'Click' chemistry N_3-R', Cu(I), ligand		Protein[29]

Table 1B

As mentioned above, the conjugation (or covalent binding) to the Fc domain is through the side chain of an amino acid residue at the conjugation site, for example, but not limited to, a cysteinyl residue. The amino acid residue, for example, a cysteinyl residue, at the internal conjugation site that is selected can be one that occupies the same amino acid residue position in a native Fc domain sequence, or the amino acid residue can be engineered into the Fc domain sequence by substitution or insertion. Such amino acid residues can have either L or D stereochemistry (except for Gly, which is neither L nor D) and the polypeptides, peptides and compositions of the present invention can comprise a combination of stereochemistries. However, the L stereochemistry is preferred. The invention also provides reverse molecules wherein the amino terminal to carboxy terminal sequence of the amino acids is reversed. For example, the reverse of a molecule having the normal sequence X_1-X_2-X_3 would be X_3-X_2-X_1. The invention also provides retro-reverse molecules wherein, as above, the amino terminal to carboxy terminal sequence of amino acids is reversed and residues that are normally "L" enantiomers are altered to the "D" stereoisomer form.

Stereoisomers (e.g., D-amino acids) of the twenty canonical amino acids, and other non-canonical amino acids, described herein, such as unnatural amino acids, can also be suitable components for polypeptide or peptide portions of certain embodiments of the inventive composition of matter.

Other examples of unnatural amino acid residues that can be particularly useful as the conjugation site in some embodiments of the inventive processes and compositions of matter include: azido-containing amino acid residues, e.g., azidohomoalanine, p-azido-phenylalanine; keto-containing amino acid residues, e.g., *p*-acetyl-phenylalanine; alkyne- containing amino acid residues, e.g., p-ethynylphenylalanine, homopropargylglycine, p-(prop-2-ynyl)-tyrosine; alkene-containing amino acid residues e.g., homoallylglycine; aryl halide- containing amino acid residues e.g. p-iodophenylalanine, p-bromophenylalanine; and 1,2-aminothiol containing amino acid residues.

The non-canonical amino acid residues can be incorporated by amino acid substitution or insertion. Non-canonical amino acid residues can be incorporated into the peptide by chemical peptide synthesis rather than by synthesis in biological systems, such as recombinantly expressing cells, or alternatively the skilled artisan can employ known techniques of protein engineering that use recombinantly expressing cells. (See, e.g., Link et al., Non-canonical amino acids in protein engineering, Current Opinion in Biotechnology, 14(6):603-609 (2003); Schultz et al., In vivo incorporation of unnatural amino acids, U.S. Patent No. 7,045,337).

The selection of the placement of the conjugation site in the overall Fc sequence is another important facet of selecting an internal conjugation site in accordance with the present invention. Any of the exposed amino acid residues on the Fc surface, or either of the Fc CH2 or CH3 loop regions or subdomains can be potentially useful conjugation sites (Figure 1) and can be mutated to cysteine or some other reactive amino acid for site-selective coupling, if not already present at the selected conjugation site of the Fc domain sequence. However, this approach does not take into account potential steric constraints that may perturb the activity of the fusion partner or limit the reactivity of the engineered mutation. For example, a cysteine engineered to be fully solvent-exposed may become oxidized during purification, leaving little or no reactive thiol for conjugation. Furthermore, the mutation introduced for conjugation, be it cysteine or any other amino acid, should not destabilize the Fc structure or interfere with expression or recovery yields of the Fc analog. Finally, in the case of an intact Fc domain, selected conjugation sites should be allosteric to the Fc dimer interface, if present. Also, some therapeutic applications may further benefit by maintaining conjugation sites distal to the Fc receptor (FcRn) interface.

In this invention a detailed topographical survey of the immunoglobulin Fc surface structure is described, which identifies solvent exposed amino acids representing potentially suitable conjugation sites for chemically coupling proteins, peptides, polymers or other small molecules (Figure 1). In this analysis, not all the hydrophilic, solvent-exposed residues were deemed suitable for conjugation. In fact, only 36 residues of a possible 115 were selected based on their juxtaposition with the FcRn binding and dimer interfaces as well as other localized steric constraints. The list of potential conjugation sites was further refined using the available Fc domain crystal structures, their receptors and numerous Fc sequence alignments to map all of the putative Fc structural loop regions (Figure 2, boldface). Specific residues that are most suitable for substitution within these loop region were identified by homology modeling and solvent accessibility (Figure 2, underlined). Finally, each of these potential conjugation sites were ranked based on their juxtaposition relative to the FcRn and dimer interface, inter-species and isotype homologies and the sites' proximity and involvement in key elements of Fc secondary structure (Table 2). This approach using structure-based homology modeling to identify Fc loop regions and to predict insertion-tolerant mutation sites has been previously validated using therapeutic peptide insertions as described in Amgen patent application U.S. Prov. Appln. No. 60/612,680 filed September 24, 2004. (See, WO 2006/036834) Based on that work, the most preferred mutation sites are Thr140, Asn78 and Glu50 (Figure 2; amino acid residue positions cited relate to reference sequence SEQ ID NO:599).

To compare the preferred conjugation sites selected from the solvent exposed surface residues highlighted in Figure 1, with the boldfaced putative loop regions and the underlined preferred conjugation sites within those loops (Figure 2), the two sequences were aligned and mapped to the human IgG1 Fc domain as shown in Figure 3. Here emerges a very consistent agreement between the surface exposure model and the loop model for selecting potential conjugation sites. Clearly, these examples demonstrate that through a detailed structural analysis and comparison of immunoglobulin Fc domains it is possible to identify an experimentally manageable number of potential conjugation sites that are not readily obvious from simple hydrophobic maps of the sequence.

Another subset of preferred mutations for coupling specifically addresses the use of cysteine analogs wherein the free thiol functionality must be preserved for efficient conjugation. This strategy presumes that cysteine mutations should be engineered into comparatively rigid elements of secondary structure, as opposed to loop regions, and the cysteine thiol should be juxtaposed within a pocket on the protein surface, providing minimal solvent exposure, to help protect it from oxidation. This strategy has been effectively demonstrated in U.S. Pat. No. 6,420,339. Under this approach, the most preferred residues for cysteine mutation are, but not limited to, Ser196, Gln143, Leu139 and Ser145 of the human Fc sequence (Figure 4), with the positions recited being relative to reference sequence SEQ ID NO: 599.

The inventors further envision as part of this invention that none of these potential conjugation sites require a full-length immunoglobulin Fc domain to provide suitable substrates for coupling proteins, peptides, polymers, or other small molecules. In fact, any truncation of Fc that still includes a potential conjugation site recognized by this invention can be used for conjugation. For example, a CH2 subdomain or CH3 subdomain of an Fc greater than about 9 kD can be a useful "Fc domain" in accordance with the invention. Thus, this invention includes isolated Fc truncations, such as the CH2 or CH3 loop regions or subdomains. Further, given the highly conserved three-dimensional structure of the "immunoglobulin fold" equivalent conjugation sites can be readily deduced in other Ig Fc isotypes, truncations and subdomains, by sequence alignment and are therefore included in this invention.

Table 2 shows human Fc surface residues (using Protein Database file 1FC1 as the data source) (S239 from the PDB file corresponds to S19 of reference sequence SEQ ID NO:600 and S20 of reference sequence SEQ ID NO:599; K246 corresponds to K26 of SEQ ID NO:600 and K27 of SEQ ID NO:599, etc.).

Table 2. Human Fc surface residues, wherein 239S (i.e., S239) corresponds to S20 of reference sequence SEQ ID NO:599. * indicates likely FcRn interacting residues based on rat structures (not good candidates); # indicates dimer interaction domains (not good candidates); + indicates best candidates for modification.

239S	289T	333E	382E*	419Q+
246K	290K	334K	383S	420G+
248K*	292R	335T	384N	421N+
249D	293E	337S	385G*	424S
254S*	294Q	338K	386Q*	430E
255R*	295Q+	339A	388E	431A
256T*	296Y	340K+	389N+	433H*
258E	297N+	341G+	390N	434N*
260T	298S+	342Q+	391Y	435H*
265D+	299T	344R	392K+	436Y*
267S+	300Y	345E	393T	437T
268H+	307T*	347Q	394T#	438Q*
269E+	310H*	350T	399D#	439K
270D	311Q*	354S	400S+	440S
272Q+	312N	355R+	401N	442S+
274K+	315D	356E+	402G+	

276N	316G	359T+	403S	
278Y	317K	360K+	407Y#	
280D+	318E+	361N+	409K#	
281G+	320K	362Q+	411T	
283Q	322K	371G	413D+	
285H	324S	373Y	414K+	
286N	326K+	375S	415S+	
287A	327A	376D	416R+	
288K*	330A+	380E	418Q+	

Table 3 below shows prioritized sites for mutation or modification in the predicted loop regions of human IgG1 Fc domain. Amino acid residue positions are numbered here in relation to reference sequence SEQ ID NO: 599.

Table 3. Prioritized sites for mutation or modification in the predicted loop regions of human IgG1 Fc domain.

Domain	Loop	Insertion
CH2	D_{46}-E_{53}	H_{49}/E_{50} – 1st E_{50} / D_{51} – 2nd
CH2	E_{74}-T_{80}	Y_{77}/N_{78} – 1st N_{78}/S_{79} – 2nd
CH2-CH3 linker	N_{106}-P_{127}	K_{107}/A_{108} – 1st N_{106}/K_{107} – 2nd
CH3	D_{137}-K_{141}	L_{139}/T_{140} – 1st E_{138}/L_{139} – 2nd
CH3	N_{165}-N_{177}	E_{169}/N_{170} – 1st N_{170}/N_{171} – 2nd
CH3	T_{175}-S_{184}	S_{181}/D_{182} – 1st V_{178}/L_{179} – 2nd
CH3	K_{195}-V_{203}	G_{201}/N_{202} –1st N_{202}/V_{203} – 2nd

CH3	NA	Q_{167}/P_{168}
CH3	NA	G_{183}/S_{184}

In summary, this specification details a systematic approach to the identification of useful conjugation sites on the surface of immunoglobulin Fc and includes all the mutation sites described herein. The identification of specific conjugation sites derives from the application of structural and sequence data to a detailed set of structure/function criteria developed by these inventors.

Structure of inventive compounds

Fc Domains. This inventive composition requires the presence of at least one Fc domain monomer, but multimeric Fc embodiments (e.g., Fc domain dimers, trimers, tetramers, pentamers, etc.) are also preferred. Both native Fcs and Fc variants are suitable Fc domains for use within the scope of this invention, as are Fc domains comprised in antibodies. A native Fc may be extensively modified to form an Fc variant in accordance with this invention, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478. In some useful embodiments, one can remove one or more sites of a native Fc that provide structural features or functional activity not required by a molecule of this invention, such as a fusion molecule. One may remove these sites by, for example, substituting or deleting amino acid residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted residues may also be altered amino acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described below.

Exemplary Fc variants include molecules and sequences in which:

1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other amino acids (e.g., alanyl, seryl). For

example, one may truncate the N-terminal segment (truncations up to about the first 20-amino acid residues of reference sequence SEQ ID NO: 599 or SEQ ID NO:600) or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 599 (positions 6 and 9 of SEQ ID NO:600). Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.

2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in E. coli such as proline iminopeptidase. One may also add an N-terminal methionine residue, especially when the molecule is expressed recombinantly in a bacterial cell such as E. coli. The Fc domain of reference sequence SEQ ID NO: 599 (Figure 2) is one such Fc variant, in which a methionine has been added to the N-terminal of SEQ ID NO: 600.
3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any or all of the first 20 amino acid residues at the N-terminus, particularly those corresponding to positions 1, 2, 3, 4 and 5 of reference sequence SEQ ID NO: 600.
4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).
5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.
6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.

7. The ADCC site is removed. ADCC sites are known in the art; see, for example, Molec. Immunol. 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.
8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

Preferred Fc variants include the following. In reference sequence SEQ ID NO: 599 (Figure 2) the leucine at position 15 may be substituted with glutamate; the glutamate at position 99, with alanine; and the lysines at positions 101 and 103, with alanines. In addition, one or more tyrosine residues can be replaced by phenyalanine residues.

In some preferred embodiments, the Fc domain is an IgG1 Fc domain comprising an amino acid sequence SEQ ID NO: 603:

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
Ser Leu Ser Leu Ser Pro Gly Lys// (SEQ ID NO: 603); and

the one or more specifically selected conjugation site(s) is selected from an amino acid residue position contained in a loop region that comprises an amino acid sequence selected from the group consisting of
Pro Pro //SEQ ID NO: 601,
Asp Val Ser His Glu Asp Pro Glu//SEQ ID NO: 602,
Val His Asn Ala//SEQ ID NO: 604,
Glu Glu Gln Tyr Asn Ser Thr//SEQ ID NO: 605,
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu//SEQ ID NO: 606,
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro//SEQ ID NO: 607,
Asp Glu Leu Thr Lys//SEQ ID NO: 608,
Asn Gly Gln Pro Glu Asn Asn//SEQ ID NO: 609,
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser//SEQ ID NO: 610,
and
Lys Ser Arg Trp Gln Gln Gly Asn Val
//SEQ ID NO: 611.

In the compositions of matter prepared in accordance with this invention, at least one additional functional moiety is covalently bound to a monomeric or multimeric Fc domain through a specifically selected conjugation site involving an amino acid residue side chain selected as described herein. Optionally, other moieties, such as a polypeptide, peptide, peptidomimetic or non-peptide organic moiety can be attached to the Fc domain through the Fc domain's N-terminus (i.e., via the α-amino site) or C-terminus (i.e., via the α-carboxy site).

Certain embodiments of the molecules of this invention may be described by the following formula I:

(I)

$$\begin{array}{c}(X^1)_a\text{-}\,F^1\text{-}(X^2)_b\\ |\\ (X^3)_g\end{array}$$

wherein:

F^1 is a monomer of the monomeric or multimeric Fc domain;

X^1 is covalently bound to the N-terminus of F^1 through the α-amino site of F^1;

X^2 is covalently bound to the C-terminus of F^1 through the α-carboxy site of F^1;

X^3 is covalently bound to the one or more specifically selected conjugation site(s) in F^1 selected from the group consisting of underlined residue positions in Figure 1, boldface residue positions in Figure 2, highlighted residue positions in Figure 3, underlined residue positions in Figure 3, and a cysteine residue added to the Fc domain by substitution at an Fc site selected from the group consisting of Leu139, Gln143, Ser145, and Ser196, or, if g >1, any combination of these members;

X^1, X^2 , and X^3 are each independently selected from $-(L^1)_c-P^0$, $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

P^0, P^1, P^2, P^3, and P^4 are each independently selected from the group consisting of:

i) a pharmaceutically acceptable polymer or dextran;

ii) a pharmacologically active polypeptide, peptide, peptidomimetic, or non-peptide organic moiety;

iii) a radioisotope, an enzyme, a biotinyl moiety, a fluorophore, or a chromophore; and

iv) an immobilized substrate, provided that in a chain comprising more than one additional functional moieties, the immobilized substrate is the moiety most distal from F^1, and there can be no more than one immobilized substrate in the chain;

L^1, L^2, L^3, and L^4 are each independently linkers;

a, b, c, d, e, and f are each independently 0 or 1; and

g is 1, 2, 3, or 4.

Those of ordinary skill in the art will appreciate that more than one additional functional moieties (X^3) can be attached to the Fc domain, and that the multiple X^3 substituents may be the same or different; for example, comprising same or different P^1 functional moiety (i.e., a P^1 in a given formula may be the same or different from any other P^1, P^2, P^3, or P^4), different linkers attached to the same peptide sequence, and so on. Likewise, X^1 and X^2 may be the same, different, or absent (i.e., a and/or b = 0), and the integers c through f may be different for X^1, X^2, and X^3.

Thus, compounds of Formula I encompass, but are not limited to, exemplary embodiments of the inventive compounds of the following formulae (II)-(XXVIII):

(II)

$$\begin{array}{l} X^1\text{-}F^1 \\ \quad\;\; | \\ \quad\;\; X^3 \end{array}$$

and multimers thereof, wherein a = 1, b = 0, F^1 is attached at the C-terminus of a polypeptide or peptide comprised in X^1, and X^3 is attached through a specifically selected internal conjugation site in F^1;

(III)

$$\begin{array}{l} F^1\text{-}X^2 \\ | \\ X^3 \end{array}$$

and multimers thereof, wherein a = 0, b = 1, F^1 is attached at the N-terminus of a polypeptide or peptide comprised in X^2, and X^3 is attached through a specifically selected internal conjugation site in F^1;

(IV)

$$\begin{array}{l} F^1\text{-}(L^1)_c\text{-}P^1 \\ | \\ (L^1)_c\text{-PEG} \end{array}$$

and multimers thereof, wherein a = 0, b = 1, F^1 is attached through the N-terminus of a polypeptide or peptide P^1 comprised in $-(L^1)_c-P^1$ and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(V)

$$\begin{array}{l} F^1\text{-}(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \\ | \\ (L^1)_c\text{-PEG} \end{array}$$

and multimers thereof, wherein a = 0, b = 1, F^1 is attached through the N-terminus of a polypeptide or peptide P^1 comprised in $-(L^1)_c$ $-P^1-(L^2)_d$ $-P^2$ and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(VI)

$$\begin{array}{l} F^1\text{-}(L^1)_c\text{-}P^0 \\ | \\ (L^1)_c\text{-PEG} \end{array}$$

and multimers thereof, wherein a = 0, b =1, F^1 is attached through the N-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c$ $–P^0$ and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(VII)

$$\begin{array}{l} F^1\text{-}(L^1)_c\text{-}P^0 \\ | \\ (L^1)_c\text{-}P^1 \end{array}$$

and multimers thereof, wherein a = 0, b =1, F^1 is attached through the N-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c$ $–P^0$ and $-(L^1)_c-P^1$ is attached through a specifically selected internal conjugation site in F^1;

(VIII)

$$\begin{array}{l} F^1\text{-}(L^1)_c\text{-}P^0 \\ | \\ (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 0, b =1, F^1 is attached through the N-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c$ $–P^0$ and $-(L^1)_c-P^1-(L^2)_d-P^2$ is attached through a specifically selected internal conjugation site in F^1;

(IX)

$$\begin{array}{c} \qquad F^1\text{-}(L^1)_c\text{-}P^0 \\ / \backslash \\ \text{PEG-}(L^1)_c \quad (L^1)_c\text{-}P^1 \end{array}$$

and multimers thereof, wherein a = 0, b =1, g =2, F^1 is attached through the N-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c-P^0$, and $-(L^1)_c$-PEG and $-(L^1)_c-P^1$ are each independently attached through specifically selected internal conjugation sites in F^1;

(X)

```
              F¹-(L¹)c-P⁰
              / \
PEG-(L¹)c   (L¹)c-P¹-(L²)d-P²
```

and multimers thereof, wherein a = 0, b =1, g = 2, F^1 is attached through the N-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c-P^0$ and $-(L^1)_c$-PEG and $-(L^1)_c-P^1-(L^2)_d-P^2$ are each independently attached through specifically selected internal conjugation sites in F^1;

(XI)

```
              F¹-P⁰
              / \
PEG-(L¹)c   (L¹)c-P¹-(L²)d-P²
```

and multimers thereof, wherein a = 0, b =1, F^1 is attached at the N-terminus of a polypeptide or peptide $-P^0$, and $-(L^1)_c$-PEG and $-(L^1)_c-P^2-(L^2)_d-P^2$ are each independently attached through specifically selected internal conjugation sites in F^1.

(XII)

```
P¹-(L¹)c-F¹
          |
        (L¹)c-PEG
```

and multimers thereof, wherein a = 1, b = 0, F^1 is attached through the C-terminus of a polypeptide or peptide P^1 comprised in $-(L^1)_c-P^1$ and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XIII)

```
P²-(L²)d-P¹-(L¹)c-F¹
                   |
                 (L¹)c-PEG
```

and multimers thereof, wherein a = 1, b = 0, F^1 is attached through the C-terminus of a polypeptide or peptide P^1 comprised in $-(L^1)_c-P^1-(L^2)_d-P^2$ and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XIV)

$$\begin{array}{l} P^0\text{-}(L^1)_c\text{-}F^1 \\ \qquad\qquad\;| \\ \qquad\quad (L^1)_c\text{-PEG} \end{array}$$

and multimers thereof, wherein a = 1, b = 0, F^1 is attached through the C-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c-P^0$ and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XV)

$$\begin{array}{l} P^0\text{-}(L^1)_c\text{-}F^1 \\ \qquad\qquad\;| \\ \qquad\quad (L^1)_c\text{-}P^1 \end{array}$$

and multimers thereof, wherein a = 1, b = 0, F^1 is attached through the C-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c-P^0$ and $(L^1)_c-P^1$ is attached through a specifically selected internal conjugation site in F^1;

(XVI)

$$\begin{array}{l} P^0\text{-}(L^1)_c\text{-}F^1 \\ \qquad\qquad\;| \\ \qquad\quad (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 1, b = 0, F^1 is attached through the C-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c-P^0$, and $-(L^1)_c-P^1-(L^2)_d-P^2$ is attached through a specifically selected internal conjugation site in F^1;

(XVII)

$$\begin{array}{l} \quad P^0\text{-}(L^1)_c\text{-}F^1 \\ \qquad\qquad\;\; / \backslash \\ \text{PEG-}(L^1)_c\;(L^1)_c\text{-}P^1 \end{array}$$

and multimers thereof, wherein a = 1, b = 0, g = 2, F^1 is attached through the C-terminus of a polypeptide or peptide P^0 comprised in $-(L^1)_c-P^0$ and $(L^1)_c$-PEG and $(L^1)_c-P^1$ are each independently attached through specifically selected internal conjugation sites in F^1;

(XVIII)

$$\begin{array}{c} P^0\text{-}F^1 \\ /\backslash \\ PEG\text{-}(L^1)_c\ (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 1, b = 0, g = 2, F^1 is attached at the C-terminus of a polypeptide or peptide $-P^0$ and $-(L^1)_c$-PEG and $-(L^1)_c-P^1-(L^2)_d-P^2$ are each independently attached through specifically selected internal conjugation sites in F^1;

(XIX)

$$\begin{array}{c} P^1\text{-}(L^1)_c\text{-}F^1 \\ /\backslash \\ PEG\text{-}(L^1)_c\ (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 1, b = 0, g = 2, F^1 is attached through the C-terminus of a polypeptide or peptide P^1 comprised in $-(L^1)_c-P^1$, and $-(L^1)_c$ –PEG and $-(L^1)_c-P^2-(L^2)_d-P^2$ are each independently attached through specifically selected internal conjugation sites in F^1;

(XX)

$$\begin{array}{c} P^0\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^1 \\ | \\ (L^1)_c\text{-}PEG \end{array}$$

and multimers thereof, wherein a = 1, b = 1, $P^0-(L^1)_c-F^1-(L^1)_c-P^1$ is attached as written from the N- terminus of a polypeptide or peptide P^0 to the C-terminus of a polypeptide or peptide P^1 and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XXI)

$$\begin{array}{c} P^0\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \\ | \\ (L^1)_c\text{-}PEG \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c =1, $P^0-(L^1)_c-F^1-(L^1)_c-P^1-(L^2)_d-P^2$ is attached as written from the N-terminus of a polypeptide or peptide P^0 to the C-terminus of a polypeptide or peptide P^1 (if P^1 but not P^2 is a polypeptide or peptide) or P^2 (if both P^1 and P^2 are a polypeptide or peptide) and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XXII)

$$\begin{array}{l} P^0\text{-}F^1\text{-}(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \\ \quad | \\ \ (L^1)_c\text{-PEG} \end{array}$$

and multimers thereof, wherein a = 1, b = 1, P^0-F^1-$(L^1)_c$-P^1-$(L^2)_d$-P^2 is attached as written from the N-terminus of a polypeptide or peptide P^0 to the C-terminus of a polypeptide or peptide P^1 (if P^1 but not P^2 is a polypeptide or peptide) or P^2 (if both P^1 and P^2 are a polypeptide or peptide), and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XXIII)

$$\begin{array}{l} P^1\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^0 \\ \qquad\qquad | \\ \qquad\ (L^1)_c\text{-PEG} \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c =1, P^1-$(L^1)_c$-F^1-$(L^1)_c$-P^0 is attached as written from the N-terminus of a polypeptide or peptide P^1 to the C-terminus of a polypeptide or peptide P^0 and $-(L^1)_c$-PEG is attached through a specifically selected internal conjugation site in F^1;

(XXIV)

$$\begin{array}{l} P^1\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^0 \\ \qquad\qquad | \\ \qquad\ (L^1)_c\text{-}P^1 \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c =1, P^1-$(L^1)_c$-F^1-$(L^1)_c$-P^0 is attached as written from the N-terminus of a polypeptide or peptide P^1 to the C-terminus of a polypeptide or peptide P^0 and $(L^1)_c$-P^1 is attached through a specifically selected internal conjugation site in F^1;

(XXV)

$$\begin{array}{l} P^1\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^0 \\ \qquad\qquad | \\ \qquad\ (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c = 1, P^1-$(L^1)_c$-F^1-$(L^1)_c$-P^0 is attached as written from the N-terminus of a polypeptide or peptide P^1 to the C-terminus of a polypeptide or peptide P^0, and -$(L^1)_c$-P^1-$(L^2)_d$-P^2 is attached through a specifically selected internal conjugation site in F^1;

(XXVI)

$$\begin{array}{c} P^1\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^0 \\ / \backslash \\ PEG\text{-}(L^1)_c \; (L^1)_c\text{-}P^1 \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c = 1, P^1-$(L^1)_c$-F^1-$(L^1)_c$-P^0 is attached as written from the N-terminus of a polypeptide or peptide P^1 to the C-terminus of a polypeptide or peptide P^0 and -$(L^1)_c$-PEG and -$(L^1)_c$-P^1 are each independently attached through specifically selected internal conjugation sites in F^1;

(XXVII)

$$\begin{array}{c} P^1\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^0 \\ / \backslash \\ PEG\text{-}(L^1)_c \; (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c = 1, P^1-$(L^1)_c$-F^1-$(L^1)_c$-P^0 is attached as written from the N-terminus of a polypeptide or peptide P^1 to the C-terminus of a polypeptide or peptide P^0, and -$(L^1)_c$-PEG and -$(L^1)_c$-P^1-$(L^2)_d$-P^2 are each independently attached through specifically selected internal conjugation sites in F^1; and

(XXVIII)

$$\begin{array}{c} P^1\text{-}(L^1)_c\text{-}F^1\text{-}(L^1)_c\text{-}P^0 \\ / \backslash \\ P^1\text{-}(L^1)_c \; (L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2 \end{array}$$

and multimers thereof, wherein a = 1, b = 1, c = 1, P^1-$(L^1)_c$-F^1-$(L^1)_c$-P^0 is attached as written from the N-terminus of a polypeptide or peptide P^1 to the C-terminus of a polypeptide or peptide P^0, and the second -$(L^1)_c$-P^1 and $(L^1)_c$-P^2-$(L^2)_d$-P^2 are each independently attached through specifically selected internal conjugation sites in F^1.

In another embodiment of the present invention, the composition of matter is an antibody modified, which comprises at least one additional functional moiety

(X^3) covalently bound to the Fc domain of the antibody through one or more specifically selected conjugation site(s) in the Fc domain. The conjugation site, or sites, are selected from: underlined residue positions in Figure 1, boldface residue positions in Figure 2, highlighted residue positions in Figure 3, underlined residue positions in Figure 3, or a cysteine residue added to the Fc domain by substitution at an Fc site selected from the group consisting of Leu139, Gln143, Ser145, and Ser196, or, if there is more than one X^3, any combination of these members. X^3 is selected from $-(L^1)_c-P^0$, $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

P^0, P^1, P^2, P^3, and P^4 are each independently selected from the group consisting of:

i) a pharmaceutically acceptable polymer or dextran;

ii) a pharmacologically active polypeptide, peptide, peptidomimetic, or non-peptide organic moiety;

iii) a radioisotope, an enzyme, a biotinyl moiety, a fluorophore, or a chromophore; and

iv) an immobilized substrate, provided that in a chain comprising more than one additional functional moieties, the immobilized substrate is the moiety most distal from the Fc domain, and there can be no more than one immobilized substrate in the chain;

L^1, L^2, L^3, and L^4 are each independently linkers;

c, d, e, and f are each independently 0 or 1.

Additional functional moiety or moieties (X^3)

Some embodiments of the additional functional moiety, or moieties, (i.e., P^0, P^1, P^2, P^3, P^4) that can be conjugated to the Fc domain, in accordance with the present invention, will now be exemplified in greater detail.

Polypeptides or peptides. One or more additional functional moieties is conjugated to the Fc domain molecules of this invention. Such additional functional moieties can include a polypeptide, a peptide, an antibody, antibody fragment, (or a non-peptide organic molecule "small molecules", e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one can use as a functional moiety a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta et al. Peptides of interest can also be selected by phage display for binding to the FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "functional moiety" in this invention. Such functional moieties can be selected, for example, for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

In other embodiments, a variety of other peptides or polypeptides can be used as the additional functional moiety in conjunction with the present invention. Exemplary polypeptides that can be used include those mentioned as fusion partners in Table 1 hereinabove. Preferred polypeptides have therapeutic utility and include the human proteins anakinra, sTNF-R2, sTNF-R1, CTLA4, OPG, GDNF, PTH fragments, glucagons fragments, GLP-1, and the like. Accordingly, a preferred polypeptide sequence is the sTNF-R2 sequence below:

QICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPVSTRSQHTQPTPE
PSTAPSTSFLLPMGPSPPAEGSTGDFALPVGLIVGVTALGLLIIGVVNCV
IMTQVKKKPLCLQREAKVPHLPADKARGTQGPEQQHLLITAPSSSSSSLE
SSASALDRRAPTRNQPQAPGVEASGAGEARASTGSSDSSPGGHGTQVNVT
CIVNVCSSSDHSSQCSSQASSTMGDTDSSPSESPKDEQVPFSKEECAFRS
QLETPETLLGSTEEKPLPLGVPDAGMKPS//(SEQ ID NO: 617)

In accordance with the present invention, one may modify Fc fusion proteins comprising such polypeptides by adding an additional functional moiety such as PEG through a selected site in the Fc domain. In this way, for example, a PEGylated derivative of etanercept is within the scope of this invention in which the PEG molecule is attached through a selected site in the Fc domain of etanercept. Such a molecule can be described by formula XIV above in which P^0-$(L^1)_c$-F^1 encodes etanercept (wherein P^0 is SEQ ID NO: 618:

1 Leu-Pro-Ala-Gln-Val-Ala-Phe-Thr-Pro-Tyr-

11 Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys-Arg-Leu-

21 Arg-Glu-Tyr-Tyr-Asp-Gln-Thr-Ala-Gln-Met-
31 Cys-Cys-Ser-Lys-Cys-Ser-Pro-Gly-Gln-His-
41 Ala-Lys-Val-Phe-Cys-Thr-Lys-Thr-Ser-Asp-
51 Thr-Val-Cys-Asp-Ser-Cys-Glu-Asp-Ser-Thr-
61 Tyr-Thr-Gln-Leu-Trp-Asn-Trp-Val-Pro-Glu-
71 Cys-Leu-Ser-Cys-Gly-Ser-Arg-Cys-Ser-Ser-
81 Asp-Gln-Val-Glu-Thr-Gln-Ala-Cys-Thr-Arg-
91 Glu-Gln-Asn-Arg-Ile-Cys-Thr-Cys-Arg-Pro-
101 Gly-Trp-Tyr-Cys-Ala-Leu-Ser-Lys-Gln-Glu-
111 Gly-Cys-Arg-Leu-Cys-Ala-Pro-Leu-Arg-Lys-
121 Cys-Arg-Pro-Gly-Phe-Gly-Val-Ala-Arg-Pro-
131 Gly-Thr-Glu-Thr-Ser-Asp-Val-Val-Cys-Lys-
141 Pro-Cys-Ala-Pro-Gly-Thr-Phe-Ser-Asn-Thr-
151 Thr-Ser-Ser-Thr-Asp-Ile-Cys-Arg-Pro-His-
161 Gln-Ile-Cys-Asn-Val-Val-Ala-Ile-Pro-Gly-
171 Asn-Ala-Ser-Met-Asp-Ala-Val-Cys-Thr-Ser-
181 Thr-Ser-Pro-Thr-Arg-Ser-Met-Ala-Pro-Gly-
191 Ala-Val-His-Leu-Pro-Gln-Pro-Val-Ser-Thr-
201 Arg-Ser-Gln-His-Thr-Gln-Pro-Thr-Pro-Glu-
211 Pro-Ser-Thr-Ala-Pro-Ser-Thr-Ser-Phe-Leu-
221 Leu-Pro-Met-Gly-Pro-Ser-Pro-Pro-Ala-Glu-
231 Gly-Ser-Thr-Gly-Asp-Glu-Pro-Lys-Ser-Cys-
241 Asp-Lys-Thr-His-Thr-Cys-Pro-Pro-Cys-Pro-
251 Ala-Pro-Glu-Leu-Leu-Gly-Gly-Pro-Ser-Val-
261 Phe-Leu-Phe-Pro-Pro-Lys-Pro-Lys-Asp-Thr-
271 Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-
281 Cys-Val-Val-Val-Asp-Val-Ser-His-Glu-Asp-
291 Pro-Glu-Val-Lys-Phe-Asn-Trp-Tyr-Val-Asp-
301 Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-
311 Pro-Arg-Glu-Glu-Gln-Tyr-Asn-Ser-Thr-Tyr-
321 Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-

331 Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-
341 Cys-Lys-Val-Ser-Asn-Lys-Ala-Leu-Pro-Ala-
351 Pro-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-
361 Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-
371 Leu-Pro-Pro-Ser-Arg-Glu-Glu-Met-Thr-Lys-
381 Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-
391 Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-
401 Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-
411 Tyr-Lys-Thr-Thr-Pro-Pro-Val-Leu-Asp-Ser-
421 Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Lys-Leu-
431 Thr-Val-Asp-Lys-Ser-Arg-Trp-Gln-Gln-Gly-
441 Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-
451 Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-
461 Leu-Ser-Leu-Ser-Pro-Gly-Lys // SEQ ID NO: 618, and c is 0) or a molecule based on the etanercept sequence with one or more modified residues to enable linkage to the $(L^1)_c$-PEG substituent.

Also in accordance with this invention, a peptide or additional polypeptide functional moiety can be linked through a selected site in the Fc domain. Alternatively, the polypeptide-Fc fusion protein can be linked to a peptide or tandem dimer, trimer, or tetramer (i.e., $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$). The peptides can be linked through a selected internal Fc site or at an available N- or C-terminus of the fusion protein. In this way, this invention encompasses an etanercept derivative comprising, for example, a BAFF-binding peptide dimer (see Table 10 hereinafter), a PEG moiety, or both. In such a molecule for example, the structure can follow formula XXI above wherein P^0 is SEQ ID NO: 617, P^1 and P^2 are BAFF-binding peptides such as LPGCKWDLLIKQWVCDPL (SEQ ID NO: 514).

Any number of peptides or polypeptides can be used in conjunction with the present invention. In some embodiments, the peptides or polypeptides bind to angiopoietin-2 (ang-2), myostatin, nerve growth factor (NGF), tumor necrosis factor (TNF), B cell activating factor (BAFF, also referred to as TALL-1) or mimic the activity of EPO, TPO, or G-CSF. Targeting peptides are also of interest, including tumor-homing peptides, membrane-transporting peptides, and the like. All of these classes of peptides or polypeptides can be discovered by methods described in the references cited in this specification and other references.

As mentioned above, phage display is useful in generating peptides for use in the present invention. It has been stated that affinity selection from libraries of random peptides can be used to identify peptide ligands for any site of any gene product. Dedman et al. (1993), J. Biol. Chem. 268: 23025-30. Phage display is particularly well suited for identifying peptides that bind to such proteins of interest as cell surface receptors or any proteins having linear epitopes. Wilson et al. (1998), Can. J. Microbiol. 44: 313-29; Kay et al. (1998), Drug Disc. Today 3: 370-8. Such proteins are extensively reviewed in Herz et al. (1997), J. Receptor & Signal Transduction Res. 17(5): 671-776, which is hereby incorporated by reference. Such proteins of interest are preferred for use in this invention.

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 et Therapiae Experimentalis 45: 353-7, which is hereby incorporated by reference. Among these receptors, most preferred are the CKRs (family I in Table 4). The receptor classification appears in Table 4.

Table 4. Cytokine Receptors Classified by Receptor Code

Cytokines (ligands)		Receptor Type	
Family	Subfamily	family	subfamily
I. Hematopoietic cytokines	1. IL-2, IL-4, IL-7, IL-9, IL-13, IL-15 2. IL-3, IL-5, GM-CSF 3. IL-6, IL-11, IL-12, LIF, OSM, CNTF,	I. Cytokine R (CKR)	1. shared γCr, IL-9R, IL-4R 2. shared GP 140 βR 3. 3.shared RP 130, IL-6 R, Leptin R

	Leptin (OB) 4. G-CSF, EPO, TPO, PRL, GH 5. IL-17, HVS-IL-17		4. "single chain" R, GCSF-R, TPO-R, GH-R 5. other R[a]
II. IL-10 ligands	IL-10, BCRF-1, HSV-IL-10	II. IL-10 R	
III. Interferons	1. IFN-αl, α2, α4, m, t, IFN-β[b] 2. IFN-γ	III. Interferon R	1. IFNAR 2. IFNGR
IV. IL-1 and IL-1 like ligands	1. IL-1α, IL-1β, IL-1Ra 2. IL-18, IL-18BP	IV. IL-1R	1. IL-1R, IL-1RAcP 2. IL-18R, IL-18RAcP
V. TNF family	1. TNF-α, TNF-β (LT), FASL, CD40 L, CD30L, CD27 L, OX40L, OPGL, TRAIL, APRIL, AGP-3, BLys, TL5, Ntn-2, KAY, Neutrokine-α	3. NGF/TNF R[c]	TNF-RI, AGP-3R, DR4, DR5, OX40, OPG, TACI, CD40, FAS, ODR

[2] Other IFN type I subtypes remain unassigned. Hematopoietic cytokines, IL-10 ligands and interferons do not possess functional intrinsic protein kinases. The signaling molecules for the cytokines are JAK's, STATs and related non-receptor molecules. IL-14, IL-16 and IL-18 have been cloned but according to the receptor code they remain unassigned.

[3] TNF receptors use multiple, distinct intracellular molecules for signal transduction including "death domain" of FAS R and 55 kDa TNF-•R that participates in their cytotoxic effects. NGF/TNF R can bind both NGF and related factors as well as TNF ligands. Chemokine receptors are seven transmembrane (7TM, serpentine) domain receptors. They are G protein-coupled.

VI. Chemokines	1. α chemokines: IL-8, GRO α, β, γ, IF-10, PF-4, SDF-1 2. β chemokines: MIP1α, MIP1β, MCP-1,2,3,4, RANTES, eotaxin 3. γ chemokines: lymphotactin	4. Chemokine R	1. CXCR 2. CCR 3. CR 4. DARC[d]
VII.Growth factors	1.1 SCF, M-CSF, PDGF-AA, AB, BB, KDR, FLT-1, FLT-3L, VEGF, SSV-PDGF, HGF, SF 1.2 FGFα, FGFβ 1.3 EGF, TGF-α, VV-F19 (EGF-like) 1.4 IGF-I, IGF-II, Insulin 1.5 NGF, BDNF, NT-3, NT-4[e] 2. TGF-β1,β2,β3	VII.RKF	1. TK sub-family 1.1 IgTK III R, VEGF-RI, VEGF-RII 1.2 IgTK IV R 1.3 Cysteine-rich TK-I 1.4 Cysteine rich TK-II, IGF-RI 1.5 Cysteine knot TK V 2. Serine-threonine kinase subfamily (STKS)[f]

[4] The Duffy blood group antigen (DARC) is an erythrocyte receptor that can bind several different chemokines. IL-1R belongs to the immunoglobulin superfamily but their signal transduction events characteristics remain unclear.

[5] The neurotrophic cytokines can associate with NGF/TNF receptors also.

[6] STKS may encompass many other TGF-β-related factors that remain unassigned. The protein kinases are intrinsic part of the intracellular domain of receptor kinase family (RKF). The enzymes participate in the signals transmission via the receptors.

Particular proteins of interest as targets for peptide generation in the present invention include, but are not limited to, the following:

αvβ3
αVβ1
Ang-2
BAFF/TALL-1
B7
B7RP1
CRP1
Calcitonin
CD28
CETP
cMet
Complement factor B
C4b
CTLA4
Glucagon
Glucagon Receptor
LIPG
MPL
myostatin
splice variants of molecules preferentially expressed on tumor cells; e.g., CD44, CD30
unglycosylated variants of mucin and Lewis Y surface glycoproteins
CD19, CD20, CD33, CD45
prostate specific membrane antigen and prostate specific cell antigen
matrix metalloproteinases (MMPs), both secreted and membrane-bound (e.g., MMP-9)
Cathepsins
angiopoietin-2
TIE-2 receptor
heparanase
urokinase plasminogen activator (UPA), UPA receptor
parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), PTH-RI, PTH-RII
Her2
Her3
Insulin

Exemplary peptides for this invention appear in Tables 4 through 20 of U.S. Pat. No. 6,660,843, which are hereby incorporated by reference. Additional preferred peptides appear in U.S. 2003/0229023, published Dec. 11, 2003; WO

03/057134, published July 17, 2003; U.S. 2003/0236193, published Dec. 25, 2003; WO 00/24770, published May 4, 2000; U.S. 2003/0176352, published Sept. 18, 2003; WO 03/031589, published April 17, 2003; U.S. Ser. No. 10/666,480, filed September 18, 2003; WO 04/026329, published April 1, 2004; U.S. Ser. No. 10/742,379, filed December 19, 2003; PCT/US03/40781, filed December 19, 2003, each of which are hereby incorporated by reference. Such peptides may be prepared by methods disclosed in the art.

The amino acid sequences of some preferred peptides and polypeptides appear in Tables 5-10 below. Single letter amino acid abbreviations are used. Any of these peptides may be linked in tandem (i.e., sequentially), with or without linkers. Any peptide containing a cysteinyl residue may be cross-linked with another Cys-containing peptide or protein. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well. Any of these peptides may be derivatized as described herein. All peptides are linked through peptide bonds unless otherwise noted.

Table 5. EPO-mimetic peptide sequences

SEQUENCE	SEQ ID NO:
YXCXXGPXTWXCXP, wherein X is any amino acid	1
GGTYSCHFGPLTWVCKPQGG	2
GGDYHCRMGPLTWVCKPLGG	3
GGVYACRMGPITWVCSPLGG	4
VGNYMCHFGPITWVCRPGGG	5
GGLYLCRFGPVTWDCGYKGG	6
GGTYSCHFGPLTWVCKPQGGSSK	7
GGTYSCHGPLTWVCKPQGG	8
VGNYMAHMGPITWVCRPGG	9
GGPHHVYACRMGPLTWIC	10
GGTYSCHFGPLTWVCKPQ	11
GGLYACHMGPMTWVCQPLRG	12
TIAQYICYMGPETWECRPSPKA	13
YSCHFGPLTWVCK	14
YCHFGPLTWVC	15
GGLYLCRFGPVTWDCGYKGG	16
GGTYSCHFGPLTWVCKPQGG	17
GGDYHCRMGPLTWVCKPLGG	18

VGNYMCHFGPITWVCRPGGG	19
GGVYACRMGPITWVCSPLGG	20
VGNYMAHMGPITWVCRPGG	21
GGTYSCHFGPLTWVCKPQ	22
GGLYACHMGPMTWVCQPLRG	23
TIAQYICYMGPETWECRPSPKA	24
YSCHFGPLTWVCK	25
YCHFGPLTWVC	26
SCHFGPLTWVCK	27

Table 6. TPO-mimetic peptide sequences

SEQUENCE	SEQ ID NO:
IEGPTLRQWLAARA	28
IEGPTLRQWLAAKA	29
IEGPTLREWLAARA	30
TLREWL	31
GRVRDQVAGW	32
GRVKDQIAQL	33
GVRDQVSWAL	34
ESVREQVMKY	35
SVRSQISASL	36
GVRETVYRHM	37
GVREVIVMHML	38
GRVRDQIWAAL	39
AGVRDQILIWL	40
GRVRDQIMLSL	41
CTLRQWLQGC	42
CTLQEFLEGC	43
CTRTEWLHGC	44
CTLREWLHGGFC	45
CTLREWVFAGLC	46
CTLRQWLILLGMC	47
CTLAEFLASGVEQC	48
CSLQEFLSHGGYVC	49
CTLREFLDPTTAVC	50
CTLKEWLVSHEVWC	51
REGPTLRQWM	52
EGPTLRQWLA	53
ERGPFWAKAC	54
REGPRCVMWM	55
CGTEGPTLSTWLDC	56
CEQDGPTLLEWLKC	57
CELVGPSLMSWLTC	58

CLTGPFVTQWLYEC	59
CRAGPTLLEWLTLC	60
CADGPTLREWISFC	61
GGCTLREWLHGGFCGG	62
GGCADGPTLREWISFCGG	63
GNADGPTLRQWLEGRRPKN	64
LAIEGPTLRQWLHGNGRDT	65
HGRVGPTLREWKTQVATKK	66
TIKGPTLRQWLKSREHTS	67
ISDGPTLKEWLSVTRGAS	68
SIEGPTLREWLTSRTPHS	69
GAREGPTLRQWLEWVRVG	70
RDLDGPTLRQWLPLPSVQ	71
ALRDGPTLKQWLEYRRQA	72
ARQEGPTLKEWLFWVRMG	73
EALLGPTLREWLAWRRAQ	74
MARDGPTLREWLRTYRMM	75
WMPEGPTLKQWLFHGRGQ	76
HIREGPTLRQWLVALRMV	77
QLGHGPTLRQWLSWYRGM	78
ELRQGPTLHEWLQHLASK	79
VGIEGPTLRQWLAQRLNP	80
WSRDGPTLREWLAWRAVG	81
AVPQGPTLKQWLLWRRCA	82
RIREGPTLKEWLAQRRGF	83
RFAEGPTLREWLEQRKLV	84
DRFQGPTLREWLAAIRSV	85
AGREGPTLREWLNMRVWQ	86
ALQEGPTLRQWLGWGQWG	87
YCDEGPTLKQWLVCLGLQ	88
WCKEGPTLREWLRWGFLC	89
CSSGGPTLREWLQCRRMQ	90
CSWGGPTLKQWLQCVRAK	91
CQLGGPTLREWLACRLGA	92
CWEGGPTLKEWLQCLVER	93
CRGGGPTLHQWLSCFRWQ	94
CRDGGPTLRQWLACLQQK	95
ELRSGPTLKEWLVWRLAQ	96
GCRSGPTLREWLACREVQ	97
TCEQGPTLRQWLLCRQGR	98
QGYCDEGPTLKQWLVCLGLQHS	99

Table 7. Ang-2 binding peptide sequences

SEQUENCE	SEQ ID NO.
WDPWT	100
WDPWTC	101
CXWDPWT (wherein X is an acidic or neutral polar amino acid residue)	102
CXWDPWTC (wherein X is an acidic or neutral polar amino acid residue)	103
PIRQEECDWDPWTCEHMWEV	104
TNIQEECEWDPWTCDHMPGK	105
WYEQDACEWDPWTCEHMAEV	106
NRLQEVCEWDPWTCEHMENV	107
AATQEECEWDPWTCEHMPRS	108
LRHQEGCEWDPWTCEHMFDW	109
VPRQKDCEWDPWTCEHMYVG	110
SISHEECEWDPWTCEHMQVG	111
WAAQEECEWDPWTCEHMGRM	112
TWPQDKCEWDPWTCEHMGST	113
GHSQEECGWDPWTCEHMGTS	114
QHWQEECEWDPWTCDHMPSK	115
NVRQEKCEWDPWTCEHMPVR	116
KSGQVECNWDPWTCEHMPRN	117
VKTQEHCDWDPWTCEHMREW	118
AWGQEGCDWDPWTCEHMLPM	119
PVNQEDCEWDPWTCEHMPPM	120
RAPQEDCEWDPWTCAHMDIK	121
HGQNMECEWDPWTCEHMFRY	122
PRLQEECVWDPWTCEHMPLR	123
RTTQEKCEWDPWTCEHMESQ	124
QTSQEDCVWDPWTCDHMVSS	125
QVIGRPCEWDPWTCEHLEGL	126
WAQQEECAWDPWTCDHMVGL	127
LPGQEDCEWDPWTCEHMVRS	128
PMNQVECDWDPWTCEHMPRS	129
FGWSHGCEWDPWTCEHMGST	130
KSTQDDCDWDPWTCEHMVGP	131
GPRISTCQWDPWTCEHMDQL	132
STIGDMCEWDPWTCAHMQVD	133
VLGGQGCEWDPWTCRLLQGW	134
VLGGQGCQWDPWTCSHLEDG	135
TTIGSMCEWDPWTCAHMQGG	136
TKGKSVCQWDPWTCSHMQSG	137
TTIGSMCQWDPWTCAHMQGG	138

WVNEVVCEWDPWTCNHWDTP	139
VVQVGMCQWDPWTCKHMRLQ	140
AVGSQTCEWDPWTCAHLVEV	141
QGMKMFCEWDPWTCAHIVYR	142
TTIGSMCQWDPWTCEHMQGG	143
TSQRVGCEWDPWTCQHLTYT	144
QWSWPPCEWDPWTCQTVWPS	145
GTSPSFCQWDPWTCSHMVQG	146
QEECEWDPWTCEHM	147
QNYKPLDELDATLYEHFIFHYT	148
LNFTPLDELEQTLYEQWTLQQS	149
TKFNPLDELEQTLYEQWTLQHQ	150
VKFKPLDALEQTLYEHWMFQQA	151
VKYKPLDELDEILYEQQTFQER	152
TNFMPMDDLEQRLYEQFILQQG	153
SKFKPLDELEQTLYEQWTLQHA	154
QKFQPLDELEQTLYEQFMLQQA	155
QNFKPMDELEDTLYKQFLFQHS	156
YKFTPLDDLEQTLYEQWTLQHV	157
QEYEPLDELDETLYNQWMFHQR	158
SNFMPLDELEQTLYEQFMLQHQ	159
QKYQPLDELDKTLYDQFMLQQG	160
QKFQPLDELEETLYKQWTLQQR	161
VKYKPLDELDEWLYHQFTLHHQ	162
QKFMPLDELDEILYEQFMFQQS	163
QTFQPLDDLEEYLYEQWIRRYH	164
EDYMPLDALDAQLYEQFILLHG	165
HTFQPLDELEETLYYQWLYDQL	166
YKFNPMDELEQTLYEEFLFQHA	167
TNYKPLDELDATLYEHWILQHS	168
QKFKPLDELEQTLYEQWTLQQR	169
TKFQPLDELDQTLYEQWTLQQR	170
TNFQPLDELDQTLYEQWTLQQR	171
KFNPLDELEETLYEQFTFQQ	172
AGGMRPYDGMLGWPNYDVQA	173
QTWDDPCMHILGPVTWRRCI	174
APGQRPYDGMLGWPTYQRIV	175
SGQLRPCEEIFGCGTQNLAL	176
FGDKRPLECMFGGPIQLCPR	177
GQDLRPCEDMFGCGTKDWYG	178
KRPCEEIFGGCTYQ	179
GFEYCDGMEDPFTFGCDKQT	180
KLEYCDGMEDPFTQGCDNQS	181

LQEWCEGVEDPFTFGCEKQR	182
AQDYCEGMEDPFTFGCEMQK	183
LLDYCEGVQDPFTFGCENLD	184
HQEYCEGMEDPFTFGCEYQG	185
MLDYCEGMDDPFTFGCDKQM	186
LQDYCEGVEDPFTFGCENQR	187
LQDYCEGVEDPFTFGCEKQR	188
FDYCEGVEDPFTFGCDNH	189

Table 8. NGF-Binding Peptide Sequences

SEQUENCE	SEQ ID NO.
TGYTEYTEEWPMGFGYQWSF	190
TDWLSDFPFYEQYFGLMPPG	191
FMRFPNPWKLVEPPQGWYYG	192
VVKAPHFEFLAPPHFHEFPF	193
FSYIWIDETPSNIDRYMLWL	194
VNFPKVPEDVEPWPWSLKLY	195
TWHPKTYEEFALPFFVPEAP	196
WHFGTPYIQQQPGVYWLQAP	197
VWNYGPFFMNFPDSTYFLHE	198
WRIHSKPLDYSHVWFFPADF	199
FWDGNQPPDILVDWPWNPPV	200
FYSLEWLKDHSEFFQTVTEW	201
QFMELLKFFNSPGDSSHHFL	202
TNVDWISNNWEHMKSFFTED	203
PNEKPYQMQSWFPPDWPVPY	204
WSHTEWVPQVWWKPPNHFYV	205
WGEWINDAQVHMHEGFISES	206
VPWEHDHDLWEIISQDWHIA	207
VLHLQDPRGWSNFPPGVLEL	208
IHGCWFTEEGCVWQ	209
YMQCQFARDGCPQW	210
KLQCQYSESGCPTI	211
FLQCEISGGACPAP	212
KLQCEFSTSGCPDL	213
KLQCEFSTQGCPDL	214
KLQCEFSTSGCPWL	215
IQGCWFTEEGCPWQ	216
SFDCDNPWGHVLQSCFGF	217
SFDCDNPWGHKLQSCFGF	218

Table 9. Myostatin binding peptide or polypeptide sequences

SEQUENCE	SEQ ID NO:
KDKCKMWHWMCKPP	616
KDLCAMWHWMCKPP	219
KDLCKMWKWMCKPP	220
KDLCKMWHWMCKPK	221
WYPCYEFHFWCYDL	222
WYPCYEGHFWCYDL	223
IFGCKWWDVQCYQF	224
IFGCKWWDVDCYQF	225
ADWCVSPNWFCMVM	226
HKFCPWWALFCWDF	227
KDLCKMWHWMCKPP	228
IDKCAIWGWMCPPL	229
WYPCGEFGMWCLNV	230
WFTCLWNCDNE	231
HTPCPWFAPLCVEW	232
KEWCWRWKWMCKPE	233
FETCPSWAYFCLDI	234
AYKCEANDWGCWWL	235
NSWCEDQWHRCWWL	236
WSACYAGHFWCYDL	237
ANWCVSPNWFCMVM	238
WTECYQQEFWCWNL	239
ENTCERWKWMCPPK	240
WLPCHQEGFWCMNF	241
STMCSQWHWMCNPF	242
IFGCHWWDVDCYQF	243
IYGCKWWDIQCYDI	244
PDWCIDPDWWCKFW	245
QGHCTRWPWMCPPY	246
WQECYREGFWCLQT	247
WFDCYGPGFKCWSP	248
GVRCPKGHLWCLYP	249
HWACGYWPWSCKWV	250
GPACHSPWWWCVFG	251
TTWCISPMWFCSQQ	252
HKFCPPWAIFCWDF	253
PDWCVSPRWYCNMW	254
VWKCHWFGMDCEPT	255

KKHCQIWTWMCAPK	256
WFQCGSTLFWCYNL	257
WSPCYDHYFYCYTI	258
SWMCGFFKEVCMWV	259
EMLCMIHPVFCNPH	260
LKTCNLWPWMCPPL	261
VVGCKWYEAWCYNK	262
PIHCTQWAWMCPPT	263
DSNCPWYFLSCVIF	264
HIWCNLAMMKCVEM	265
NLQCIYFLGKCIYF	266
AWRCMWFSDVCTPG	267
WFRCFLDADWCTSV	268
EKICQMWSWMCAPP	269
WFYCHLNKSECTEP	270
FWRCAIGIDKCKRV	271
NLGCKWYEVWCFTY	272
IDLCNMWDGMCYPP	273
EMPCNIWGWMCPPV	274
WFRCVLTGIVDWSECFGL	275
GFSCTFGLDEFYVDCSPF	276
LPWCHDQVNADWGFCMLW	277
YPTCSEKFWIYGQTCVLW	278
LGPCPIHHGPWPQYCVYW	279
PFPCETHQISWLGHCLSF	280
HWGCEDLMWSWHPLCRRP	281
LPLCDADMMPTIGFCVAY	282
SHWCETTFWMNYAKCVHA	283
LPKCTHVPFDQGGFCLWY	284
FSSCWSPVSRQDMFCVFY	285
SHKCEYSGWLQPLCYRP	286
PWWCQDNYVQHMLHCDSP	287
WFRCMLMNSFDAFQCVSY	288
PDACRDQPWYMFMGCMLG	289
FLACFVEFELCFDS	290
SAYCIITESDPYVLCVPL	291
PSICESYSTMWLPMCQHN	292
WLDCHDDSWAWTKMCRSH	293
YLNCVMMNTSPFVECVFN	294
YPWCDGFMIQQGITCMFY	295
FDYCTWLNGFKDWKCWSR	296
LPLCNLKEISHVQACVLF	297
SPECAFARWLGIEQCQRD	298
YPQCFNLHLLEWTECDWF	299

RWRCEIYDSEFLPKCWFF	300
LVGCDNVWHRCKLF	301
AGWCHVWGEMFGMGCSAL	302
HHECEWMARWMSLDCVGL	303
FPMCGIAGMKDFDFCVWY	304
RDDCTFWPEWLWKLCERP	305
YNFCSYLFGVSKEACQLP	306
AHWCEQGPWRYGNICMAY	307
NLVCGKISAWGDEACARA	308
HNVCTIMGPSMKWFCWND	309
NDLCAMWGWRNTIWCQNS	310
PPFCQNDNDMLQSLCKLL	311
WYDCNVPNELLSGLCRLF	312
YGDCDQNHWMWPFTCLSL	313
GWMCHFDLHDWGATCQPD	314
YFHCMFGGHEFEVHCESF	315
AYWCWHGQCVRF	316
SEHWTFTDWDGNEWWVRPF	317
MEMLDSLFELLKDMVPISKA	318
SPPEEALMEWLGWQYGKFT	319
SPENLLNDLYILMTKQEWYG	320
FHWEEGIPFHVVTPYSYDRM	321
KRLLEQFMNDLAELVSGHS	322
DTRDALFQEFYEFVRSRLVI	323
RMSAAPRPLTYRDIMDQYWH	324
NDKAHFFEMFMFDVHNFVES	325
QTQAQKIDGLWELLQSIRNQ	326
MLSEFEEFLGNLVHRQEA	327
YTPKMGSEWTSFWHNRIHYL	328
LNDTLLRELKMVLNSLSDMK	329
FDVERDLMRWLEGFMQSAAT	330
HHGWNYLRKGSAPQWFEAWV	331
VESLHQLQMWLDQKLASGPH	332
RATLLKDFWQLVEGYGDN	333
EELLREFYRFVSAFDY	334
GLLDEFSHFIAEQFYQMPGG	335
YREMSMLEGLLDVLERLQHY	336
HNSSQMLLSELIMLVGSMMQ	337
WREHFLNSDYIRDKLIAIDG	338
QFPFYVFDDLPAQLEYWIA	339
EFFHWLHNHRSEVNHWLDMN	340
EALFQNFFRDVLTLSEREY	341
QYWEQQWMTYFRENGLHVQY	342
NQRMMLEDLWRIMTPMFGRS	343

FLDELKAELSRHYALDDLDE	344
GKLIEGLLNELMQLETFMPD	345
ILLLDEYKKDWKSWF	346
QGHCTRWPWMCPPYGSGSATGGSGSTAS SGSGSATGQGHCTRWPWMCPPY	347
WYPCYEGHFWCYDLGSGSTASSGSGSAT GWYPCYEGHFWCYDL	348
HTPCPWFAPLCVEWGSGSATGGSGSTAS SGSGSATGHTPCPWFAPLCVEW	349
PDWCIDPDWWCKFWGSGSATGGSGSTA SSGSGSATGPDWCIDPDWWCKFW	350
ANWCVSPNWFCMVMGSGSATGGSGSTA SSGSGSATGANWCVSPNWFCMVM	351
PDWCIDPDWWCKFWGSGSATGGSGSTA SSGSGSATGPDWCIDPDWWCKFW	352
HWACGYWPWSCKWVGSGSATGGSGST ASSGSGSATGHWACGYWPWSCKWV	353
KKHCQIWTWMCAPKGSGSATGGSGSTAS SGSGSATGQGHCTRWPWMCPPY	354
QGHCTRWPWMCPPYGSGSATGGSGSTAS SGSGSATGKKHCQIWTWMCAPK	355
KKHCQIWTWMCAPKGSGSATGGSGSTAS SGSGSATGQGHCTRWPWMCPPY	356
KKHCQIWTWMCAPKGGGGGGGGQGHC TRWPWMCPPY	357
QGHCTRWPWMCPPYGGGGGGKKHCQI WTWMCAPK	358
VALHGQCTRWPWMCPPQREG	359
YPEQGLCTRWPWMCPPQTLA	360
GLNQGHCTRWPWMCPPQDSN	361
MITQGQCTRWPWMCPPQPSG	362
AGAQEHCTRWPWMCAPNDWI	363
GVNQGQCTRWRWMCPPNGWE	364
LADHGQCIRWPWMCPPEGWE	365
ILEQAQCTRWPWMCPPQRGG	366
TQTHAQCTRWPWMCPPQWEG	367
VVTQGHCTLWPWMCPPQRWR	368
IYPHDQCTRWPWMCPPQPYP	369
SYWQGQCTRWPWMCPPQWRG	370
MWQQGHCTRWPWMCPPQGWG	371
EFTQWHCTRWPWMCPPQRSQ	372
LDDQWQCTRWPWMCPPQGFS	373
YQTQGLCTRWPWMCPPQSQR	374
ESNQGQCTRWPWMCPPQGGW	375

WTDRGPCTRWPWMCPPQANG	376
VGTQGQCTRWPWMCPPYETG	377
PYEQGKCTRWPWMCPPYEVE	378
SEYQGLCTRWPWMCPPQGWK	379
TFSQGHCTRWPWMCPPQGWG	380
PGAHDHCTRWPWMCPPQSRY	381
VAEEWHCRRWPWMCPPQDWR	382
VGTQGHCTRWPWMCPPQPAG	383
EEDQAHCRSWPWMCPPQGWV	384
ADTQGHCTRWPWMCPPQHWF	385
SGPQGHCTRWPWMCAPQGWF	386
TLVQGHCTRWPWMCPPQRWV	387
GMAHGKCTRWAWMCPPQSWK	388
ELYHGQCTRWPWMCPPQSWA	389
VADHGHCTRWPWMCPPQGWG	390
PESQGHCTRWPWMCPPQGWG	391
IPAHGHCTRWPWMCPPQRWR	392
FTVHGHCTRWPWMCPPYGWV	393
PDFPGHCTRWRWMCPPQGWE	394
QLWQGPCTQWPWMCPPKGRY	395
HANDGHCTRWQWMCPPQWGG	396
ETDHGLCTRWPWMCPPYGAR	397
GTWQGLCTRWPWMCPPQGWQ	398
VATQGQCTRWPWMCPPQGWG	399
VATQGQCTRWPWMCPPQRWG	400
QREWYPCYGGHLWCYDLHKA	401
ISAWYSCYAGHFWCWDLKQK	402
WTGWYQCYGGHLWCYDLRRK	403
KTFWYPCYDGHFWCYNLKSS	404
ESRWYPCYEGHLWCFDLTET	405
MEMLDSLFELLKDMVPISKA	406
RMEMLESLLELLKEIVPMSKAG	407
RMEMLESLLELLKEIVPMSKAR	408
RMEMLESLLELLKDIVPMSKPS	409
GMEMLESLFELLQEIVPMSKAP	410
RMEMLESLLELLKDIVPISNPP	411
RIEMLESLLELLQEIVPISKAE	412
RMEMLQSLLELLKDIVPMSNAR	413
RMEMLESLLELLKEIVPTSNGT	414
RMEMLESLFELLKEIVPMSKAG	415
RMEMLGSLLELLKEIVPMSKAR	416
QMELLDSLFELLKEIVPKSQPA	417
RMEMLDSLLELLKEIVPMSNAR	418
RMEMLESLLELLHEIVPMSQAG	419

QMEMLESLLQLLKEIVPMSKAS	420
RMEMLDSLLELLKDMVPMTTGA	421
RIEMLESLLELLKDMVPMANAS	422
RMEMLESLLQLLNEIVPMSRAR	423
RMEMLESLFDLLKELVPMSKGV	424
RIEMLESLLELLKDIVPIQKAR	425
RMELLESLFELLKDMVPMSDSS	426
RMEMLESLLEVLQEIVPRAKGA	427
RMEMLDSLLQLLNEIVPMSHAR	428
RMEMLESLLELLKDIVPMSNAG	429
RMEMLQSLFELLKGMVPISKAG	430
RMEMLESLLELLKEIVPNSTAA	431
RMEMLQSLLELLKEIVPISKAG	432
RIEMLDSLLELLNELVPMSKAR	433
HHGWNYLRKGSAPQWFEAWV	434
QVESLQQLLMWLDQKLASGPQG	435
RMELLESLFELLKEMVPRSKAV	436
QAVSLQHLLMWLDQKLASGPQH	437
DEDSLQQLLMWLDQKLASGPQL	438
PVASLQQLLIWLDQKLAQGPHA	439
EVDELQQLLNWLDHKLASGPLQ	440
DVESLEQLLMWLDHQLASGPHG	441
QVDSLQQVLLWLEHKLALGPQV	442
GDESLQHLLMWLEQKLALGPHG	443
QIEMLESLLDLLRDMVPMSNAF	444
EVDSLQQLLMWLDQKLASGPQA	445
EDESLQQLLIYLDKMLSSGPQV	446
AMDQLHQLLIWLDHKLASGPQA	447
RIEMLESLLELLDEIALIPKAW	448
EVVSLQHLLMWLEHKLASGPDG	449
GGESLQQLLMWLDQQLASGPQR	450
GVESLQQLLIFLDHMLVSGPHD	451
NVESLEHLMMWLERLLASGPYA	452
QVDSLQQLLIWLDHQLASGPKR	453
EVESLQQLLMWLEHKLAQGPQG	454
EVDSLQQLLMWLDQKLASGPHA	455
EVDSLQQLLMWLDQQLASGPQK	456
GVEQLPQLLMWLEQKLASGPQR	457
GEDSLQQLLMWLDQQLAAGPQV	458
ADDSLQQLLMWLDRKLASGPHV	459
PVDSLQQLLIWLDQKLASGPQG	460
RATLLKDFWQLVEGYGDN	461
DWRATLLKEFWQLVEGLGDNLV	462
QSRATLLKEFWQLVEGLGDKQA	463

DGRATLLTEFWQLVQGLGQKEA	464
LARATLLKEFWQLVEGLGEKVV	465
GSRDTLLKEFWQLVVGLGDMQT	466
DARATLLKEFWQLVDAYGDRMV	467
NDRAQLLRDFWQLVDGLGVKSW	468
GVRETLLYELWYLLKGLGANQG	469
QARATLLKEFCQLVGCQGDKLS	470
QERATLLKEFWQLVAGLGQNMR	471
SGRATLLKEFWQLVQGLGEYRW	472
TMRATLLKEFWLFVDGQREMQW	473
GERATLLNDFWQLVDGQGDNTG	474
DERETLLKEFWQLVHGWGDNVA	475
GGRATLLKELWQLLEGQGANLV	476
TARATLLNELVQLVKGYGDKLV	477
GMRATLLQEFWQLVGGQGDNWM	478
STRATLLNDLWQLMKGWAEDRG	479
SERATLLKELWQLVGGWGDNFG	480
VGRATLLKEFWQLVEGLVGQSR	481
EIRATLLKEFWQLVDEWREQPN	482
QLRATLLKEFLQLVHGLGETDS	483
TQRATLLKEFWQLIEGLGGKHV	484
HYRATLLKEFWQLVDGLREQGV	485
QSRVTLLREFWQLVESYRPIVN	486
LSRATLLNEFWQFVDGQRDKRM	487
WDRATLLNDFWHLMEELSQKPG	488
QERATLLKEFWRMVEGLGKNRG	489
NERATLLREFWQLVGGYGVNQR	490
YREMSMLEGLLDVLERLQHY	491
HQRDMSMLWELLDVLDGLRQYS	492
TQRDMSMLDGLLEVLDQLRQQR	493
TSRDMSLLWELLEELDRLGHQR	494
MQHDMSMLYGLVELLESLGHQI	495
WNRDMRMLESLFEVLDGLRQQV	496
GYRDMSMLEGLLAVLDRLGPQL	497
TQRDMSMLEGLLEVLDRLGQQR	498
WYRDMSMLEGLLEVLDRLGQQR	499
HNSSQMLLSELIMLVGSMMQ	500
TQNSRQMLLSDFMMLVGSMIQG	501
MQTSRHILLSEFMMLVGSIMHG	502
HDNSRQMLLSDLLHLVGTMIQG	503
MENSRQNLLRELIMLVGNMSHQ	504
QDTSRHMLLREFMMLVGEMIQG	505
DQNSRQMLLSDLMILVGSMIQG	506
EFFHWLHNHRSEVNHWLDMN	507

NVFFQWVQKHGRVVYQWLDINV	508
FDFLQWLQNHRSEVEHWLVMDV	509

Table 10. BAFF binding peptide sequences

SEQUENCE	SEQ ID NO:
PGTCFPFPWECTHA	510
WGACWPFPWECFKE	511
VPFCDLLTKHCFEA	512
GSRCKYKWDVLTKQCFHH	513
LPGCKWDLLIKQWVCDPL	514
SADCYFDILTKSDVCTSS	515
SDDCMYDQLTRMFICSNL	516
DLNCKYDELTYKEWCQFN	517
FHDCKYDLLTRQMVCHGL	518
RNHCFWDHLLKQDICPSP	519
ANQCWWDSLTKKNVCEFF	520
YKGRQQMWDILTRSWVVSL	521
QQDVGLWWDILTRAWMPNI	522
QQNAQRVWDLLIRTWVYPQ	523
GWNEAWWDELTKIWVLEQQ	524
RITCDTWDSLIKKCVPQQS	525
GAIMQQFWDSLTKTWLRQS	526
WLHSGWWDPLTKHWLQQKV	527
SEWFFWFDPLTRAQQLKFR	528
GVWFWWFDPLTKQWTQQAG	529
MQQCKGYYDILTKWCVTNG	530
LWSKEVWDILTKSWVSQQA	531
KAAGWWFDWLTKVWVPAP	532
AYQQTWFWDSLTRLWLSTT	533
SGQQHFWWDLLTRSWTPST	534
LGVGQQKWDPLTKQWVSRG	535
VGKMCQQWDPLIKRTVCVG	536
CRQGAKFDLLTKQCLLGR	537
GQAIRHWDVLTKQWVDSQQ	538
RGPCGSWDLLTKHCLDSQQ	539
WQWKQQQWDLLTKQMVWVG	540
PITICRKDLLTKQVVCLD	541
KTCNGKWDLLTKQCLQQQA	542
KCLKGKWDLLTKQCVTEV	543
RCWNGKWDLLTKQCIHPW	544
NRDMRKWDPLIKQWIVRP	545
QQAAAATWDLLTKQWLVPP	546

PEGGPKWDPLTKQQFLPPV	547
QQTPQQKKWDLLTKQWFTRN	548
IGSPCKWDLLTKQMICQQT	549
CTAAGKWDLLTKQCIQQEK	550
VSQCMKWDLLTKQCLQQGW	551
VWGTWKWDLLTKQYLPPQQ	552
GWWEMKWDLLTKQWYRPQQ	553
TAQQVSKWDLLTKQWLPLA	554
QLWGTKWDLLTKQYIQQIM	555
WATSQKWDLLTKQWVQQNM	556
QQRQCAKWDLLTKQCVLFY	557
KTTDCKWDLLTKQRICQQV	558
LLCQQGKWDLLTKQCLKLR	559
LMWFWKWDLLTKQLVPTF	560
QQTWAWKWDLLTKQWIGPM	561
NKELLKWDLLTKQCRGRS	562
GQQKDLKWDLLTKQYVRQS	563
PKPCQQKWDLLTKQCLGSV	564
GQIGWKWDLLTKQWIQQTR	565
VWLDWKWDLLTKQWIHPQQ	566
QQEWEYKWDLLTKQWGWLR	567
HWDSWKWDLLTKQWVVQQA	568
TRPLQQKWDLLTKQWLRVG	569
SDQWQQKWDLLTKQWFWDV	570
QQQTFMKWDLLTKQWIRRH	571
QQGECRKWDLLTKQCFPGQ	572
GQQMGWRWDPLIKMCLGPS	573
QQLDGCKWDLLTKQKVCIP	574
HGYWQQKWDLLTKQWVSSE	575
HQQGQCGWDLLTRIYLPCH	576
LHKACKWDLLTKQCWPMQQ	577
GPPGSVWDLLTKIWIQQTG	578
ITQQDWRFDTLTRLWLPLR	579
QQGGFAAWDVLTKMWITVP	580
GHGTPWWDALTRIWILGV	581
VWPWQQKWDLLTKQFVFQD	582
WQQWSWKWDLLTRQYISSS	583
NQQTLWKWDLLTKQFITYM	584
PVYQQGWWDTLTKLYIWDG	585
WLDGGWRDPLIKRSVQQLG	586
GHQQQFKWDLLTKQWVQSN	587
QQRVGQFWDVLTKMFITGS	588
QQAQGWSYDALIKTWIRWP	589
GWMHWKWDPLTKQQALPWM	590

GHPTYKWDLLTKQWILQQM	591
WNNWSLWDPLTKLWLQQQN	592
WQWGWKWDLLTKQWVQQQ	593
GQMGWRWDPLTKMWLGTS	594

In addition to peptides and polypeptides having amino acid sequences set forth in Tables 5-10, polypeptides that can be useful in accordance with the invention include the Ang-2 binding polypeptide having amino acid sequence SEQ ID NO: 612:

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Glu His Met Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys// SEQ ID NO:612;

And the myostatin binding polypeptide having amino acid sequence SEQ ID NO: 613:

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro Glu Gly Trp Glu Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys//SEQ ID NO: 613;

And the EPO-mimetic polypeptide having amino acid sequence SEQ ID NO: 614:

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys// SEQ ID NO: 614;

And the TPO-mimetic polypeptide having amino acid sequence SEQ ID NO: 615:

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys// SEQ ID NO: 615.

Pharmaceutically acceptable polymers. The invention further embraces molecules covalently modified to include one or more water soluble polymer attachments. Pharmaceutically acceptable polymers useful in accordance with the present invention include, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol, as described U.S. Patent Nos.: 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; and 4,179,337. Still other useful polymers known in the art include, but are not limited to, monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers (e.g., hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose), poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) polyvinyl alcohol, polylactic acid, polyglycolic acid, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl pyrrolidone and polyproline, hyaluronic acid, poly-1,3-dioxolane and poly-1,3,6-tioxocane, pectin, starch, gelatin, as well as mixtures of any of these polymers.

A preferred polymer is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kD, more preferably from about 5 kDa to about 50 kDa, most preferably from about 5 kD to about 20 kD. The PEG groups will generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, maleimide, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, thiol or ester group).

Covalent conjugation of proteins and peptides with poly(ethylene glycol) (PEG) has been widely recognized as an approach to significantly extend the *in vivo* circulating half-lives of therapeutic proteins. PEGylation achieves this effect predominately by retarding renal clearance, since the PEG moiety adds considerable hydrodynamic radius to the protein. (Zalipsky, S., et al., Use of functionalized poly(ethylene glycol)s for modification of polypeptides., in poly(ethylene glycol) chemistry: Biotechnical and biomedical applications., J.M. Harris, Ed., Plenum Press: New York., 347-370 (1992)). Additional benefits often conferred by PEGylation of proteins and peptides include increased solubility, resistance to proteolytic degradation, and reduced immunogenicity of the therapeutic polypeptide. The merits of protein PEGylation are evidenced by the commercialization of several PEGylated proteins including PEG-Adenosine deaminase (Adagen™/Enzon Corp.), PEG-L-asparaginase (Oncaspar™/Enzon Corp.), PEG-Interferon α-2b (PEG-Intron™/Schering/Enzon), PEG-Interferon α-2a (PEGASYS™/Roche) and PEG-G-CSF (Neulasta™/Amgen) as well as many others in clinical trials.

Briefly, the PEG groups are generally attached to the peptide portion of the composition of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a polypeptide or peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The polypeptides or peptides can be easily prepared with conventional solid phase synthesis. The polypeptides or peptides are "preactivated" with an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the polypeptide or peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated polypeptides or peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

PEG is a well-known, water soluble polymer that is commercially available or can be prepared by ring-opening polymerization of ethylene glycol according to methods well known in the art (Sandler and Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, pages 138-161). In the present application, the term "PEG" is used broadly to encompass any polyethylene glycol molecule, in mono-, bi-, or poly- functional form, without regard to size or to modification at an end of the PEG, and can be represented by the formula:

$$X\text{-}O(CH_2CH_2O)_{n-1}CH_2CH_2OH, \qquad \text{(XXIX)}$$

where n is 20 to 2300 and X is H or a terminal modification, e.g., a C_{1-4} alkyl.

In some useful embodiments, a PEG used in the invention terminates on one end with hydroxy or methoxy, i.e., X is H or CH_3 ("methoxy PEG"). It is noted that the other end of the PEG, which is shown in formula (II) terminating in OH, covalently attaches to an activating moiety via an ether oxygen bond, an amine linkage, or amide linkage. When used in a chemical structure, the term

"PEG" includes the formula (II) above without the hydrogen of the hydroxyl group shown, leaving the oxygen available to react with a free carbon atom of a linker to form an ether bond. More specifically, in order to conjugate PEG to a peptide, the peptide must be reacted with PEG in an "activated" form. Activated PEG can be represented by the formula:

$$(PEG)\text{-}(A) \qquad (XXX)$$

where PEG (defined *supra*) covalently attaches to a carbon atom of the activation moiety (A) to form an ether bond, an amine linkage, or amide linkage, and (A) contains a reactive group which can react with an amino, imino, or thiol group on an amino acid residue of a polypeptide, peptide or a linker moiety covalently attached to the peptide portion.

Techniques for the preparation of activated PEG and its conjugation to biologically active peptides are well known in the art. (E.g., see U.S. Pat. Nos. 5,643,575, 5,919,455, 5,932,462, and 5,990,237; Thompson et al., PEGylation of polypeptides, EP 0575545 B1; Petit, Site specific protein modification, US Patent Nos. 6,451,986, and 6,548,644; S. Herman et al., Poly(ethylene glycol) with reactive endgroups: I. Modification of proteins, J. Bioactive Compatible Polymers, 10:145-187 (1995); Y. Lu et al., Pegylated peptides III: Solid-phase synthesis with PEGylating reagents of varying molecular weight: synthesis of multiply PEGylated peptides, Reactive Polymers, 22:221-229 (1994); A.M. Felix et al., PEGylated Peptides IV: Enhanced biological activity of site-directed PEGylated GRF analogs, Int. J. Peptide Protein Res., 46:253-264 (1995); A.M. Felix, Site-specific poly(ethylene glycol)ylation of peptides, ACS Symposium Series 680(poly(ethylene glycol)): 218-238 (1997); Y. Ikeda et al., Polyethylene glycol derivatives, their modified peptides, methods for producing them and use of the modified peptides, EP 0473084 B1; G.E. Means et al., Selected techniques for the modification of protein side chains, in: Chemical modification of proteins, Holden Day, Inc., 219 (1971)).

Activated PEG, such as PEG-aldehydes or PEG-aldehyde hydrates, can be chemically synthesized by known means or obtained from commercial sources, e.g., Shearwater Polymers, (Huntsville, AL) or Enzon, Inc. (Piscataway, NJ).

An example of a useful activated PEG for purposes of the present invention is a PEG-aldehyde compound (e.g., a methoxy PEG-aldehyde), such as PEG-propionaldehyde, which is commercially available from Shearwater Polymers (Huntsville, Al). PEG-propionaldehyde is represented by the formula PEG-CH_2CH_2CHO. (See, e.g., U.S. Pat. No. 5,252,714). Other examples of useful activated PEG are PEG acetaldehyde hydrate and PEG bis aldehyde hydrate, which latter yields a bifunctionally activated structure. (See., e.g., Bentley et al., Poly(ethylene glycol) aldehyde hydrates and related polymers and applications in modifying amines, US Patent No. 5,990,237).

Another useful activated PEG for generating PEG-conjugated polypeptides or peptides of the present invention is a PEG-maleimide compound, such as, but not limited to, a methoxy PEG-maleimide, such as maleimido monomethoxy PEG, are particularly useful for generating the PEG-conjugated peptides of the invention. (E.g., Shen, *N*-maleimidyl polymer derivatives, US Patent No. 6,602,498; C. Delgado et al., The uses and properties of PEG-linked proteins., Crit. Rev. Therap. Drug Carrier Systems, 9:249-304 (1992); S. Zalipsky et al., Use of functionalized poly(ethylene glycol)s for modification of polypeptides, in: Poly(ethylene glycol) chemistry: Biotechnical and biomedical applications (J.M. Harris, Editor, Plenum Press: New York, 347-370 (1992); S. Herman et al., Poly(ethylene glycol) with reactive endgroups: I. Modification of proteins, J. Bioactive Compatible Polymers, 10:145-187 (1995); P.J. Shadle et al., Conjugation of polymer to colony stimulating factor-1, U.S. Patent No. 4,847,325; G. Shaw et al., Cysteine added variants IL-3 and chemical modifications thereof, U.S. Patent No. 5,166,322 and EP 0469074 B1; G. Shaw et al., Cysteine added variants of EPO and chemical modifications thereof, EP 0668353 A1; G. Shaw et al., Cysteine added variants G-CSF and chemical modifications thereof, EP 0668354 A1; N.V. Katre et al., Interleukin-2 muteins and polymer conjugation thereof, U.S. Patent No. 5,206,344; R.J. Goodson and N.V. Katre, Site-directed pegylation of recombinant interleukin-2 at its glycosylation site, Biotechnology, 8:343-346 (1990)).

A poly(ethylene glycol) vinyl sulfone is another useful activated PEG for generating the PEG-conjugated peptides of the present invention by conjugation at thiolated amino acid residues, e.g., at C residues. (E.g., M. Morpurgo et al., Preparation and characterization of poly(ethylene glycol) vinyl sulfone, Bioconj. Chem., 7:363-368 (1996); see also Harris, Functionalization of polyethylene glycol for formation of active sulfone-terminated PEG derivatives for binding to proteins and biologically compatible materials, U.S. Patent Nos. 5,446,090; 5,739,208; 5,900,461; 6,610,281 and 6,894,025; and Harris, Water soluble active sulfones of poly(ethylene glycol), WO 95/13312 A1).

Another activated form of PEG that is useful in accordance with the present invention, is a PEG-N-hydroxysuccinimide ester compound, for example, methoxy PEG-N-hydroxysuccinimidyl (NHS) ester.

Heterobifunctionally activated forms of PEG are also useful. (See, e.g., Thompson et al., PEGylation reagents and biologically active compounds formed therewith, U.S. Patent No. 6,552,170).

Typically, a polypeptide or peptide of interest is reacted by known chemical techniques with an activated PEG compound, such as but not limited to, a thiol-activated PEG compound, a diol-activated PEG compound, a PEG-hydrazide compound, a PEG-oxyamine compound, or a PEG-bromoacetyl compound. (See, e.g., S. Herman, Poly(ethylene glycol) with Reactive Endgroups: I. Modification of Proteins, J. Bioactive and Compatible Polymers, 10:145-187 (1995); S. Zalipsky, Chemistry of Polyethylene Glycol Conjugates with Biologically Active Molecules, Advanced Drug Delivery Reviews, 16:157-182 (1995); R. Greenwald et al., Poly(ethylene glycol) conjugated drugs and prodrugs: a comprehensive review, Critical Reviews in Therapeutic Drug Carrier Systems, 17:101-161 (2000)).

Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextrans are polysaccharide polymers comprised of individual subunits of glucose predominantly linked by α1-6 linkages The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention by itself or in combination with a different additional functional moiety(e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference. Dextran of about 1 kD to about 20 kD is preferred when dextran is used in accordance with the present invention.

Linkers. Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer, which can be useful in optimizing pharamcologial activity of some embodiments of the inventive composition. The linker is preferably made up of amino acids linked together by peptide bonds. As stated herein above, the linker moiety, if present, can be independently the same or different from any other linker, or linkers, that may be present in the inventive composition. For example, an "$(L)_c$" can represent the same linker moiety as, or a different linker moiety from, any other "$(L)_c$ " or any "$(L)_d$", "$(L)_e$", or "$(L)_f$", in accordance with the invention. The linker is preferably made up of amino acids linked together by peptide bonds. Thus, in some embodiments, the linker is made up of from 1 to about 30 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. Some of these amino acids may be glycosylated, as is well understood by those in the art. For example, a useful linker sequence constituting a sialylation site is $X_1X_2NX_4X_5G$ (SEQ ID NO: 619), wherein X_1, X_2,X_4 and X_5 are each independently any amino acid residue.

In a more preferred embodiment, the 1 to 30 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Even more preferably, a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, preferred linkers include polyglycines (particularly (Gly)4, (Gly)5), poly(Gly-Ala), and polyalanines. Other preferred linkers are those identified herein as "L5" (GGGGS; SEQ ID NO:

620), "L10" (GGGGSGGGGS; SEQ ID NO: 621), "L25" GGGGSGGGGSGGGGSGGGGSGGGGS; SEQ ID NO: 622) and any linkers used in the working examples hereinafter. The linkers described herein, however, are exemplary; linkers within the scope of this invention can be much longer and can include other residues. Thus, preferred linkers are polyglycines (particularly $(Gly)_4$, $(Gly)_5$), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 595);
$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 596);
$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 597); and
GlyProAsnGlyGly (SEQ ID NO: 598).

To explain the above nomenclature, for example, $(Gly)_3Lys(Gly)_4$ means Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly. Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary; linkers within the scope of this invention may be much longer and may include other residues.

In some embodiments of the compositions of this invention, which comprise a peptide linker moiety (L), acidic residues, for example, glutamate or aspartate residues, are placed in the amino acid sequence of the linker moiety (L). Examples include the following peptide linker sequences:

GGEGGG (SEQ ID NO: 623);
GGEEEGGG (SEQ ID NO: 624);
GEEEG (SEQ ID NO: 625);
GEEE (SEQ ID NO: 626);
GGDGGG (SEQ ID NO: 627);
GGDDDGG (SEQ ID NO: 628);
GDDDG (SEQ ID NO: 629);
GDDD (SEQ ID NO: 630);
GGGGSDDSDEGSDGEDGGGGS (SEQ ID NO: 631);
WEWEW (SEQ ID NO: 632);
FEFEF (SEQ ID NO: 633);
EEEWWW (SEQ ID NO: 634);

EEEFFF (SEQ ID NO: 635);

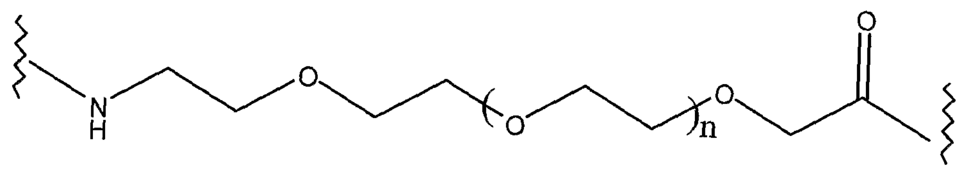
WWEEEWW (SEQ ID NO: 636); or

FFEEEFF (SEQ ID NO: 637).

In other embodiments, the linker constitutes a phosphorylation site, e.g., $X_1X_2YX_3X_4G$ (SEQ ID NO: 638), wherein X_1, X_2,X_3 and X_4 are each independently any amino acid residue; $X_1X_2SX_3X_4G$ (SEQ ID NO: 639), wherein X_1, X_2,X_3 and X_4 are each independently any amino acid residue; or $X_1X_2TX_3X_4G$ (SEQ ID NO: 640), wherein X_1, X_2,X_3 and X_4 are each independently any amino acid residue.

Non-peptide linkers are also possible. For example, alkyl linkers such as -NH-$(CH_2)_s$-C(O)-, wherein s = 2-20 could be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2, phenyl, etc. An exemplary non-peptide linker is a PEG linker,

(XXXI)



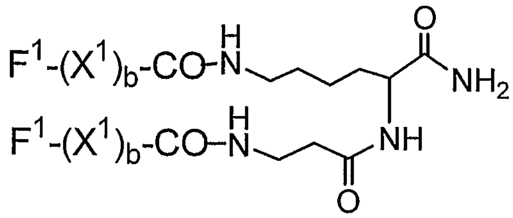
wherein n is such that the linker has a molecular weight of 100 to 5000 kD, preferably 100 to 500 kD. The peptide linkers may be altered to form derivatives in the same manner as described above.

Derivatives. The compositions of matter of the present invention also encompass "derivatives" that include polypeptide or peptide portions bearing modifications other than, or in addition to, insertions, deletions, or substitutions of amino acid residues. Preferably, the modifications are covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Derivatives of the invention may be prepared to increase circulating half-life of a molecule; to improve targeting capacity for the molecule to desired cells, tissues, or organs; to improve the solubility or absorption of a molecule; or to eliminate or attenuate any undesirable side-effect of a molecule.

Exemplary derivatives include compounds in which:

1. The compound or some portion thereof is cyclic. For example, the peptide portion may be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation.
2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound may also be cross-linked through its C-terminus, as in the molecule shown below.

(XXXII)



3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH_2-carbamate [-CH_2-OC(O)NR-], phosphonate , -CH_2-sulfonamide [-CH_2-$S(O)_2$NR-], urea [-NHC(O)NH-], -CH_2-secondary amine, and alkylated peptide [-C(O)NR^6- wherein R^6 is lower alkyl].
4. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR^1 (other than -NH_2), -NRC(O)R^1, -NRC(O)OR^1, -NRS$(O)_2R^1$, -NHC(O)NHR^1, succinimide, or benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R^1 are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, chloro, and bromo.
5. The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated. For example, one may use methods described in the art to add (NH-CH_2-CH_2-$NH_2)_2$ to compounds of this invention. Likewise, one may use methods described in the art to add -NH_2 to compounds of this invention. Exemplary C-terminal derivative groups include, for example, -C(O)R^2 wherein R^2 is lower alkoxy or -NR^3R^4 wherein R^3 and R^4 are independently hydrogen or C_1-C_8 alkyl (preferably C_1-C_4 alkyl).
6. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9; Alberts et al. (1993) Thirteenth Am. Pep. Symp., 357-9.

7. One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected side chains or terminal residues, as described in detail below.

Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl side chain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R'-N=C=N-R') such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9.

Derivatization with bifunctional agents is useful for cross-linking the peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins. Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

Such derivatized moieties preferably improve one or more characteristics including anti-angiogenic activity, solubility, absorption, biological half life, and the like of the compounds. Alternatively, derivatized moieties may result in compounds that have the same, or essentially the same, characteristics and/or properties of the compound that is not derivatized. The moieties may alternatively eliminate or attenuate any undesirable side effect of the compounds and the like.

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence encoding any portion of the compound may be changed to codons more compatible with the chosen host cell. For E. coli, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

Isotope- and toxin-conjugated derivatives. Another set of useful derivatives are the above-described molecules conjugated to toxins, tracers, or radioisotopes. Such conjugation is especially useful for molecules comprising peptide sequences that bind to tumor cells or pathogens. Such molecules may be used as therapeutic agents or as an aid to surgery (e.g., radioimmunoguided surgery or RIGS) or as diagnostic agents (e.g., radioimmunodiagnostics or RID).

As therapeutic agents, these conjugated derivatives possess a number of advantages. They facilitate use of toxins and radioisotopes that would be toxic if administered without the specific binding provided by the peptide sequence. They also can reduce the side-effects that attend the use of radiation and chemotherapy by facilitating lower effective doses of the conjugation partner.

Useful conjugation partners include:

- radioisotopes, such as ^{90}Yttrium, ^{131}Iodine, ^{225}Actinium, and ^{213}Bismuth;
- ricin A toxin, microbially derived toxins such as Pseudomonas endotoxin (e.g., PE38, PE40), and the like;
- partner molecules in capture systems (see below);
- biotin, streptavidin (useful as either partner molecules in capture systems or as tracers, especially for diagnostic use); and
- cytotoxic agents (e.g., doxorubicin).

One useful adaptation of these conjugated derivatives is use in a capture system. In such a system, the molecule of the present invention would comprise a benign capture molecule. This capture molecule would be able to specifically bind to a separate effector molecule comprising, for example, a toxin or radioisotope. Both the vehicle-conjugated molecule and the effector molecule would be administered to the patient. In such a system, the effector molecule would have a short half-life except when bound to the vehicle-conjugated capture molecule, thus minimizing any toxic side-effects. The vehicle-conjugated molecule would have a relatively long half-life but would be benign and non-toxic. The specific binding portions of both molecules can be part of a known specific binding pair (e.g., biotin, streptavidin) or can result from peptide generation methods such as those described herein.

Such conjugated derivatives may be prepared by methods known in the art. In the case of protein effector molecules (e.g., Pseudomonas endotoxin), such molecules can be expressed as fusion proteins from correlative DNA constructs. Radioisotope conjugated derivatives may be prepared, for example, as described for the BEXA antibody (Coulter). Derivatives comprising cytotoxic agents or microbial toxins may be prepared, for example, as described for the BR96 antibody (Bristol-Myers Squibb). Molecules employed in capture systems may be prepared, for example, as described by the patents, patent applications, and publications from NeoRx. Molecules employed for RIGS and RID may be prepared, for example, by the patents, patent applications, and publications from NeoProbe.

Preparing a peptide derivative for conjugation to a Fc domain in accordance with the present invention can be useful. Tumor cells, for example, exhibit epitopes not found on their normal counterparts. Such epitopes include, for example, different post-translational modifications resulting from their rapid proliferation. Thus, one aspect of this invention is a process comprising:

a) selecting at least one randomized peptide that specifically binds to a target epitope; and

b) preparing a pharmacologic agent comprising (i) at least one Fc domain monomer, (ii) at least one amino acid sequence of the selected peptide or peptides, and (iii) an effector molecule.

The target epitope is preferably a tumor-specific epitope or an epitope specific to a pathogenic organism. The effector molecule may be any of the above-noted conjugation partners and is preferably a radioisotope.

Variants. Variants of polypeptide or peptide portions of the inventive composition of matter (e.g., additional functional moiety, linker, or Fc domain portions), are also included within the scope of the present invention. Included within variants are insertional, deletional, and substitutional variants. It is understood that a particular molecule of the present invention may contain one, two or all three types of variant polypeptides or peptides. Insertional and substitutional variants may contain canonical amino acids, non-canonical amino acids (as set forth herein), or both. It is also understood that, in accordance with the present invention, polypeptide or peptide variants can be made before chemical conjugation to an Fc domain or can be designed to be expressed as part of a fusion protein with the Fc domain, as desired in various embodiments of the inventive composition of matter.

In one example, insertional variants are provided wherein one or more amino acid residues, either naturally occurring or unconventional amino acids, supplement a peptide or a polypeptide amino acid sequence. Insertions may be located at either or both termini, or may be positioned within internal regions of the amino acid sequence. Insertional variants with additional residues at either or both termini can include, for example, fusion proteins and proteins including amino acid tags or labels. Insertional variants include peptides and peptibodies wherein one or more amino acid residues are added to the peptide or polypeptide amino acid sequence, or fragment thereof.

Variants of the invention also include mature peptides and polypeptides wherein leader or signal sequences are removed, and the resulting proteins having additional amino terminal residues, which amino acids may be natural or non-natural. Molecules of this invention (such as peptibodies) with an additional methionyl residue at amino acid position -1 (Met^{-1}-peptibody) are contemplated, as are specific binding agents with additional methionine and lysine residues at positions -2 and -1 (Met^{-2}-Lys^{-1}-) conjugated to Fc domain as additional moieties in accordance with the invention. Variants having additional Met, Met-Lys, Lys residues (or one or more basic residues, in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

The invention also embraces variants having additional amino acid residues that arise from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at amino acid position -1 after cleavage of the GST component from the desired polypeptide. Variants which result from expression in other vector systems are also contemplated, including those wherein poly-histidine tags are incorporated into the amino acid sequence, generally at the carboxy and/or amino terminus of the sequence.

Insertional variants also include fusion proteins wherein the amino and/or carboxy termini of the peptide or peptibody is fused to another polypeptide, a fragment thereof or amino acids which are not generally recognized to be part of any specific protein sequence. Examples of such fusion proteins are immunogenic polypeptides, proteins with long circulating half lives, such as immunoglobulin constant regions, marker proteins, proteins or polypeptides that facilitate purification of the desired peptide or peptibody, and polypeptide sequences that promote formation of multimeric proteins (such as leucine zipper motifs that are useful in dimer formation/stability).

This type of insertional variant generally has all or a substantial portion of the native molecule, linked at the N- or C-terminus, to all or a portion of a second polypeptide. For example, fusion proteins typically employ leader sequences from other species to permit the recombinant expression of a protein in a heterologous host. Another useful fusion protein includes the addition of an immunologically active domain, such as an antibody epitope, to facilitate purification of the fusion protein. Inclusion of a cleavage site at or near the fusion junction will facilitate removal of the extraneous polypeptide after purification. Other useful fusions include linking of functional domains, such as active sites from enzymes, glycosylation domains, cellular targeting signals or transmembrane regions.

There are various commercially available fusion protein expression systems that may be used in the present invention. Particularly useful systems include but are not limited to the glutathione-S-transferase (GST) system (Pharmacia), the maltose binding protein system (NEB, Beverley, MA), the FLAG system (IBI, New Haven, CT), and the 6xHis system (Qiagen, Chatsworth, CA). These systems are capable of producing recombinant peptides and/or peptibodies bearing only a small number of additional amino acids, which are unlikely to significantly affect the activity of the peptide or peptibody. For example, both the FLAG system and the 6xHis system add only short sequences, both of which are known to be poorly antigenic and which do not adversely affect folding of a polypeptide to its native conformation. Another N-terminal fusion that is contemplated to be useful is the fusion of a Met-Lys dipeptide at the N-terminal region of the protein or peptides. Such a fusion may produce beneficial increases in protein expression or activity.

Other fusion systems produce polypeptide hybrids where it is desirable to excise the fusion partner from the desired peptide or peptibody. In one embodiment, the fusion partner is linked to the recombinant peptibody by a peptide sequence containing a specific recognition sequence for a protease.

Examples of suitable sequences are those recognized by the Tobacco Etch Virus protease (Life Technologies, Gaithersburg, MD) or Factor Xa (New England Biolabs, Beverley, MA).

In some embodiments of the inventive composition of matter, fusion polypeptides comprise all or part.of the molecule, in combination with truncated tissue factor (tTF). tTF is a vascular targeting agent consisting of a truncated form of a human coagulation-inducing protein that acts as a tumor blood vessel clotting agent, as described U.S. Patent Nos.: 5,877,289; 6,004,555; 6,132,729; 6,132,730; 6,156,321; and European Patent No. EP 0988056. The fusion of tTF to the anti-Ang-2 peptibody or peptide, or fragments thereof facilitates the delivery of anti-Ang-2 to target cells.

In some embodiments of the present invention,, deletion variants can be useful, wherein one or more amino acid residues in a peptide or polypeptide portion of the composition of matter are removed. Deletions can be effected at one or both termini of the polypeptide or peptide portion, or from removal of one or more non-terminal residues within the amino acid sequence. Deletion variants necessarily include all fragments of a peptide or polypeptide portion of the inventive composition of matter.

In other embodiments of the present invention, substitution variants can be useful. Substitution variants include those peptides and polypeptide portions wherein one or more amino acid residues are removed and replaced with one or more alternative amino acids, which amino acids may be naturally occurring or non-naturally occurring. Substitutional variants generate peptides or polypeptides that are “similar” to the original peptide or polypeptide, in that the two have sequences with a certain percentage of amino acids that are identical. Substitution variants include substitutions of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, amino acids within a peptide or peptibody, wherein the number of substitutions may be up to ten percent or more, of the amino acids of the peptide or peptibody. The substitutions can be conservative in nature, however, the invention embraces substitutions that are also non-conservative and also includes non-canonical amino acids.

Identity and similarity of related peptides and peptibodies can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York (1988); Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York (1993); Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey (1994); Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press (1987); Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York (1991); and Carillo et al., SIAM J. Applied Math., 48:1073 (1988).

Preferred methods to determine the relatedness or percent identity of two peptides or polypeptides, or a polypeptide and a peptide, are designed to give the largest match between the sequences tested. Methods to determine identity are described in publicly available computer programs. Preferred computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, including GAP (Devereux et al., Nucl. Acid. Res., 12:387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI, BLASTP, BLASTN, and FASTA (Altschul et al., J. Mol. Biol., 215:403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul et al. NCB/NLM/NIH Bethesda, MD 20894; Altschul et al., supra (1990)). The well-known Smith Waterman algorithm may also be used to determine identity.

Certain alignment schemes for aligning two amino acid sequences may result in the matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, in certain embodiments, the selected alignment method (GAP program) will result in an alignment that spans at least ten percent of the full length of the target polypeptide being compared, i.e., at least 40 contiguous amino acids where sequences of at least 400 amino acids are being compared, 30 contiguous amino acids where sequences of at least 300 to about 400 amino acids are being compared, at least 20 contiguous amino acids where sequences of 200 to about 300 amino acids are being compared, and at least 10 contiguous amino acids where sequences of about 100 to 200 amino acids are being compared.

For example, using the computer algorithm GAP (Genetics Computer Group, University of Wisconsin, Madison, WI), two polypeptides for which the percent sequence identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span", as determined by the algorithm). In certain embodiments, a gap opening penalty (which is typically calculated as 3X the average diagonal; the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, one may also use a standard comparison matrix in the algorithm, See Dayhoff et al., Atlas of Protein Sequence and Structure, 5(3)(1978) for the PAM 250 comparison matrix; and Henikoff et al., Proc. Natl. Acad. Sci USA, 89:10915-10919 (1992) for the BLOSUM 62 comparison matrix.

In certain embodiments, the parameters for a polypeptide sequence comparison include the following:

Algorithm: Needleman et al., J. Mol. Biol., 48:443-453 (1970);

Comparison matrix: BLOSUM 62 from Henikoff et al., supra (1992);

Gap Penalty: 12

Gap Length Penalty: 4

Threshold of Similarity: 0

The GAP program may be useful with the above parameters. In certain embodiments, the aforementioned parameters are the default parameters for polypeptide comparisons (along with no penalty for end gaps) using the GAP algorithm.

In certain embodiments, the parameters for polynucleotide molecule sequence (as opposed to an amino acid sequence) comparisons include the following:

Algorithm: Needleman <u>et al.</u>, <u>supra</u> (1970);

Comparison matrix: matches = +10, mismatch = 0

Gap Penalty: 50

Gap Length Penalty: 3

The GAP program may also be useful with the above parameters. The aforementioned parameters are the default parameters for polynucleotide molecule comparisons.

Other exemplary algorithms, gap opening penalties, gap extension penalties, comparison matrices, thresholds of similarity, etc. may be used, including those set forth in the Program Manual, Wisconsin Package, Version 9, September, 1997. The particular choices to be made will be apparent to those of skill in the art and will depend on the specific comparison to be made, such as DNA-to-DNA, protein-to-protein, protein-to-DNA; and additionally, whether the comparison is between given pairs of sequences (in which case GAP or BestFit are generally preferred) or between one sequence and a large database of sequences (in which case FASTA or BLASTA are preferred).

It will be appreciated that amino acid residues can be divided into classes based on their common side chain properties:

1. <u>Neutral Hydrophobic</u>: Alanine (Ala; A), Valine (Val; V), Leucine (Leu; L), Isoleucine (Ile; I), Proline (Pro; P), Tryptophan (Trp; W), Phenylalanine (Phe; F), and Methionine (Met, M).

2. Neutral Polar: Glycine (Gly; G); Serine (Ser; S), Threonine (Thr; T), Tyrosine (Tyr; Y), Cysteine (Cys; C), Glutamine (Glu; Q), Asparagine (Asn; N), and Norleucine.

3. Acidic: Aspartic Acid (Asp; D), Glutamic Acid (Glu; E);

4) Basic: Lysine (Lys; K), Arginine (Arg; R), Histidine (His; H).

See Lewin, B., Genes V, Oxford University Press (1994), p.11.

Conservative amino acid substitutions may encompass unconventional amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include, without limitation, peptidomimetics and other reversed or inverted forms of amino acid moieties. Non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class.

In making such changes, according to certain embodiments, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., J. Mol. Biol., 157:105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ±2 is included. In certain embodiments, those which are within ±1 are included, and in certain embodiments, those within ±0.5 are included.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional peptibody or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ±2 is included, in certain embodiments, those which are within ±1 are included, and in certain embodiments, those within ±0.5 are included. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

Exemplary amino acid substitutions are set forth in Table 11 below.

Table 11. Amino Acid Substitutions

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln, Glu, Asp	Gln
Asp	Glu, Gln, Asp	Glu
Cys	Ser, Ala	Ser
Gln	Asn, Glu, Asp	Asn
Glu	Asp, Gln, Asn	Asp

Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

A skilled artisan will be able to determine suitable variants of useful polypeptide or peptides as set forth herein using well-known techniques. In certain embodiments, one skilled in the art may identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. In certain embodiments, one can identify residues and portions of the molecules that are conserved among similar peptides or polypeptides. In certain embodiments, one may even subject areas important for biological activity or for structure to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art may predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. In certain embodiments, one skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such variants could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change may be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., Curr. Op. in Biotech., 7(4):422-427 (1996), Chou et al., Biochemistry, 13(2):222-245 (1974); Chou et al., Biochemistry, 113(2):211-222 (1974); Chou et al., Adv. Enzymol. Relat. Areas Mol. Biol., 47:45-148 (1978); Chou et al., Ann. Rev. Biochem., 47:251-276 and Chou et al., Biophys. J., 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins that have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., Nucl. Acid. Res., 27(1): 244-247 (1999). It has been suggested (Brenner et al., Curr. Op. Struct. Biol., 7(3): 369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

Additional methods of predicting secondary structure include "threading" (Jones, D., Curr. Opin. Struct. Biol., 7(3):377-87 (1997); Sippl et al., Structure, 4(1):15-19 (1996)), "profile analysis" (Bowie et al., Science, 253:164-170 (1991); Gribskov et al., Meth. Enzym., 183:146-159 (1990); Gribskov et al., Proc. Nat. Acad. Sci., 84(13):4355-4358 (1987)), and "evolutionary linkage" (See Holm, supra (1999), and Brenner, supra (1997)).

In certain embodiments, peptibody variants include glycosylation variants wherein one or more glycosylation sites, such as a N-linked glycosylation site, has been added to the peptibody. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. The substitution or addition of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created.

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be changed to codons more compatible with the chosen host cell. For E. coli, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected host cell. The Fc domain-, linker-, polypeptide-, and/or peptide-encoding DNA sequences may be modified to include any of the foregoing sequence changes. Thus, all modifications, substitution, derivitizations, etc. discussed herein apply equally to all polypeptide or peptide portions of the inventive composition of matter.

One embodiment of the present invention includes "affinity matured" peptides and polypeptide portions, including peptibody embodiments. This procedure contemplates increasing the affinity or the bio-activity of the peptides and ppolypeptides using phage display or other selection technologies. Based on a consensus sequence (which is generated for a collection of related peptides), directed secondary phage display libraries can be generated in which the "core" amino acids (determined from the consensus sequence) are held constant or are biased in frequency of occurrence. Alternatively, an individual peptide sequence can be used to generate a biased, directed phage display library. Panning of such libraries can yield peptides (which can be converted to peptibodies) with enhanced binding to the target or with enhanced bio-activity.

Non-Peptide Analogs/Protein Mimetics. Furthermore, non-peptide analogs of peptides that provide a stabilized structure or lessened biodegradation, are also useful. Peptide mimetic analogs can be prepared based on a selected inhibitory peptide by replacement of one or more residues by nonpeptide moieties. Preferably, the nonpeptide moieties permit the peptide to retain its natural confirmation, or stabilize a preferred, e.g., bioactive, confirmation which retains the ability to recognize and bind Ang-2. In one aspect, the resulting analog/mimetic exhibits increased binding affinity for Ang-2. One example of methods for preparation of nonpeptide mimetic analogs from peptides is described in Nachman et al., Regul. Pept. 57:359-370 (1995). If desired, the peptides of the invention can be modified, for instance, by glycosylation, amidation, carboxylation, or phosphorylation, or by the creation of acid addition salts, amides, esters, in particular C-terminal esters, and N-acyl derivatives of the peptides of the invention. The peptibodies also can be modified to create peptide derivatives by forming covalent or noncovalent complexes with other moieties. Covalently-bound complexes can be prepared by linking the chemical moieties to functional groups on the side chains of amino acids comprising the peptibodies, or at the N- or C-terminus.

The peptides can be conjugated to a reporter group, including, but not limited to a radiolabel, a fluorescent label, an enzyme (e.g., that catalyzes a colorimetric or fluorometric reaction), a substrate, a solid matrix, or a carrier (e.g., biotin or avidin). The invention accordingly provides a molecule comprising a peptibody molecule, wherein the molecule preferably further comprises a reporter group selected from the group consisting of a radiolabel, a fluorescent label, an enzyme, a substrate, a solid matrix, and a carrier. Such labels are well known to those of skill in the art, e.g., biotin labels are particularly contemplated. The use of such labels is well known to those of skill in the art and is described in, e.g., U.S. Patent Nos.3,817,837; 3,850,752; 3,996,345; and 4,277,437. Other labels that will be useful include but are not limited to radioactive labels, fluorescent labels and chemiluminescent labels. U.S. Patents concerning use of such labels include, for example, U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; and 3,996,345. Any of the peptibodies of the present invention may comprise one, two, or more of any of these labels.

Recombinant methods. In general, the peptide or polypeptide portions of the inventive compounds of this invention (including peptides or polypeptides as additional moieties, linkers, and/or Fc domains) largely can be made in transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

Accordingly, the present invention also relates to nucleic acids, expression vectors and host cells useful in producing polypeptide compositions of the present invention. Host cells can be eukaryotic cells, with mammalian cells preferred, e.g., CHO cells and HEK293 cells. Host cells can also be prokaryotic cells, with E. coli cells most preferred.

The compounds of this invention largely can be made in transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

The invention also includes a vector capable of expressing the peptides in an appropriate host. The vector comprises the DNA molecule that codes for the peptides operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal binding sites, start signals, stop signals, cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation.

The resulting vector having the DNA molecule thereon is used to transform an appropriate host. This transformation can be performed using methods well known in the art.

Any of a large number of available and well-known host cells can be used in the practice of this invention. The selection of a particular host is dependent upon a number of factors recognized by the art. These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of transformation, ease of recovery of the peptides, expression characteristics, bio-safety and costs. A balance of these factors must be struck with the understanding that not all host cells can be equally effective for the expression of a particular DNA sequence. Within these general guidelines, useful microbial host cells include bacteria (such as E. coli sp.), yeast (such as Saccharomyces sp.) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

Next, the transformed host cell is cultured and purified. Host cells can be cultured under conventional fermentation conditions so that the desired compounds are expressed. Such fermentation conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

The compounds can also be made by synthetic methods. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides. For example, well known solid phase synthesis techniques include the use of protecting groups, linkers, and solid phase supports, as well as specific protection and deprotection reaction conditions, linker cleavage conditions, use of scavengers, and other aspects of solid phase peptide synthesis. Suitable techniques are well known in the art. (E.g., Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al. (1985), Biochem. Intl. 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527; "Protecting Groups in Organic Synthesis," 3rd Edition, T. W. Greene and P. G. M. Wuts, Eds., John Wiley & Sons, Inc., 1999; NovaBiochem Catalog, 2000; "Synthetic Peptides, A User's Guide," G. A. Grant, Ed., W.H. Freeman & Company, New York, N.Y., 1992; "Advanced Chemtech Handbook of Combinatorial & Solid Phase Organic Chemistry," W. D. Bennet, J. W. Christensen, L. K. Hamaker, M. L. Peterson, M. R. Rhodes, and H. H. Saneii, Eds., Advanced Chemtech, 1998; "Principles of Peptide Synthesis, 2nd ed.," M. Bodanszky, Ed., Springer-Verlag, 1993; "The Practice of Peptide Synthesis, 2nd ed.," M. Bodanszky and A. Bodanszky, Eds., Springer-Verlag, 1994; "Protecting

Groups," P. J. Kocienski, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1994; "Fmoc Solid Phase Peptide Synthesis, A Practical Approach," W. C. Chan and P. D. White, Eds., Oxford Press, 2000, G. B. Fields et al., Synthetic Peptides: A User's Guide, 1990, 77-183).

Whether the compositions of the present invention are prepared by synthetic or recombinant techniques, suitable protein purification techniques can also be involved, when applicable. In some embodiments of the compositions of the invention, the toxin peptide portion and/or the half-life extending portion, or any other portion, can be prepared to include a suitable isotopic label (e.g., ^{125}I, ^{14}C, ^{13}C, ^{35}S, ^{3}H, ^{2}H, ^{13}N, ^{15}N, ^{18}O, ^{17}O, *etc.*), for ease of quantification or detection.

Compounds that contain derivatized peptides or polypeptides, or which contain non-peptide groups can be synthesized by well-known organic chemistry techniques.

Uses of the inventive compounds

In general. The compounds of this invention have pharmacologic activity resulting from their ability to bind to proteins of interest as agonists, mimetics or antagonists of the native ligands of such proteins of interest. By way of example, the utility of a variety of specific compounds is shown in Tables 5 - 10. The activity of these compounds can be measured by assays known in the art.

In addition to therapeutic uses, the compounds of the present invention are useful in diagnosing diseases characterized by dysfunction of their associated protein of interest. For some of these diagnostic embodiments and for other detection (including semi-quantitative and quantitative) purposes, conjugation of the Fc domain to an immobilized substrate as an additional functional moiety, such as but not limited to, a plate surface, a chip, a bead, a matrix or a particle, can be useful. Also a moiety detectably labeled with a radioisotope, an enzyme (e.g., a peroxidase or a kinase), a biotinyl moiety, a fluorophore, or a chromophore can be useful for such puposes.

In one embodiment, a method of detecting in a biological sample a protein of interest (e.g., a receptor) that is capable of being activated comprising the steps of: (a) contacting the sample with a compound of this invention; and (b) detecting activation of the protein of interest by the compound. The biological samples include tissue specimens, intact cells, or extracts thereof. The compounds of this invention may be used as part of a kit to detect the presence of their associated proteins of interest in a biological sample. Such kits employ the compounds of the invention having an attached label to allow for detection. The compounds are useful for identifying normal or abnormal proteins of interest. For the EPO-mimetic compounds, for example, presence of abnormal protein of interest in a biological sample may be indicative of such disorders as Diamond Blackfan anemia, where it is believed that the EPO receptor is dysfunctional.

Therapeutic uses of EPO-mimetic molecules

The EPO-mimetic compounds of the invention are useful for treating disorders characterized by low red blood cell levels. Included in the invention are methods of modulating the endogenous activity of an EPO receptor in a mammal, preferably methods of increasing the activity of an EPO receptor. In general, any condition treatable by erythropoietin, such as anemia, may also be treated by the EPO-mimetic compounds of the invention. These compounds are administered by an amount and route of delivery that is appropriate for the nature and severity of the condition being treated and may be ascertained by one skilled in the art. Preferably, administration is by injection, either subcutaneous, intramuscular, or intravenous.

Therapeutic uses of TPO-mimetic compounds

For the TPO-mimetic compounds, one can utilize such standard assays as those described in WO95/26746 entitled "Compositions and Methods for Stimulating Megakaryocyte Growth and Differentiation." The conditions to be treated are generally those that involve an existing megakaryocyte/platelet deficiency or an expected megakaryocyte/platelet deficiency (e.g., because of planned surgery or platelet donation). Such conditions will usually be the result of a deficiency (temporary or permanent) of active Mpl ligand in vivo. The generic term for platelet deficiency is thrombocytopenia, and hence the methods and compositions of the present invention are generally available for treating thrombocytopenia in patients in need thereof.

Thrombocytopenia (platelet deficiencies) may be present for various reasons, including chemotherapy and other therapy with a variety of drugs, radiation therapy, surgery, accidental blood loss, and other specific disease conditions. Exemplary specific disease conditions that involve thrombocytopenia and may be treated in accordance with this invention are: aplastic anemia, idiopathic thrombocytopenia, metastatic tumors which result in thrombocytopenia, systemic lupus erythematosus, splenomegaly, Fanconi's syndrome, vitamin B12 deficiency, folic acid deficiency, May-Hegglin anomaly, Wiskott-Aldrich syndrome, and paroxysmal nocturnal hemoglobinuria. Also, certain treatments for AIDS result in thrombocytopenia (e.g., AZT). Certain wound healing disorders might also benefit from an increase in platelet numbers.

With regard to anticipated platelet deficiencies, e.g., due to future surgery, a compound of the present invention could be administered several days to several hours prior to the need for platelets. With regard to acute situations, e.g., accidental and massive blood loss, a compound of this invention could be administered along with blood or purified platelets.

The TPO-mimetic compounds of this invention may also be useful in stimulating certain cell types other than megakaryocytes if such cells are found to express Mpl receptor. Conditions associated with such cells that express the Mpl receptor, which are responsive to stimulation by the Mpl ligand, are also within the scope of this invention.

The TPO-mimetic compounds of this invention may be used in any situation in which production of platelets or platelet precursor cells is desired, or in which stimulation of the c-Mpl receptor is desired. Thus, for example, the compounds of this invention may be used to treat any condition in a mammal wherein there is a need of platelets, megakaryocytes, and the like. Such conditions are described in detail in the following exemplary sources: WO95/26746; WO95/21919; WO95/18858; WO95/21920 and are incorporated herein.

The TPO-mimetic compounds of this invention may also be useful in maintaining the viability or storage life of platelets and/or megakaryocytes and related cells. Accordingly, it could be useful to include an effective amount of one or more such compounds in a composition containing such cells.

Therapeutic uses of Ang-2 binding molecules

Agents that modulate Ang-2 binding activity, or other cellular activity, may be used in combination with other therapeutic agents to enhance their therapeutic effects or decrease potential side effects.

In one aspect, the present invention provides reagents and methods useful for treating diseases and conditions characterized by undesirable or aberrant levels of Ang-2 activity in a cell. These diseases include cancers, and other hyperproliferative conditions, such as hyperplasia, psoriasis, contact dermatitis, immunological disorders, and infertility.

The present invention also provides methods of treating cancer in an animal, including humans, comprising administering to the animal an effective amount of a specific binding agent, such as a peptibody, that inhibits or decreases Ang-2 activity. The invention is further directed to methods of inhibiting cancer cell growth, including processes of cellular proliferation, invasiveness, and metastasis in biological systems. Methods include use of a compound of the invention as an inhibitor of cancer cell growth. Preferably, the methods are employed to inhibit or reduce cancer cell growth, invasiveness, metastasis, or tumor incidence in living animals, such as mammals. Methods of the invention are also readily adaptable for use in assay systems, e.g., assaying cancer cell growth and properties thereof, as well as identifying compounds that affect cancer cell growth.

The cancers treatable by methods of the present invention preferably occur in mammals. Mammals include, for example, humans and other primates, as well as pet or companion animals such as dogs and cats, laboratory animals such as rats, mice and rabbits, and farm animals such as horses, pigs, sheep, and cattle.

Tumors or neoplasms include growths of tissue cells in which the multiplication of the cells is uncontrolled and progressive. Some such growths are benign, but others are termed malignant and may lead to death of the organism. Malignant neoplasms or cancers are distinguished from benign growths in that, in addition to exhibiting aggressive cellular proliferation, they may invade surrounding tissues and metastasize. Moreover, malignant neoplasms are characterized in that they show a greater loss of differentiation (greater dedifferentiation), and of their organization relative to one another and their surrounding tissues. This property is also called "anaplasia."

Neoplasms treatable by the present invention also include solid tumors, i.e., carcinomas and sarcomas. Carcinomas include those malignant neoplasms derived from epithelial cells that infiltrate (invade) the surrounding tissues and give rise to metastases. Adenocarcinomas are carcinomas derived from glandular tissue, or which form recognizable glandular structures. Another broad category or cancers includes sarcomas, which are tumors whose cells are embedded in a fibrillar or homogeneous substance like embryonic connective tissue. The invention also enables treatment of cancers of the myeloid or lymphoid systems, including leukemias, lymphomas and other cancers that typically do not present as a tumor mass, but are distributed in the vascular or lymphoreticular systems.

The ang-2 binding molecules of this invention are thus useful for the treatment of a wide variety of cancers, including solid tumors and leukemias. Types of cancer or tumor cells amenable to treatment according to the invention include, for example, ACTH-producing tumor; acute lymphocytic leukemia; acute nonlymphocytic leukemia; adenoma; cancer of the adrenal cortex; adenocarcinoma of the breast, prostate, and colon; ameloblastoma; apudoma; bladder cancer; brain cancer; branchioma; breast cancer; all forms of bronchogenic carcinoma of the lung; carcinoid heart disease; carcinoma (e.g., Walker, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, Krebs 2, merkel cell, mucinous, non-small cell lung, oat cell, papillary, scirrhous, bronchiolar, bronchogenic, squamous cell, and transitional cell); malignant carcinoid syndrome; immunoproliferative small lung cell carcinoma; cementoma; cervical cancer; chondroblastoma; chondroma; chondrosarcoma; choristoma; chronic lymphocytic leukemia; chronic myelocytic leukemia; colorectal cancer;

chordoma; craniopharyngioma; cutaneous T-cell lymphoma; dysgerminoma; endometrial cancer; esophageal cancer; Ewing's sarcoma; fibroma; fibrosarcoma; gallbladder cancer; giant cell tumors; glioma; hairy cell leukemia; hamartoma; head and neck cancer; hepatoma; histiocytic disorders; histiocytosis; Hodgkin's lymphoma; Kaposi's sarcoma; kidney cancer; lipoma; liposarcoma; liver cancer; lung cancer (small and non-small cell); malignant peritoneal effusion; malignant pleural effusion; melanoma; mesenchymoma; mesonephroma; mesothelioma; multiple myeloma; myosarcoma; myxoma; myxosarcoma; neuroblastoma; non-Hodgkin's lymphoma; odontoma; osteoma; osteosarcoma; ovarian cancer; ovarian (germ cell) cancer; pancreatic cancer; papilloma; penile cancer; plasmacytoma; prostate cancer; reticuloendotheliosis; retinoblastoma; skin cancer; soft tissue sarcoma; squamous cell carcinomas; stomach cancer; teratoma; testicular cancer; thymoma; thyroid cancer; trophoblastic neoplasms; uterine cancer; vaginal cancer; cancer of the vulva; Wilms' tumor.

Further, the following types of cancers may also be treated: cholangioma; cholesteatoma; cyclindroma; cystadenocarcinoma; cystadenoma; granulosa cell tumor; gynandroblastoma; hidradenoma; islet cell tumor; Leydig cell tumor; papilloma; Sertoli cell tumor; theca cell tumor; leiomyoma; leiomyosarcoma; myoblastoma; myoma; myosarcoma; rhabdomyoma; rhabdomyosarcoma; ependymoma; ganglioneuroma; glioma; medulloblastoma; meningioma; neurilemmoma; neuroblastoma; neuroepithelioma; neurofibroma; neuroma; paraganglioma; paraganglioma nonchromaffin; angiokeratoma; angiolymphoid hyperplasia with eosinophilia; angioma sclerosing; angiomatosis; glomangioma; hemangioendothelioma; hemangioma; hemangiopericytoma; hemangiosarcoma; lymphangioma; lymphangiomyoma; lymphangiosarcoma; pinealoma; carcinosarcoma; chondrosarcoma; cystosarcoma phyllodes; fibrosarcoma; hemangiosarcoma; leiomyosarcoma; leukosarcoma; liposarcoma; lymphangiosarcoma; myosarcoma; myxosarcoma; ovarian carcinoma; rhabdomyosarcoma; sarcoma; neoplasms; nerofibromatosis; and cervical dysplasia.

<u>Therapeutic uses of NGF binding molecules</u>

The NGF binding molecules may be used in the prevention or treatment of NGF-related diseases and disorders. Such indications include but are not limited to pain (including, but not limited to, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, acute pain, tension headache, migraine, dental pain, pain from trauma, surgical pain, pain resulting from amputation or abscess, causalgia, demyelinating diseases, and trigeminal neuralgia). The peptides and modified peptides of the invention have therapeutic value for the prevention or treatment of other diseases linked to NGF as a causative agent, including, but not limited to, asthma, urge incontinence (i.e., hyperactive bladder), psoriasis, cancer (especially, pancreatic cancer and melanoma), chronic alcoholism, stroke, thalamic pain syndrome, diabetes, acquired immune deficiency syndrome ("AIDS"), toxins and chemotherapy, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, general inflammation, arthritis, rheumatic diseases, lupus, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, sunburn, carditis, dermatitis, myositis, neuritis, collagen vascular diseases, chronic inflammatory conditions, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritis, vitiligo, general gastrointestinal disorders, colitis, gastric ulceration, duodenal ulcers, vasomotor or allergic rhinitis, or bronchial disorders.

Therapeutic uses of myostatin binding molecules

The myostatin binding agents of the present invention bind to myostatin and block or inhibit myostatin signaling within targeted cells. The present invention provides methods and reagents for reducing the amount or activity of myostatin in an animal by administering an effective dosage of one or more myostatin binding agents to the animal. In one aspect, the present invention provides methods and reagents for treating myostatin-related disorders in an animal comprising administering an effective dosage of one or more binding agents to the animal. These myostatin-related disorders include but are not limited to various forms of muscle wasting, as well as metabolic disorders such as diabetes and related disorders, and bone degenerative diseases such as osteoporosis.

As shown in the Example 8 of U.S. Ser. No. 10/742,379, exemplary peptibodies of the present invention dramatically increases lean muscle mass in the CD1 nu/nu mouse model. This in vivo activity correlates to the in vitro binding and inhibitory activity described below for the same peptibodies.

Muscle wasting disorders include dystrophies such as Duchenne's muscular dystrophy, progressive muscular dystrophy, Becker's type muscular dystrophy, Dejerine-Landouzy muscular dystrophy, Erb's muscular dystrophy, and infantile neuroaxonal muscular dystrophy. For example, blocking myostatin through use of antibodies in vivo improved the dystrophic phenotype of the mdx mouse model of Duchenne muscular dystrophy (Bogdanovich et al. (2002), Nature 420: 28). Use of an exemplary peptibody increases lean muscle mass and increases the ratio of lean muscle to fat in mdx mouse models as described in Example 9 below.

Additional muscle wasting disorders arise from chronic disease such as amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, cancer, AIDS, renal failure, and rheumatoid arthritis. For example, cachexia or muscle wasting and loss of body weight was induced in athymic nude mice by a systemically administered myostatin (Zimmers et al., supra). In another example, serum and intramuscular concentrations of myostatin-immunoreactive protein was found to be increased in men exhibiting AIDS-related muscle wasting and was inversely related to fat-free mass (Gonzalez-Cadavid et al. (1998), PNAS USA **95**: 14938-14943). Additional conditions resulting in muscle wasting may arise from inactivity due to disability such as confinement in a wheelchair, prolonged bedrest due to stroke, illness, bone fracture or trauma, and muscular atrophy in a microgravity environment (space flight). For example, plasma myostatin immunoreactive protein was found to increase after prolonged bedrest (Zachwieja et al. J Gravit Physiol. 6(2):11(1999). It was also found that the muscles of rats exposed to a microgravity environment during a space shuttle flight expressed an increased amount of myostatin compared with the muscles of rats which were not exposed (Lalani et al. (2000), J.Endocrin. 167(3):417-28).

In addition, age-related increases in fat to muscle ratios, and age-related muscular atrophy appear to be related to myostatin. For example, the average serum myostatin-immunoreactive protein increased with age in groups of young (19-35 yr old), middle-aged (36-75 yr old), and elderly (76-92 yr old) men and women, while the average muscle mass and fat-free mass declined with age in these groups (Yarasheski et al. J Nutr Aging 6(5):343-8 (2002)). It has also been shown that myostatin gene knockout in mice increased myogenesis and decreased adipogenesis (Lin et al. (2002), Biochem Biophys Res Commun 291(3):701-6, resulting in adults with increased muscle mass and decreased fat accumulation and leptin secretion. Exemplary molecules improve the lean muscle mass to fat ratio in aged mdx mice as shown below.

In addition, myostatin has now been found to be expressed at low levels in heart muscle and expression is upregulated after cardiomyocytes after infarct (Sharma et al. (1999), J Cell Physiol. 180(1):1-9). Therefore, reducing myostatin levels in the heart muscle may improve recovery of heart muscle after infarct.

Myostatin also appears to influence metabolic disorders including type 2 diabetes, noninsulin-dependent diabetes mellitus, hyperglycemia, and obesity. For example, lack of myostatin has been shown to improve the obese and diabetic phenotypes of two mouse models (Yen et al. supra). In addition, increasing muscle mass by reducing myostatin levels may improve bone strength and reduce osteoporosis and other degenerative bone diseases. It has been found, for example, that myostatin-deficient mice showed increased mineral content and density of the mouse humerus and increased mineral content of both trabecular and cortical bone at the regions where the muscles attach, as well as increased muscle mass (Hamrick et al. (2002), Calcif Tissue Int 71(1): 63-8). In the present invention, an exemplary peptibody increases the lean muscle mass to fat ratio in mdx mouse models as shown below.

The present invention also provides methods and reagents for increasing muscle mass in food animals by administering an effective dosage of the myostatin binding agent to the animal. Since the mature C-terminal myostatin polypeptide is identical in all species tested, myostatin binding agents would be expected to be effective for increasing muscle mass and reducing fat in any agriculturally important species including cattle, chicken, turkeys, and pigs.

The myostatin-binding molecules of the present invention may be used alone or in combination with other therapeutic agents to enhance their therapeutic effects or decrease potential side effects. The molecules of the present invention possess one or more desirable but unexpected combination of properties to improve the therapeutic value of the agents. These properties include increased activity, increased solubility, reduced degradation, increased half-life, reduced toxicity, and reduced immunogenicity. Thus the molecules of the present invention are useful for extended treatment regimes. In addition, the properties of hydrophilicity and hydrophobicity of the compounds of the invention are well balanced, thereby enhancing their utility for both in vitro and especially in vivo uses. Specifically, compounds of the invention have an appropriate degree of solubility in aqueous media that permits absorption and bioavailability in the body, while also having a degree of solubility in lipids that permits the compounds to traverse the cell membrane to a putative site of action, such as a particular muscle mass.

The myostatin-binding molecules of the present invention are useful for treating a "subject" or any animal, including humans, when administered in an effective dosages in a suitable composition.

In addition, the mystatin-binding molecules of the present invention are useful for detecting and quantitating myostatin in a number of assays. These assays are described in detail in U.S. Ser. No. 10/742,379.

In general, the myostatin-binding molecules of the present invention are useful as capture agents to bind and immobilize myostatin in a variety of assays, similar to those described, for example, in Asai, ed., Methods in Cell Biology, **37**, Antibodies in Cell Biology, Academic Press, Inc., New York (1993). The myostatin-binding molecule may be labeled in some manner or may react with a third molecule such as an anti-binding molecule antibody which is labeled to enable myostatin to be detected and quantitated. For example, a myostatin-binding molecule or a third molecule can be modified with a detectable moiety, such as biotin, which can then be bound by a fourth molecule, such as enzyme-labeled streptavidin, or other proteins. (Akerstrom (1985), J Immunol 135:2589; Chaubert (1997), Mod Pathol 10:585).

Throughout any particular assay, incubation and/or washing steps may be required after each combination of reagents. Incubation steps can vary from about 5 seconds to several hours, preferably from about 5 minutes to about 24 hours. However, the incubation time will depend upon the assay format, volume of solution, concentrations, and the like. Usually, the assays will be carried out at ambient temperature, although they can be conducted over a range of temperatures.

Therapeutic uses of BAFF-binding molecules. BAFF-binding molecules of this invention may be particularly useful in treatment of B-cell mediated autoimmune diseases. In particular, they may be useful in treating, preventing, ameliorating, diagnosing or prognosing lupus, including systemic lupus erythematosus (SLE), and lupus-associated diseases and conditions. Other preferred indications include B-cell mediated cancers, including B-cell lymphoma.

The compounds of this invention can also be used to treat inflammatory conditions of the joints. Inflammatory conditions of a joint are chronic joint diseases that afflict and disable, to varying degrees, millions of people worldwide. Rheumatoid arthritis is a disease of articular joints in which the cartilage and bone are slowly eroded away by a proliferative, invasive connective tissue called pannus, which is derived from the synovial membrane. The disease may involve peri-articular structures such as bursae, tendon sheaths and tendons as well as extra-articular tissues such as the subcutis, cardiovascular system, lungs, spleen, lymph nodes, skeletal muscles, nervous system (central and peripheral) and eyes (Silberberg (1985), Anderson's Pathology, Kissane (ed.), II:1828). Osteoarthritis is a common joint disease characterized by degenerative changes in articular cartilage and reactive proliferation of bone and cartilage around the joint. Osteoarthritis is a cell-mediated active process that may result from the inappropriate response of chondrocytes to catabolic and anabolic stimuli. Changes in some matrix molecules of articular cartilage reportedly occur in early osteoarthritis (Thonar et al. (1993), Rheumatic disease clinics of North America, Moskowitz (ed.), 19:635-657 and Shinmei et al. (1992), Arthritis Rheum., 35:1304-1308). TALL-1, TALL-1R and modulators thereof are believed to be useful in the treatment of these and related conditions.

BAFF-binding molecules may also be useful in treatment of a number of additional diseases and disorders, including acute pancreatitis; ALS; Alzheimer's disease; asthma; atherosclerosis; autoimmune hemolytic anemia; cancer, particularly cancers related to B cells; cachexia/anorexia; chronic fatigue syndrome; cirrhosis (e.g., primary biliary cirrhosis); diabetes (e.g., insulin diabetes); fever; glomerulonephritis, including IgA glomerulonephritis and primary glomerulonephritis; Goodpasture's syndrome; Guillain-Barre syndrome; graft versus host disease; Hashimoto's thyroiditis; hemorrhagic shock; hyperalgesia; inflammatory bowel disease; inflammatory conditions of a joint, including osteoarthritis, psoriatic arthritis and rheumatoid arthritis; inflammatory conditions resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes; insulin-dependent diabetes mellitus; ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); learning impairment; lung diseases (e.g., ARDS); lupus, particularly systemic lupus erythematosus (SLE); multiple myeloma; multiple sclerosis; Myasthenia gravis; myelogenous (e.g., AML and CML) and other leukemias; myopathies (e.g., muscle protein metabolism, esp. in sepsis); neurotoxicity (e.g., as induced by HIV); osteoporosis; pain; Parkinson's disease; Pemphigus; polymyositis/dermatomyositis; pulmonary inflammation, including autoimmune pulmonary inflammation; pre-term labor; psoriasis; Reiter's disease; reperfusion injury; septic shock; side effects from radiation therapy; Sjogren's syndrome; sleep disturbance; temporal mandibular joint disease; thrombocytopenia, including idiopathic thrombocytopenia and autoimmune neonatal thrombocytopenia; tumor metastasis; uveitis; and vasculitis.

Combination Therapy. The therapeutic methods, compositions and compounds of the present invention may also be employed, alone or in combination with other cytokines, soluble Mpl receptor, hematopoietic factors, interleukins, growth factors or antibodies in the treatment of disease states characterized by other symptoms as well as platelet deficiencies. It is anticipated that the inventive compound will prove useful in treating some forms of thrombocytopenia in combination with general stimulators of hematopoiesis, such as IL-3 or GM-CSF. Other megakaryocytic stimulatory factors, i.e., meg-CSF, stem cell factor (SCF), leukemia inhibitory factor (LIF), oncostatin M (OSM), or other molecules with megakaryocyte stimulating activity may also be employed with Mpl ligand. Additional exemplary cytokines or hematopoietic factors for such co-administration include IL-1 alpha, IL-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, colony stimulating factor-1 (CSF-1), SCF, GM-CSF, granulocyte colony stimulating factor (G-CSF), EPO, interferon-alpha (IFN-alpha), consensus interferon, IFN-beta, or IFN-gamma. It may further be useful to administer, either simultaneously or sequentially, an effective amount of a soluble mammalian Mpl receptor, which appears to have an effect of causing megakaryocytes to fragment into platelets once the megakaryocytes have reached mature form. Thus, administration of an inventive compound (to enhance the number of mature megakaryocytes) followed by administration of the soluble Mpl receptor (to inactivate the ligand and allow the mature megakaryocytes to produce platelets) is expected to be a particularly effective means of stimulating platelet production. The dosage recited above would be adjusted to compensate for such additional components in the therapeutic composition. Progress of the treated patient can be monitored by conventional methods.

In cases where the inventive compounds are added to compositions of platelets and/or megakaryocytes and related cells, the amount to be included will generally be ascertained experimentally by techniques and assays known in the art. An exemplary range of amounts is 0.1 μg—1 mg inventive compound per 10^6 cells.

Therapeutics incorporating toxin peptides. Some embodiments of the inventive composition of matter incorporate toxin peptides as additional functional moieties, which toxin peptides can have pharmacologic activity resulting from the ability to bind to ion channels of interest as agonists, mimetics or antagonists of the native ligands of such ion channels of interest. Consequently such embodiments of the inventive composition of matter can have utility in the treatment of pathologies associated with ion channels. Heritable diseases that have a known linkage to ion channels ("channelopathies") cover various fields of medicine, some of which include neurology, nephrology, myology and cardiology. A list of inherited disorders attributed to ion channels (channel types in parentheses) includes:

- cystic fibrosis (Cl^- channel; CFTR),
- Dent's disease (proteinuria and hypercalciuria; Cl^- channel; CLCN5),
- osteopetrosis (Cl^- channel; CLCN7),
- familial hyperinsulinemia (SUR1; KCNJ11; K channel),
- diabetes (KATP / SUR channel),
- Andersen syndrome (KCNJ2, Kir2.1 K channel),
- Bartter syndrome (KCNJ1; Kir1.1/ROMK; K channel),
- hereditary hearing loss (KCNQ4; K channel),
- hereditary hypertension (Liddle's syndrome; SCNN1; epithelial Na channel),
- dilated cardiomyopathy (SUR2, K channel),
- long-QT syndrome or cardiac arrhythmias (cardiac potassium and sodium channels),
- Thymothy syndrome (CACNA1C, Cav1.2),
- myasthenic syndromes (CHRNA,CHRNB,CNRNE; nAChR), and a variety of other myopathies,
- hyperkalemic periodic paralysis (Na and K channels),

- epilepsy (Na^+ and K^+ channels),
- hemiplegic migraine (CACNA1A, Cav2.1 Ca^{2+} channel and ATP1A2),
- central core disease (RYR1, RyR1; Ca^{2+} channel), and
- paramyotonia and myotonia (Na^+, Cl^- channels)

See L.J. Ptacek and Y-H Fu (2004), Arch. Neurol. 61: 166-8; B.A. Niemeyer et al. (2001), EMBO reports 21: 568-73; F. Lehmann-Horn and K. Jurkat-Rott (1999), Physiol. Rev. 79: 1317-72. Although the foregoing list concerned disorders of inherited origin, molecules targeting the channels cited in these disorders can also be useful in treating related disorders of other, or indeterminate, origin.

In addition to the aforementioned disorders, evidence has also been provided supporting ion channels as targets for treatment of:

☐ sickle cell anemia (IKCa1) – in sickle cell anemia, water loss from erythrocytes leads to hemoglobin polymerization and subsequent hemolysis and vascular obstruction. The water loss is consequent to potassium efflux through the so-called Gardos channel i.e., IKCa1. Therefore, block of IKCa1 is a potential therapeutic treatment for sickle cell anemia.

☐ glaucoma (BKCa), – in glaucoma the intraocular pressure is too high leading to optic nerve damage, abnormal eye function and possibly blindness. Block of BKCa potassium channels can reduce intraocular fluid secretion and increase smooth muscle contraction, possibly leading to lower intraocular pressure and neuroprotection in the eye.

☐ multiple sclerosis (Kv, KCa),

☐ psoriasis (Kv, KCa),

☐ arthritis (Kv, KCa),

☐ asthma (KCa, Kv),

☐ allergy(KCa, Kv),

☐ COPD (KCa, Kv, Ca),

☐ allergic rhinitis (KCa, Kv),

☐ pulmonary fibrosis,

☐ lupus (IKCa1, Kv),

- transplantation, GvHD (KCa, Kv),
- inflammatory bone resorption (KCa, Kv),
- periodontal disease (KCa, Kv),
- diabetes, type I (Kv), – type I diabetes is an autoimmune disease that is characterized by abnormal glucose, protein and lipid metabolism and is associated with insulin deficiency or resistance. In this disease, Kv1.3-expressing T-lymphocytes attack and destroy pancreatic islets leading to loss of beta-cells. Block of Kv1.3 decreases inflammatory cytokines. In addition block of Kv1.3 facilitates the translocation of GLUT4 to the plasma membrane, thereby increasing insulin sensitivity.
- obesity (Kv), – Kv1.3 appears to play a critical role in controlling energy homeostasis and in protecting against diet-induced obesity. Consequently, Kv1.3 blockers could increase metabolic rate, leading to greater energy utilization and decreased body weight.
- restenosis (KCa, Ca^{2+}), – proliferation and migration of vascular smooth muscle cells can lead to neointimal thickening and vascular restenosis. Excessive neointimal vascular smooth muscle cell proliferation is associated with elevated expression of IKCa1. Therefore, block of IKCa1 could represent a therapeutic strategy to prevent restenosis after angioplasty.
- ischaemia (KCa, Ca^{2+}), – in neuronal or cardiac ischemia, depolarization of cell membranes leads to opening of voltage-gated sodium and calcium channels. In turn this can lead to calcium overload, which is cytotoxic. Block of voltage-gated sodium and/or calcium channels can reduce calcium overload and provide cytoprotective effects. In addition, due to their critical role in controlling and stabilizing cell membrane potential, modulators of voltage- and calcium-activated potassium channels can also act to reduce calcium overload and protect cells.
- renal incontinence (KCa), renal incontinence is associated with overactive bladder smooth muscle cells. Calcium-activated potassium channels

are expressed in bladder smooth muscle cells, where they control the membrane potential and indirectly control the force and frequency of cell contraction. Openers of calcium-activated potassium channels therefore provide a mechanism to dampen electrical and contractile activity in bladder, leading to reduced urge to urinate.

- osteoporosis (Kv),
- pain, including migraine (Na_v, TRP [transient receptor potential channels], P2X, Ca^{2+}), N-type voltage-gated calcium channels are key regulators of nociceptive neurotransmission in the spinal cord. Ziconotide, a peptide blocker of N-type calcium channels reduces nociceptive neurotransmission and is approved worldwide for the symptomatic alleviation of severe chronic pain in humans. Novel blockers of nociceptor-specific N-type calcium channels would be improved analgesics with reduced side-effect profiles.
- hypertension (Ca^{2+}), – L-type and T-type voltage-gated calcium channels are expressed in vascular smooth muscle cells where they control excitation-contraction coupling and cellular proliferation. In particular, T-type calcium channel activity has been linked to neointima formation during hypertension. Blockers of L-type and T-type calcium channels are useful for the clinical treatment of hypertension because they reduce calcium influx and inhibit smooth muscle cell contraction.
- wound healing, cell migration serves a key role in wound healing. Intracellular calcium gradients have been implicated as important regulators of cellular migration machinery in keratinocytes and fibroblasts. In addition, ion flux across cell membranes is associated with cell volume changes. By controlling cell volume, ion channels contribute to the intracellular environment that is required for operation of the cellular migration machinery. In particular, IKCa1 appears to be required universally for cell migration. In addition, Kv1.3, Kv3.1, NMDA receptors and N-type calcium channels are associated with the migration of lymphocytes and neurons.

- stroke,
- Alzheimer's,

  Parkenson's Disease (nACHR, Nav)

  Bipolar Disorder (Nav, Cav)
- cancer, many potassium channel genes are amplified and protein subunits are upregulated in many cancerous condition. Consistent with a pathophysiological role for potassium channel upregulation, potassium channel blockers have been shown to suppress proliferation of uterine cancer cells and hepatocarcinoma cells, presumably through inhibition of calcium influx and effects on calcium-dependent gene expression.
- a variety of neurological, cardiovascular, metabolic and autoimmune diseases.

Both agonists and antagonists of ion channels can achieve therapeutic benefit. Therapeutic benefits can result, for example, from antagonizing Kv1.3, IKCa1, SKCa, BKCa, N-type or T-type Ca^{2+} channels and the like. Small molecule and peptide antagonists of these channels have been shown to possess utility in vitro and in vivo.

The diseases and pharmacologically active additional moieties described herein are merely exemplary and in no way limit the range of inventive pharmacologically active compounds and compositions that can be prepared using the inventive method or the diseases and disorders that can be treated with the benefit of the present invention.

Pharmaceutical Compositions

In General. The present invention also provides pharmaceutical compositions comprising the inventive composition of matter and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be configured for administration to a patient by a wide variety of delivery routes, e.g., an intravascular delivery route such as by injection or infusion, subcutaneous, intramuscular, intraperitoneal, epidural, or intrathecal delivery routes, or for oral, enteral, pulmonary (e.g., inhalant), intranasal, transmucosal (e.g., sublingual administration), transdermal or other delivery routes and/or forms of administration known in the art. The inventive pharmaceutical compositions may be prepared in liquid form, or may be in dried powder form, such as lyophilized form. For oral or enteral use, the pharmaceutical compositions can be configured, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs or enteral formulas.

In the practice of this invention the "pharmaceutically acceptable carrier" is any physiologically tolerated substance known to those of ordinary skill in the art useful in formulating pharmaceutical compositions, including, any pharmaceutically acceptable diluents, excipients, dispersants, binders, fillers, glidants, anti-frictional agents, compression aids, tablet-disintegrating agents (disintegrants), suspending agents, lubricants, flavorants, odorants, sweeteners, permeation or penetration enhancers, preservatives, surfactants, solubilizers, emulsifiers, thickeners, adjuvants, dyes, coatings, encapsulating material(s), and/or other additives singly or in combination. Such pharmaceutical compositions can include diluents of various buffer content (*e.g.*, Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (*e.g.*, Tween® 80, Polysorbate 80), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), preservatives (*e.g.*, Thimersol®, benzyl alcohol) and bulking substances (*e.g.*, lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid can also be used, and this can have the effect of promoting sustained duration in the circulation. Such compositions can influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712, which are herein incorporated by reference in their entirety. The compositions can be prepared in liquid form, or can be in dried powder, such as lyophilized form. Implantable sustained release formulations are also useful, as are transdermal or transmucosal formulations. Additionally (or alternatively), the present invention provides compositions for use in any of the various slow or sustained release formulations or microparticle formulations known to the skilled artisan, for example, sustained release microparticle formulations, which can be administered via pulmonary, intranasal, or subcutaneous delivery routes.

One can dilute the inventive compositions or increase the volume of the pharmaceutical compositions of the invention with an inert material. Such diluents can include carbohydrates, especially, mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers, including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

A variety of conventional thickeners are useful in creams, ointments, suppository and gel configurations of the pharmaceutical composition, such as, but not limited to, alginate, xanthan gum, or petrolatum, may also be employed in such configurations of the pharmaceutical composition of the present invention. A permeation or penetration enhancer, such as polyethylene glycol monolaurate, dimethyl sulfoxide, N-vinyl-2-pyrrolidone, N-(2-hydroxyethyl)-pyrrolidone, or 3-hydroxy-N-methyl-2-pyrrolidone can also be employed. Useful techniques for producing hydrogel matrices are known. (E.g., Feijen, Biodegradable hydrogel matrices for the controlled release of pharmacologically active agents, U.S. Patent No. 4,925,677; Shah et al., Biodegradable pH/thermosensitive hydrogels for sustained delivery of biologically active agents, WO 00/38651 A1). Such biodegradable gel matrices can be formed, for example, by crosslinking a proteinaceous component and a polysaccharide or mucopolysaccharide component, then loading with the inventive composition of matter to be delivered.

Liquid pharmaceutical compositions of the present invention that are sterile solutions or suspensions can be administered to a patient by injection, for example, intramuscularly, intrathecally, epidurally, intravascularly (e.g., intravenously or intraarterially), intraperitoneally or subcutaneously. (See, e.g., Goldenberg et al., Suspensions for the sustained release of proteins, U.S. Patent No. 6,245,740 and WO 00/38652 A1). Sterile solutions can also be administered by intravenous infusion. The inventive composition can be included in a sterile solid pharmaceutical composition, such as a lyophilized powder, which can be dissolved or suspended at a convenient time before administration to a patient using sterile water, saline, buffered saline or other appropriate sterile injectable medium.

Implantable sustained release formulations are also useful embodiments of the inventive pharmaceutical compositions. For example, the pharmaceutically acceptable carrier, being a biodegradable matrix implanted within the body or under the skin of a human or non-human vertebrate, can be a hydrogel similar to those described above. Alternatively, it may be formed from a poly-alpha-amino acid component. (Sidman, Biodegradable, implantable drug delivery device, and process for preparing and using same, U.S. Patent No. 4,351,337). Other techniques for making implants for delivery of drugs are also known and useful in accordance with the present invention.

In powder forms, the pharmaceutically acceptable carrier is a finely divided solid, which is in admixture with finely divided active ingredient(s), including the inventive composition. For example, in some embodiments, a powder form is useful when the pharmaceutical composition is configured as an inhalant. (See, e.g., Zeng et al., Method of preparing dry powder inhalation compositions, WO 2004/017918; Trunk et al., Salts of the CGRP antagonist BIBN4096 and inhalable powdered medicaments containing them, U.S. Patent No. 6,900,317).

One can dilute or increase the volume of the compound of the invention with an inert material. These diluents could include carbohydrates, especially mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts can also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo™, Emdex™, STA-Rx™ 1500, Emcompress™ and Avicell™.

Disintegrants can be included in the formulation of the pharmaceutical composition into a solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab™. Sodium starch glycolate, Amberlite™, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite can all be used.

Insoluble cationic exchange resin is another form of disintegrant. Powdered gums can be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders can be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An antifrictional agent can be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants can be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants can also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants can include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the compound of this invention into the aqueous environment a surfactant might be added as a wetting agent. Surfactants can include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose.

These surfactants could be present in the formulation of the protein or derivative either alone or as a mixture in different ratios.

Oral dosage forms. Also useful are oral dosage forms of the inventive compositionss. If necessary, the composition can be chemically modified so that oral delivery is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound and increase in circulation time in the body. Moieties useful as covalently attached half-life extending moieties in this invention can also be used for this purpose. Examples of such moieties include: PEG, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and Davis (1981), Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (Hocenberg and Roberts, eds.), Wiley-Interscience, New York, NY, pp 367-83; Newmark, et al. (1982), J. Appl. Biochem. 4:185-9. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are PEG moieties.

For oral delivery dosage forms, it is also possible to use a salt of a modified aliphatic amino acid, such as sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), as a carrier to enhance absorption of the therapeutic compounds of this invention. The clinical efficacy of a heparin formulation using SNAC has been demonstrated in a Phase II trial conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods."

In one embodiment, the pharmaceutically acceptable carrier can be a liquid and the pharmaceutical composition is prepared in the form of a solution, suspension, emulsion, syrup, elixir or pressurized composition. The active ingredient(s) (e.g., the inventive composition of matter) can be dissolved, diluted or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fats.

The liquid carrier can contain other suitable pharmaceutical additives such as detergents and/or solubilizers (e.g., Tween 80, Polysorbate 80), emulsifiers, buffers at appropriate pH (e.g., Tris-HCl, acetate, phosphate), adjuvants, anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol), sweeteners, flavoring agents, suspending agents, thickening agents, bulking substances (e.g., lactose, mannitol), colors, viscosity regulators, stabilizers, electrolytes, osmolutes or osmo-regulators. Additives can also be included in the formulation to enhance uptake of the inventive composition. Additives potentially having this property are for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Useful are oral solid dosage forms, which are described generally in Remington's Pharmaceutical Sciences (1990), supra, in Chapter 89, which is hereby incorporated by reference in its entirety. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets or pellets. Also, liposomal or proteinoid encapsulation can be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation can be used and the liposomes can be derivatized with various polymers (e.g., U.S. Patent No. 5,013,556). A description of possible solid dosage forms for the therapeutic is given in Marshall, K., Modern Pharmaceutics (1979), edited by G. S. Banker and C. T. Rhodes, in Chapter 10, which is hereby incorporated by reference in its entirety. In general, the formulation will include the inventive compound, and inert ingredients that allow for protection against the stomach environment, and release of the biologically active material in the intestine.

The composition of this invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents can all be included. For example, the protein (or derivative) can be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

In tablet form, the active ingredient(s) are mixed with a pharmaceutically acceptable carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired.
The powders and tablets preferably contain up to 99% of the active ingredient(s). Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Controlled release formulation can be desirable. The composition of this invention could be incorporated into an inert matrix that permits release by either diffusion or leaching mechanisms e.g., gums. Slowly degenerating matrices can also be incorporated into the formulation, e.g., alginates, polysaccharides. Another form of a controlled release of the compositions of this invention is by a method based on the Oros™ therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. Some enteric coatings also have a delayed release effect.

Other coatings can be used for the formulation. These include a variety of sugars that could be applied in a coating pan. The therapeutic agent could also be given in a film-coated tablet and the materials used in this instance are divided into 2 groups. The first are the nonenteric materials and include methylcellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxymethyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating can be carried out in a pan coater or in a fluidized bed or by compression coating.

<u>Pulmonary delivery forms</u>. Pulmonary delivery of the inventive compositions is also useful. The protein (or derivative) is delivered to the lungs of

a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. (Other reports of this include Adjei et al., Pharma. Res. (1990) 7: 565-9; Adjei et al. (1990), Internatl. J. Pharmaceutics 63: 135-44 (leuprolide acetate); Braquet et al. (1989), J. Cardiovasc. Pharmacol. 13 (suppl.5): s.143-146 (endothelin-1); Hubbard et al. (1989), Annals Int. Med. 3: 206-12 (α1-antitrypsin); Smith et al. (1989), J. Clin. Invest. 84: 1145-6 (α1-proteinase); Oswein et al. (March 1990), "Aerosolization of Proteins," Proc. Symp. Resp. Drug Delivery II, Keystone, Colorado (recombinant human growth hormone); Debs et al. (1988), J. Immunol. 140: 3482-8 (interferon-γ and tumor necrosis factor α) and Platz et al., U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor). Useful in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts. (See, e.g., Helgesson et al., Inhalation device, U.S. Patent No. 6,892,728; McDerment et al., Dry powder inhaler, WO 02/11801 A1; Ohki et al., Inhalant medicator, U.S. Patent No. 6,273,086).

All such devices require the use of formulations suitable for the dispensing of the inventive compound. Typically, each formulation is specific to the type of device employed and can involve the use of an appropriate propellant material, in addition to diluents, adjuvants and/or carriers useful in therapy.

The inventive compound should most advantageously be prepared in particulate form with an average particle size of less than 10 μm (or microns), most preferably 0.5 to 5 μm, for most effective delivery to the distal lung.

Pharmaceutically acceptable carriers include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations can include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants can be used. PEG can be used (even apart from its use in derivatizing the protein or analog). Dextrans, such as cyclodextran, can be used. Bile salts and other related enhancers can be used. Cellulose and cellulose derivatives can be used. Amino acids can be used, such as use in a buffer formulation.

Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise the inventive compound dissolved in water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation can also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure). The nebulizer formulation can also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the inventive compound suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid can also be useful as a surfactant. (See, e.g., Bäckström et al., Aerosol drug formulations containing hydrofluoroalkanes and alkyl saccharides, U.S. Patent No. 6,932,962).

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing the inventive compound and can also include a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation.

Nasal delivery forms. In accordance with the present invention, intranasal delivery of the inventive composition of matter and/or pharmaceutical compositions is also useful, which allows passage thereof to the blood stream directly after administration to the inside of the nose, without the necessity for deposition of the product in the lung. Formulations suitable for intransal administration include those with dextran or cyclodextran, and intranasal delivery devices are known. (See, e.g, Freezer, Inhaler, U.S. Patent No. 4,083,368).

Transdermal and transmucosal (e.g., buccal) delivery forms). In some embodiments, the inventive composition is configured as a part of a pharmaceutically acceptable transdermal or transmucosal patch or a troche. Transdermal patch drug delivery systems, for example, matrix type transdermal patches, are known and useful for practicing some embodiments of the present pharmaceutical compositions. (E.g., Chien et al., Transdermal estrogen/progestin dosage unit, system and process, U.S. Patent Nos. 4,906,169 and 5,023,084; Cleary et al., Diffusion matrix for transdermal drug administration and transdermal drug delivery devices including same, U.S. Patent No. 4,911,916; Teillaud et al., EVA-based transdermal matrix system for the administration of an estrogen and/or a progestogen, U.S. Patent No. 5.605,702; Venkateshwaran et al., Transdermal drug delivery matrix for coadministering estradiol and another steroid, U.S. Patent No. 5,783,208; Ebert et al., Methods for providing testosterone and optionally estrogen replacement therapy to women, U.S. Patent No. 5,460,820). A variety of pharmaceutically acceptable systems for transmucosal delivery of therapeutic agents are also known in the art and are compatible with the practice of the present invention. (E.g., Heiber et al., Transmucosal delivery of macromolecular drugs, U.S. Patent Nos. 5,346,701 and 5,516,523; Longenecker et al., Transmembrane formulations for drug administration, U.S. Patent No. 4,994,439).

Buccal delivery of the inventive compositions is also useful. Buccal delivery formulations are known in the art for use with peptides. For example, known tablet or patch systems configured for drug delivery through the oral mucosa (e.g., sublingual mucosa), include some embodiments that comprise an inner layer containing the drug, a permeation enhancer, such as a bile salt or fusidate, and a hydrophilic polymer, such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, dextran, pectin, polyvinyl pyrrolidone, starch, gelatin, or any number of other polymers known to be useful for this purpose. This inner layer can have one surface adapted to contact and adhere to the moist mucosal tissue of the oral cavity and can have an opposing surface adhering to an overlying non-adhesive inert layer. Optionally, such a transmucosal delivery system can be in the form of a bilayer tablet, in which the inner layer also contains additional binding agents, flavoring agents, or fillers. Some useful systems employ a non-ionic detergent along with a permeation enhancer. Transmucosal delivery devices may be in free form, such as a cream, gel, or ointment, or may comprise a determinate form such as a tablet, patch or troche. For example, delivery of the inventive composition can be via a transmucosal delivery system comprising a laminated composite of, for example, an adhesive layer, a backing layer, a permeable membrane defining a reservoir containing the inventive composition, a peel seal disc underlying the membrane, one or more heat seals, and a removable release liner. (E.g., Ebert et al., Transdermal delivery system with adhesive overlay and peel seal disc, U.S. Patent No. 5,662,925; Chang et al., Device for administering an active agent to the skin or mucosa, U.S. Patent Nos. 4,849,224 and 4,983,395). These examples are merely illustrative of available transmucosal drug delivery technology and are not limiting of the present invention.

Dosages. The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the inventive compound per kilogram of body weight, preferably 0.1-150 micrograms per kilogram.

The following working examples are illustrative and not to be construed in any way as limiting the scope of the present invention.

EXAMPLES

Example 1

huFc(IgG1) variants constructed for bacterial expression

By way of example, four variants of human Fc domain (huFc(IgG1) were constructed.

1) huFc(IgG1) with a Q143C mutation (at position 143 of SEQ ID NO:599; designated "Strain 13300") was made as follows. Two PCR fragments introducing the Q143C mutation were amplified from a plasmid encoding the huFc(IgG1). The first PCR fragment was amplified by the following two primers:

3430-37

GAGGAATAACATATGGACAAAACTCACACATGTCCACCT (SEQ ID NO: 641), which encodes the first 8 amino acids of huFc(IgG1) plus a 15-nucleotide 5' extension including a NdeI site; and

4220-28

GGTCAGGCTGACGCAGTTCTTGGTCAG (SEQ ID NO: 642), which encodes 9 amino acids of huFc(IgG1) from the 139th to the 147th amino acid with the 143th amino acid mutated from Glutamine to Cysteine in the 3' orientation.

The second PCR fragment was amplified by the following two primers:

4220-27

CTGACCAAGAACTGCGTCAGCCTGACC (SEQ ID NO: 643), which encodes 9 amino acids of huFc(IgG1) from the 139th to the 147th amino acid with the 143th amino acid mutated from Glutamine to Cysteine in the 5' orientation.

3421-87

CCGCGGCGTCTCGAGATTATTTACCCGGAGACAGGGAGAGGCT (SEQ ID NO: 644), which encodes the last 8 amino acids of huFc(IgG1), a stop codon and a 15-nucleotide 3' extension including a XhoI site.

The 2 PCR fragments were again amplified with primers 3430-37 and 3421-87. The PCR product was cloned in pAMG21 vector and sequence-confirmed by DNA sequencing. The E.coli strain that harbors this plasmid is named strain 13300.

The relevant coding sequence of Strain 13300 is:

1 ATGGACAAAA CTCACACATG TCCACCTTGC CCAGCACCTG AACTCCTGGG
51 GGGACCGTCA GTTTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA
101 TCTCCCGGAC CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA
151 GACCCTGAGG TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA
201 TGCCAAGACA AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG
251 TCAGCGTCCT CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC
301 AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT
351 CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC
401 CATCCCGGGA TGAGCTGACC AAGAACTGCG TCAGCCTGAC CTGCCTGGTC
451 AAAGGCTTCT ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA
501 GCCGGAGAAC AACTACAAGA CCACGCCTCC CGTGCTGGAC TCCGACGGCT
551 CCTTCTTCCT CTACAGCAAG CTCACCGTGG ACAAGAGCAG GTGGCAGCAG
601 GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA
651 CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATAAT//SEQ ID NO: 645

The translation of this nucleotide sequence is as follows:

Strain 13300 (huFC(IgG1)Q143C):

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNCVSLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGK// (SEQ ID NO: 646).

2) huFc(IgG1) with a L139C mutation (at position 139 of SEQ ID NO:599; designated "Strain 13322") was made following procedures similar to those described in (1) above using the following primers and procedures.

The first PCR fragment was amplified by the following two primers:

<u>3430-37</u>

GAGGAATAACATATGGACAAAACTCACACATGTCCACCT (SEQ ID NO: 641), which encodes the first 8 amino acids of huFc(IgG1) plus a 15-nucleotide 5' extension including a NdeI site and

<u>4220-26</u>

CTGGTTCTTGGTGCACTCATCCCGGGA (SEQ ID NO: 647), which encodes 9 amino acids of huFc(IgG1) from the 135th to the 143th amino acid with the 138th amino acid mutated from Leucine to Cysteine in the 3' orientation.

The second PCR fragment was amplified by the following two primers:

<u>4220-25</u>

TCCCGGGATGAGTGCACCAAGAACCAG (SEQ ID NO: 648), which encodes 9 amino acids of huFc(IgG1) from the 135th to the 143th amino acid with the 138th amino acid mutated from Leucine to Cysteine in the 5' orientation.

<u>3421-87</u>

CCGCGGCGTCTCGAGATTATTTACCCGGAGACAGGGAGAGGCT (SEQ ID NO: 644), which encodes the last 8 amino acids of huFc(IgG1), a stop codon and a 15-nucleotide 3' extension including a XhoI site. The 2 PCR fragments were again amplified with primers 3430-37 and 3421-87. The PCR product was cloned in pAMG21 vector and sequenced-confirmed by DNA sequencing. The E.coli strain that harbors this plasmid is named strain 13322.

The relevant coding sequence of Strain 13322 is:

1 ATGGACAAAA CTCACACATG TCCACCTTGC CCAGCACCTG AACTCCTGGG
51 GGGACCGTCA GTTTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA
101 TCTCCCGGAC CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA
151 GACCCTGAGG TCAAGTTTAA CTGGTACGTG GACGGCGTGG AGGTGCATAA
201 TGCCAAGACA AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG
251 TCAGCGTCCT CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC
301 AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT
351 CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC
401 CATCCCGGGA TGAGTGCACC AAGAACCAGG TCAGCCTGAC CTGCCTGGTC
451 AAAGGCTTCT ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA
501 GCCGGAGAAC AACTACAAGA CCACGCCTCC CGTGCTGGAC TCCGACGGCT
551 CCTTCTTCCT CTACAGCAAG CTCACCGTGG ACAAGAGCAG GTGGCAGCAG
601 GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA
651 CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATAAT// SEQ ID NO: 649.

The translation of this nucleotide sequence is as follows:

Strain 13322 (huFc(IgG1)L139C):

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE

51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY

101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDECT KNQVSLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGK//(SEQ ID NO: 650).

3) huFc(IgG1) with a S145C mutation (at position 145 of SEQ ID NO:599; designated "Strain 13323") was made following procedures similar to those described in (1) above using the following primers and procedures. The first PCR fragment was amplified by the following two primers:

<u>3430-37</u>

GAGGAATAACATATGGACAAAACTCACACATGTCCACCT (SEQ ID NO: 641) which encodes the first 8 amino acids of huFc(IgG1) plus a 15-nucleotide 5' extension including a NdeI site and

<u>4220-30</u>

CAGGCAGGTCAGGCAGACCTGGTTCTT (SEQ ID NO: 651), which encodes the 9 amino acids of huFc(IgG1) from the 141th to the 149th amino acid with the 145th amino acid mutated from Serine to Cysteine in the 3' orientation.

The second PCR fragment was amplified by the following two primers:

<u>4220-29</u>

AAGAACCAGGTCTGCCTGACCTGCCTG (SEQ ID NO: 652), which encodes the 9 amino acids of huFc(IgG1) from the 141th to the 149th amino acid with the 145th amino acid mutated from Serine to Cysteine in the 5' orientation.

<u>3421-87</u>

CCGCGGCGTCTCGAGATTATTTACCCGGAGACAGGGAGAGGCT (SEQ ID NO: 644), which encodes the last 8 amino acids of huFc(IgG1), a stop codon and a 15-nucleotide 3' extension including a XhoI site. The 2 PCR fragments were again amplified with primers 3430-37 and 3421-87. The PCR product was cloned in pAMG21 vector and sequence-confirmed by DNA sequencing. The E.coli strain that harbors this plasmid is named strain 13323.

The relevant coding sequence of Strain 13323 is:

1 ATGGACAAAA CTCACACATG TCCACCTTGC CCAGCACCTG AACTCCTGGG
51 GGGACCGTCA GTTTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA
101 TCTCCCGGAC CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA
151 GACCCTGAGG TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA
201 TGCCAAGACA AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG
251 TCAGCGTCCT CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC
301 AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT
351 CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC
401 CATCCCGGGA TGAGCTGACC AAGAACCAGG TCTGCCTGAC CTGCCTGGTC
451 AAAGGCTTCT ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA
501 GCCGGAGAAC AACTACAAGA CCACGCCTCC CGTGCTGGAC TCCGACGGCT
551 CCTTCTTCCT CTACAGCAAG CTCACCGTGG ACAAGAGCAG GTGGCAGCAG
601 GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA
651 CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATAAT// SEQ ID NO: 653

The translation of this sequence is as follows:

Strain 13323 (huFc(IgG1)S145C):

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVCLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGK//(SEQ ID NO: 654).

4) huFc(IgG1) with a S196C mutation (at position 196 of SEQ ID NO:599; designated "Strain 13324") was made following procedures similar to those described in (1) above using the following primers and procedures. The first PCR fragment was amplified by the following two primers:

<u>3430-37</u>

GAGGAATAACATATGGACAAAACTCACACATGTCCACCT (SEQ ID NO: 641), which encodes the first 8 amino acids of huFc(IgG1) plus a 15-nucleotide 5' extension including a NdeI site and

<u>4220-32</u>

CTGCTGCCACCTGCACTTGTCCACGGT (SEQ ID NO: 655), which encodes 9 amino acids of huFc(IgG1) from the 192th to the 200th amino acid with the 196th amino acid mutated from Serine to Cysteine in the 3' orientation.

The second PCR fragment was amplified by the following two primers:

<u>4220-31</u>

ACCGTGGACAAGTGCAGGTGGCAGCAG (SEQ ID NO: 656), which encodes 9 amino acids of huFc(IgG1) from the 192th to the 200th amino acid with the 196th amino acid mutated from Serine to Cysteine in the 5' orientation.

<u>3421-87</u>

CCGCGGCGTCTCGAGATTATTTACCCGGAGACAGGGAGAGGCT (SEQ ID NO: 644), which encodes the last 8 amino acids of huFc(IgG1), a stop codon and a 15-nucleotide 3' extension including a XhoI site. The 2 PCR fragments were again amplified with primers 3430-37 and 3421-87. The PCR product was cloned in pAMG21 vector and sequenced-confirmed by DNA sequencing. The E.coli strain that harbors this plasmid is named strain 13324.

The relevant coding sequence of Strain 13324 is:

1 ATGGACAAAA CTCACACATG TCCACCTTGC CCAGCACCTG AACTCCTGGG
51 GGGACCGTCA GTTTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA
101 TCTCCCGGAC CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA
151 GACCCTGAGG TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA
201 TGCCAAGACA AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG
251 TCAGCGTCCT CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC
301 AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT
351 CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC
401 CATCCCGGGA TGAGCTGACC AAGAACCAGG TCAGCCTGAC CTGCCTGGTC
451 AAAGGCTTCT ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA
501 GCCGGAGAAC AACTACAAGA CCACGCCTCC CGTGCTGGAC TCCGACGGCT
551 CCTTCTTCCT CTACAGCAAG CTCACCGTGG ACAAGTGCAG GTGGCAGCAG
601 GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA
651 CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATAAT//SEQ ID NO: 657

The translation of this nucleotide sequence is as follows:

Strain 13324 (huFC(IgG1)S196C):

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE

51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY

101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKCRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGK//(SEQ ID NO: 658).

Example 2

Purification of Fc-Cysteine Analogs

The cDNA clones constructed as described in Example 1 hereinabove: Strain 13300 (huFc(IgG1)Q143C), Strain 13322 (huFc(IgG1)L139C), Strain 13323 (huFc(IgG1)S145C) and Strain 13324 (huFc(IgG1)S196C) were transformed in *E. coli* and expressed in inclusion bodies. Cell pastes from each strain were resuspended in 10ml water/g paste, lysed by three passages through a microfluidizer and the insoluble inclusion body (IB) fraction was collected by centrifugation. The IBs were subsequently washed with 1% deoxycholate, centrifuged and washed again with water. The final pellet of deoxycholate washed inclusion bodies (DWIBs) was weighed and frozen at -80° C.

The frozen DWIBs, from each clone, were then thawed and resuspended in 1ml water/g DWIBs, then solubilized and reduced by the addition of 9 ml of 8 M buffered Gdn-HCl, 11 mM DTT. The solubilization proceeded at room temperature, with stirring, for 1 hour.

Each huFc-cysteine analog was then refolded by rapid dilution (20-fold) of the solubilized DWIBs into a refolding buffer consisting of 2 M Urea, 150 mM Arginine, 50 mM Tris, 1 mM Cysteine, 3 mM Cystamine, pH 8.5. The refolding reaction was allowed to proceed for 48-72 hours with gentle stirring at 4° C.

Purification of the huFc-cysteine analogs began affinity column chromatography using MAb Select resin (GE Healthcare, Piscataway, NJ). Briefly, the refold reaction was clarified by centrifugation followed by 0.45 micron filtration. The filtered refold was then loaded to a MAb select column pre-equilibrated in PBS. After loading, the column was further washed with 3 column volumes PBS, then eluted with 0.1 N acetic acid. The protein fraction that was acid eluted from the MAb Select column was immediately dialyzed into 10 mM NaOAc, 50 mM NaCl, pH 5.0.

Additional purification was achieved by cation exchange chromatography using SP Sepharose HP resin (GE Healthcare, Piscataway, NJ). Briefly, after dialysis, the MAb Select eluted pool was loaded to the ion exchange column, pre-equilibrated in 10 mM NaOAc, 50 mM NaCl, pH 5.0, washed with 3 column volumes of equilibration buffer, then eluted with a linear 50-500 mM NaCl gradient. The eluted peaks were evaluated by SDS-PAGE and the peaks containing protein of approximately 51 kD were pooled and concentrated. The concentrated pools were then dialyzed into PBS and concentrations determined spectrascopically using calculated extinction coefficients.

The final pools were analyzed by SDS-PAGE, SEC-HPLC, RP-HPLC and LC-MS. Figure 5 shows the purity by SDS-PAGE gel of the 4 purified huFc-cysteine analogs. Figure 6 shows the purity of clone 13324 huFCS196C by SEC-HPLC. Figure 7 shows the purity and mass determinations of clone 13324 huFc(S196C) by LC-MS. Additional mass observed is consistent with cystamine adducts carried over from the refold reaction. The observed mass differential disappears when the samples are reduced prior to LC-MS analyses, further indicating a mixed disulphide adduct is present.

<u>Example 3</u>

<u>Conjugation of Polyethylene glycol (PEG) to Fc-cysteine Analogs</u>

The huFc (S196C) analog, clone #13324, was selected as representative of the huFc-cysteine analogs produced, as described in Example 2 herein above, for the purpose of developing a site-selective conjugation process for the Fc-cysteine analogs. Since the LC-MS analyses of the purified huFc-cysteine analogs indicated the presence of mixed disulphides with low molecular weight adducts, a limited reduction step was undertaken prior to conjugation. This was followed by thiol specific PEGylation to assess the degree and site-selectivity of conjugation at the engineered cysteine.

Briefly, the huFc (S196C) analog described in Example 2 was partially reduced by titrating ris(2-carboxyethylphosphine) hydrochloride (TCEP) from 0-5 molar excess stoichiometries relative to the concentration of engineered cysteine. The reduction reaction was incubated 2 hours, at room temperature, in 50 mM sodium phosphate, 5 mM EDTA, pH 6.0 at a protein concentration of 1 mg/ml. TCEP and reduced adduct were removed by gel filtration using disposable Zebra desalt spin columns (Pierce, Rockford, IL) equilibrated in 50 mM sodium phosphate, 5 mM EDTA, pH 6.0. The reduced protein eluted from the gel filtration was then reacted with 20 kD mPEG-maleimide (Nektar Inc., Huntsville, AL) in a 2-fold molar excess over the engineered cysteine concentration. The PEGylation reaction was allowed to proceed overnight, at room temperature. The extent of modification was determined by SDS-PAGE (Figure 8A and Figure 8B) and by SEC-HPLC (Figure 9).

Next, the PEGylation reaction was scaled up using a 1:1.25 molar ratio of engineered cysteine to TCEP and the PEG-huFc(S196C) analog was purified by cation exchange chromatography. Purification was achieved with an SP Sepharose HP column (GE Healthcare, Piscataway, NJ) equilibrated in 20 mM sodium acetate, pH 4.0 and was eluted with a linear 0-0.5 M sodium chloride gradient. The eluted peaks were evaluated by SDS-PAGE and SEC-LS and were pooled and concentrated based on size. Figure 9 shows the SEC-LS result identifying the isolated PEG-huFc(S196C) conjugate, demonstrating a mass consistent with two 20 kD PEG molecules conjugated to one Fc dimmer (~53 kD). Subsequent peptide mapping confirmed Cys196 as the site of PEGylation in this pool.

Abbreviations

Abbreviations used throughout this specification are as defined below, unless otherwise defined in specific circumstances.

Ac	acetyl (used to refer to acetylated residues)
AcBpa	acetylated p-benzoyl-L-phenylalanine
ADCC	antibody-dependent cellular cytotoxicity
Aib	aminoisobutyric acid
bA	beta-alanine
Bpa	p-benzoyl-L-phenylalanine
BrAc	bromoacetyl ($BrCH_2C(O)$)
BSA	Bovine serum albumin
Bzl	Benzyl
Cap	Caproic acid
CTL	Cytotoxic T lymphocytes
CTLA4	Cytotoxic T lymphocyte antigen 4
DARC	Duffy blood group antigen receptor
DCC	Dicylcohexylcarbodiimide
Dde	1-(4,4-dimethyl-2,6-dioxo-cyclohexylidene)ethyl
EDTA	ethylene diamine tetraacetic acid
EMP	Erythropoietin-mimetic peptide
ESI-MS	Electron spray ionization mass spectrometry
EPO	Erythropoietin
Fmoc	fluorenylmethoxycarbonyl
G-CSF	Granulocyte colony stimulating factor
GH	Growth hormone
HCT	hematocrit
HGB	hemoglobin
hGH	Human growth hormone
HOBt	1-Hydroxybenzotriazole

HPLC	high performance liquid chromatography
IL	interleukin
IL-R	interleukin receptor
IL-1R	interleukin-1 receptor
IL-1ra	interleukin-1 receptor antagonist
Lau	Lauric acid
LPS	lipopolysaccharide
LYMPH	lymphocytes
MALDI-MS	Matrix-assisted laser desorption ionization mass spectrometry
Me	methyl
MeO	methoxy
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
MMPI	matrix metalloproteinase inhibitor
1-Nap	1-napthylalanine
NEUT	neutrophils
NGF	nerve growth factor
Nle	norleucine
NMP	N-methyl-2-pyrrolidinone
PAGE	polyacrylamide gel electrophoresis
PBS	Phosphate-buffered saline
Pbf	2,2,4,6,7-pendamethyldihydrobenzofuran-5-sulfonyl
PCR	polymerase chain reaction
Pec	pipecolic acid
PEG	Poly(ethylene glycol)
pGlu	pyroglutamic acid
Pic	picolinic acid
PLT	platelets
pY	phosphotyrosine
PTFE	polytetrafluoroethylene

RBC	red blood cells
RBS	ribosome binding site
RP-HPLC	reversed phase HPLC
RT	room temperature (25 °C)
Sar	sarcosine
SDS	sodium dodecyl sulfate
STK	serine-threonine kinases
t-Boc	tert-Butoxycarbonyl
tBu	tert-Butyl
TGF	tissue growth factor
THF	thymic humoral factor
TK	tyrosine kinase
TMP	Thrombopoietin-mimetic peptide
TNF	Tissue necrosis factor
TPO	Thrombopoietin
TRAIL	TNF-related apoptosis-inducing ligand
Trt	trityl
UK	urokinase
UKR	urokinase receptor
VEGF	vascular endothelial cell growth factor
VIP	vasoactive intestinal peptide
WBC	white blood cells

What is claimed is:

1. A composition of matter, which comprises a monomeric or multimeric Fc domain having at least one additional functional moiety that is covalently bound to one or more specifically selected conjugation site(s) in the Fc domain through the side chain of an amino acid residue at the conjugation site(s).
2. The composition of matter of claim 1, wherein the additional functional moiety is a pharmacologically active moiety.
3. The composition of matter of claim 2, wherein the pharmacologically active moiety is a polypeptide, a peptide, or a peptidomimetic moiety.
4. The composition of matter of claim 3, wherein the peptide is a toxin peptide.
5. The composition of matter of claim 3, wherein the peptide comprises a cyclic peptide.
6. The composition of matter of claim 2, wherein the pharmacologically active moiety is a non-peptide organic moiety.
7. The composition of matter of Claim 1, wherein the conjugation site(s) is part of a loop region.
8. The composition of matter of Claim 7, wherein the loop region comprises a CH2 or CH3 loop region.
9. The composition of matter of claim 1, wherein the additional functional moiety is a labeled moiety comprising a radioisotope, an enzyme, a biotinyl moiety, a fluorophore, or a chromophore.
10. The composition of matter of claim 1, wherein the additional functional moiety is an immobilized substrate.
11. The composition of matter of claim 1, wherein the additional functional moiety is a half-life extending moiety.
12. The composition of matter of claim 11, wherein the half-life extending moiety is a polyethylene glycol, a copolymer of ethylene glycol, a polypropylene glycol, a copolymer of propylene glycol, a carboxymethylcellulose, a polyvinyl pyrrolidone, a poly-1,3-dioxolane,

a poly-1,3,6-trioxane, an ethylene/maleic anhydride copolymer, a polyaminoacid, a dextran n-vinyl pyrrolidone, a poly n-vinyl pyrrolidone, a propylene glycol homopolymer, a propylene oxide polymer, an ethylene oxide polymer, a polyoxyethylated polyol, a polyvinyl alcohol, a linear or branched glycosylated chain, a polyacetal, a long chain fatty acid, a long chain hydrophobic aliphatic group, an immunoglobulin F_c domain, an albumin, a transthyretin, a thyroxine-binding globulin, or a ligand that has an affinity for a long half-life serum protein, said ligand being selected from the group consisting of peptide ligands and small molecule ligands;

or a combination of any of these members.

13. The composition of matter of claim 1, wherein the one or more specifically selected conjugation site(s) is selected from the group consisting of underlined amino acid residue positions in Figure 1, boldface amino acid residue positions in Figure 2, highlighted amino acid residue positions in Figure 3, or a combination of any of these.

14. The composition of matter of claim 1, wherein the one or more specifically selected conjugation site(s) is selected from the group consisting of underlined amino acid residue positions in Figure 3.

15. The composition of matter of claim 1, wherein the one or more specifically selected conjugation site(s) corresponds to a site selected from the group consisting of position 1 of SEQ ID NO: 600, position 2 of SEQ ID NO: 600, position 3 of SEQ ID NO: 600, position 4 of SEQ ID NO: 600, position 5 of SEQ ID NO: 600, position 6 of SEQ ID NO: 600, position 9 of SEQ ID NO: 600, position 11 of SEQ ID NO: 600, position 13 of SEQ ID NO: 600, position 16 of SEQ ID NO: 600, position 17 of SEQ ID NO: 600, position 226 of SEQ ID NO: 600, and position 227 of SEQ ID NO: 600, or a combination of any of these.

16. The composition of matter of claim 1, wherein the amino acid residue at the specifically selected conjugation site is a cysteine residue added to the Fc domain by substitution at an Fc site selected from the group

consisting of Leu139, Gln143, Ser145, and Ser196, relative to reference sequence SEQ ID NO:599, or at a combination of any of these.

17. The composition of matter of claim 1, wherein the one or more specifically selected conjugation site(s) is a site selected from a loop region identified in Table 3.

18. The composition of matter of claim1, wherein the amino acid residue at the specifically selected conjugation site is a cysteinyl residue.

19. The composition of matter of claim 18, wherein the cysteinyl residue is in a position of the amino acid sequence of the Fc domain, which in a native Fc domain sequence is not occupied by a cysteinyl residue.

20. The composition of matter of claim 1, wherein the additional functional moiety is a polymer.

21. The composition of matter of claim 1, wherein the additional functional moiety is polyethylene glycol.

22. The composition of matter of claim 1 of the formula

$$\begin{array}{c}(X^1)_a\text{-}\ F^1\ \text{-}(X^2)_b\\ |\\ (X^3)_g\end{array}$$

wherein:

F^1 is a monomer of the monomeric or multimeric Fc domain;

X^1 is covalently bound to the N-terminus of F^1 through the α-amino site of F^1;

X^2 is covalently bound to the C-terminus of F^1 through the α-carboxy site of F^1;

X^3 is covalently bound to the one or more specifically selected conjugation site(s) in F^1 selected from the group consisting of underlined residue positions in Figure 1, boldface residue positions in Figure 2, highlighted residue positions in Figure 3, underlined residue positions in Figure 3, and a cysteine residue added to the Fc domain by substitution at an Fc site selected from the group consisting of Leu139, Gln143, Ser145, and Ser196, relative to reference sequence SEQ ID NO:599, or, if g >1, any combination of these members;

X^1, X^2, and X^3 are each independently selected from $-(L^1)_c-P^0$, $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

P^0, P^1, P^2, P^3, and P^4 are each independently selected from the group consisting of:

i) a pharmaceutically acceptable polymer or dextran;

ii) a pharmacologically active polypeptide, peptide, peptidomimetic, or non-peptide organic moiety;

iii) a radioisotope, an enzyme, a biotinyl moiety, a fluorophore, or a chromophore; and

iv) an immobilized substrate, provided that in a chain comprising more than one additional functional moieties, the immobilized substrate is the moiety most distal from F^1, and there can be no more than one immobilized substrate in the chain;

L^1, L^2, L^3, and L^4 are each independently linkers;

a, b, c, d, e, and f are each independently 0 or 1; and

g is 1, 2, 3, or 4.

23. The composition of matter of Claim 22 wherein the Fc domain comprises an IgG Fc domain.

24. The composition of matter of claim 1 wherein the Fc domain comprises an IgG1 Fc domain.

25. The composition of matter of Claim 24, wherein the IgG1 Fc domain comprises SEQ ID NO: 600 or SEQ ID NO: 603.

26. The composition of matter of Claim 22, wherein a = 0 and b = 1.

27. The composition of matter of Claim 22, wherein a = 1 and b = 0.

28. The composition of matter of Claim 22, wherein a = 1 and b = 1.

29. The composition of matter of Claim 22, wherein a = 0 and b = 0.

30. The composition of matter of Claim 22, wherein X^3 comprises polyethylene glycol (PEG).

31. The composition of matter of Claim 22, wherein X^3 has the structure -$(L^1)_c$-P^1 .

32. The composition of matter of Claim 22, wherein X^3 has the structure -$(L^1)_c$-P^1-$(L^2)_d$-P^2.

33. The composition of matter of Claim 22, wherein g = 1 or 2.

34. The composition of matter of Claim 1, wherein the Fc domain is an IgG1 Fc domain comprising an amino acid sequence SEQ ID NO: 603, and the one or more specifically selected conjugation site(s) is selected from an amino acid residue position contained in a loop region that comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 601, 602, 604, 605, 606, 607, 608, 609, 610, and 611.

35. The composition of matter of Claim 1, comprising an angiotensin-2 (ang-2) binding peptide or polypeptide.

36. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises an angiotensin-2 (ang-2) binding peptide or polypeptide.

37. The composition of matter of Claim 36, wherein the ang-2 binding peptide or polypeptide comprises an amino acid sequence selected from SEQ ID NOS: 100 to 189 and 612.

38. The composition of matter of Claim 36, wherein the ang-2 binding peptide comprises SEQ ID NO: 147.

39. The composition of matter of Claim 36, wherein F^1 comprises an IgG1 Fc domain.

40. The composition of matter of Claim 1, comprising a myostatin binding peptide or polypeptide.

41. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises a myostatin binding peptide or polypeptide.

42. The composition of matter of Claim 41, wherein the myostatin binding peptide or polypeptide comprises an amino acid sequence selected from SEQ ID NOS: 219 to 509, 613, and 616.

43. The composition of matter of Claim 41, wherein the myostatin binding peptide comprises SEQ ID NO: 365.

44. The composition of matter of Claim 41, wherein F^1 comprises an IgG1 Fc domain.

45. The composition of matter of Claim 1, comprising an erythropoietin-mimetic (EPO-mimetic) peptide or polypeptide.

46. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises an erythropoietin-mimetic (EPO-mimetic) peptide or polypeptide.

47. The composition of matter of Claim 46, wherein the EPO-mimetic peptide or polypeptide comprises an amino acid sequence selected from SEQ ID NOS: 1 to 27 and 614.

48. The composition of matter of Claim 46, wherein the EPO-mimetic peptide comprises SEQ ID NO: 2.

49. The composition of matter of Claim 46, wherein F^1 comprises an IgG1 Fc domain.

50. The composition of matter of Claim 1 comprising a thrombopoietin-mimetic (TPO-mimetic) peptide or polypeptide.

51. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises a thrombopoietin-mimetic (TPO-mimetic) peptide or polypeptide.

52. The composition of matter of Claim 51, wherein the TPO-mimetic peptide or polypeptide comprises an amino acid sequence selected from SEQ ID NOS: 28 to 99 and 615.

53. The composition of matter of Claim 51, wherein the TPO-mimetic peptide comprises SEQ ID NO: 28.

54. The composition of matter of Claim 51, wherein F^1 comprises an IgG1 Fc domain

55. The composition of matter of Claim 1, comprising a nerve growth factor (NGF) binding peptide or polypeptide.

56. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises a nerve growth factor (NGF) binding peptide or polypeptide.

57. The composition of matter of Claim 56, wherein the NGF binding peptide or polypeptide comprises an amino acid sequence selected from SEQ ID NOS: 190 to 218.

58. The composition of matter of Claim 1, comprising a B cell activating factor (BAFF) binding peptide or polypeptide.

59. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises a B cell activating factor (BAFF) binding peptide polypeptide.

60. The composition of matter of Claim 59, wherein the BAFF binding peptide or polypeptide comprises an amino acid sequence selected from SEQ ID NOS: 510 to 594.

61. A pharmaceutical composition, comprising the composition of matter of Claim 1 and a pharmaceutically acceptable carrier.

62. A DNA encoding a composition of matter of Claim 1.

63. An expression vector comprising the DNA of Claim 62.

64. A host cell comprising the expression vector of Claim 63.

65. The host cell of Claim 64, wherein the cell is a bacterial or mammalian cell.

66. A process for preparing a pharmacologically active compound, which comprises:

a) selecting at least one internal conjugation site of an Fc domain sequence, said conjugation site being amenable to conjugation of an additional functional moiety by a defined conjugation chemistry through the side chain of an amino acid residue at the conjugation site; and

b) conjugating a predetermined functional moiety to the selected conjugation site by employing the defined conjugation chemistry.

67. The process of Claim 66, wherein the internal conjugation site of the Fc domain is in a loop region.

68. The process of Claim 66, wherein selecting the at least one internal conjugation site further comprises substituting a cysteinyl residue for

an amino acid residue in the selected internal conjugation site, or inserting a cysteinyl residue into the selected internal conjugation site, whereby the additional functional moiety is conjugated through the side chain of said cysteinyl residue.

69. The process of Claim 66, wherein selecting the at least one internal conjugation site further comprises substituting a non-canonical amino acid residue for an amino acid residue in the selected internal conjugation site, or inserting a non-canonical amino acid residue into the selected internal conjugation site, whereby the additional functional moiety is conjugated through the side chain of said non-canonical amino acid residue.

70. The process of Claim 69, wherein the non-canonical amino acid residue is selected from the group consisting of azido-containing amino acid residues, keto-containing amino acid residues; alkyne-containing amino acid residues, alkene- containing amino acid residues, aryl halide-containing amino acid residues; and 1,2-aminothiol-containing amino acid residues.

71. The process of Claim 66, wherein a gene construct encoding the Fc domain sequence is expressed in a bacterial or a mammalian cell.

72. The composition of matter of Claim 1, wherein:
(a) the composition of matter is an antibody modified so that it comprises at least one X^3 additional functional moiety covalently bound to the Fc domain of the antibody through one or more specifically selected conjugation site(s) in the Fc domain selected from the group consisting of underlined residue positions in Figure 1, boldface residue positions in Figure 2, highlighted residue positions in Figure 3, underlined residue positions in Figure 3, and a cysteine residue added to the Fc domain by substitution at an Fc site selected from the group consisting of Leu139, Gln143, Ser145, and Ser196, relative to reference sequence SEQ ID NO:599, or, if there is more than one X^3, any combination of these members;

(b) X^3 is selected from $-(L^1)_c-P^0$, $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

P^0, P^1, P^2, P^3, and P^4 are each independently selected from the group consisting of:

i) a pharmaceutically acceptable polymer or dextran;

ii) a pharmacologically active polypeptide, peptide, peptidomimetic, or non-peptide organic moiety;

iii) a radioisotope, an enzyme, a biotinyl moiety, a fluorophore, or a chromophore; and

iv) an immobilized substrate, provided that in a chain comprising more than one additional functional moieties, the immobilized substrate is the moiety most distal from the Fc domain, and there can be no more than one immobilized substrate in the chain;

L^1, L^2, L^3, and L^4 are each independently linkers;

c, d, e, and f are each independently 0 or 1.

73. The composition of matter of Claim 22, wherein any of X^1, X^2, or X^3 comprises a polypeptide comprising SEQ ID NO: 617.

Figure 1.

Human Fc:

```
       1 DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED
PEVKFNWYVD
      61 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
PIEKTISKAK
     121 GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN
YKTTPPVLDS
     181 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
```

*IgG1 Fc_*

human Fc alone

1 MDKTHTCPPC PAPELLGGPS VFLF**PP**KPKD TLMISRTPEV TCVVV**DVSHE**

51 **DPE**VKFNWYV DGVE**VHNA**KT KPR**EEQYNST** YRVVSVLT**VL HQDWLNGKE**Y

101 KCKVS**NKALP APIEKTISKA KGQPREP**QVY TLPPSR**DELT K**NQVSLTCLV

151 KGFYPSDIAV EWES**NGQPEN N**YK**TTPPVLD SDGS**FFLYSK LTVD**KSRWQQ**

201 **GNV**FSCSVMH EALHNHYTQK SLSLSPGK*

Figure 3

IgG1 Fc_

human Fc alone

1 MDKTHTCPPC PAPELLGGPS VFLF**PP**KPKD TLMISRTPEV TCVVV**DVSHE**

51 **DPE**VKFNWYV DGVE**VHNA**KT KPR**EEQYNST** YRVVSVLT**VL** **HQDWLNGKE**Y

101 KCKVS**NKALP** **APIEKTISKA** **KGQPREP**QVY TLPPSR**DELT** **K**NQVSLTCLV

151 KGFYPSDIAV EWES**NGQPEN** **N**YK**TTPPVLD** **SDGS**FFLYSK LTVD**KSRWQQ**

201 **GNV**FSCSVMH EALHNHYTQK SLSLSPGK*

Figure 4

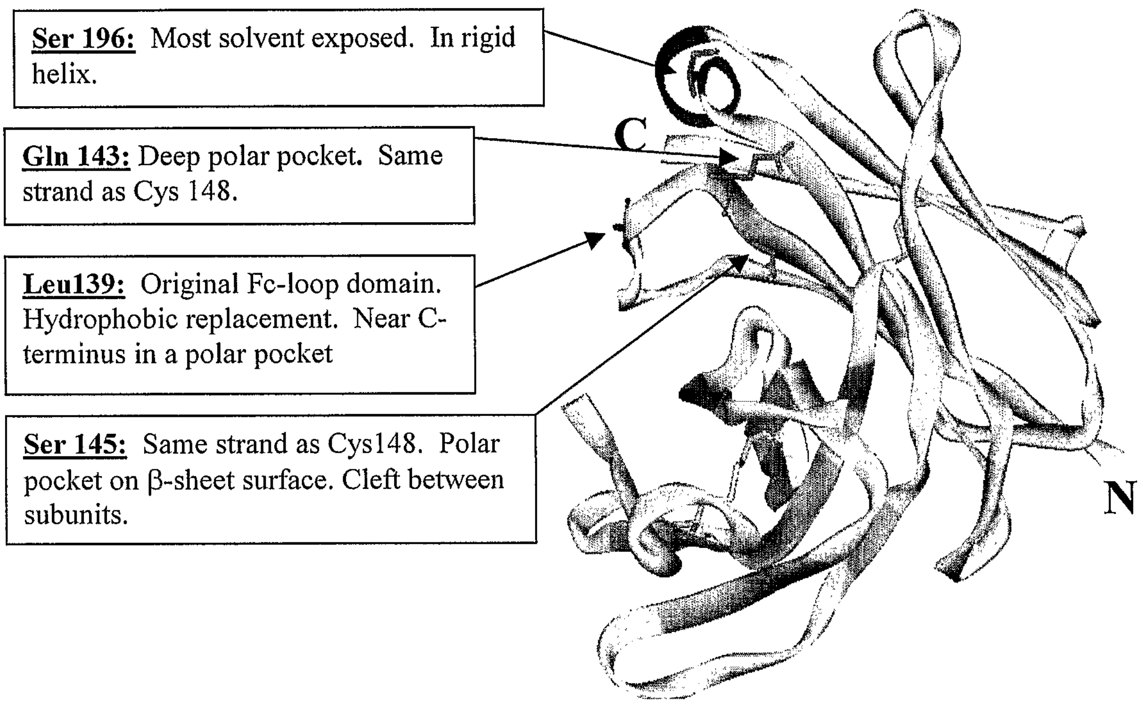

Ser 196: Most solvent exposed. In rigid helix.
Gln 143: Deep polar pocket. Same strand as Cys 148.
Leu139: Original Fc-loop domain. Hydrophobic replacement. Near C-terminus in a polar pocket
Ser 145: Same strand as Cys148. Polar pocket on β-sheet surface. Cleft between subunits.
C
N

FIGURE 5

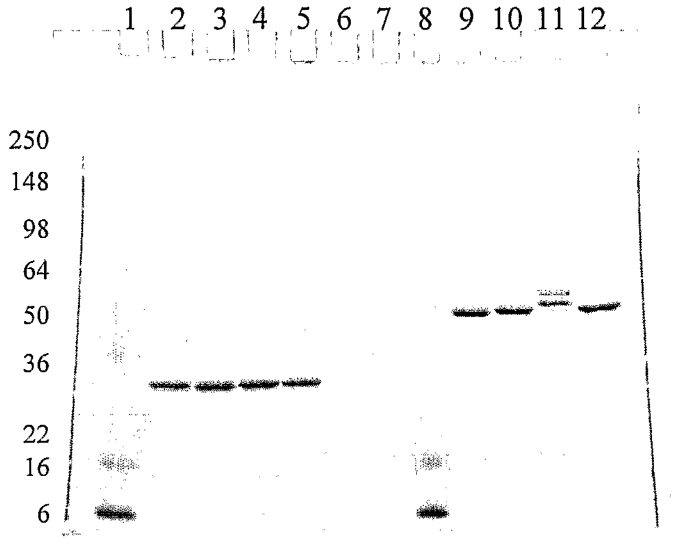


FIGURE 6

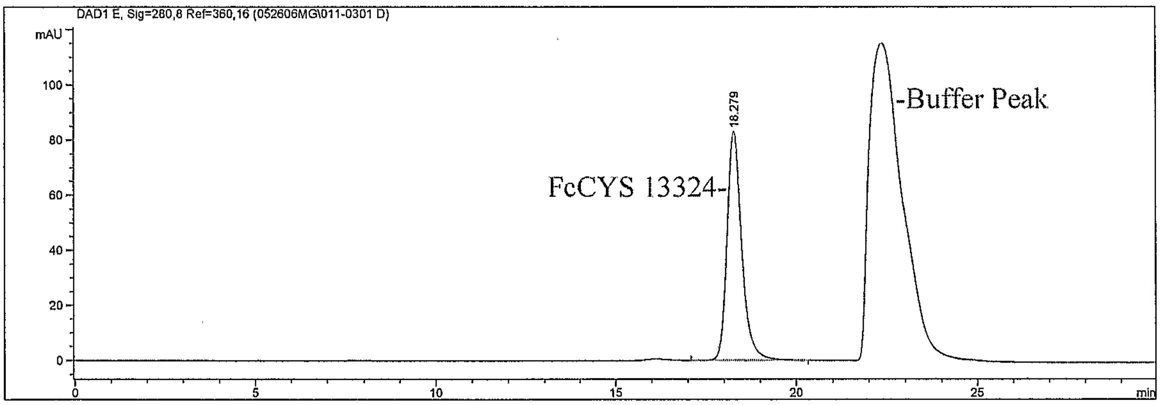


FIGURE 7

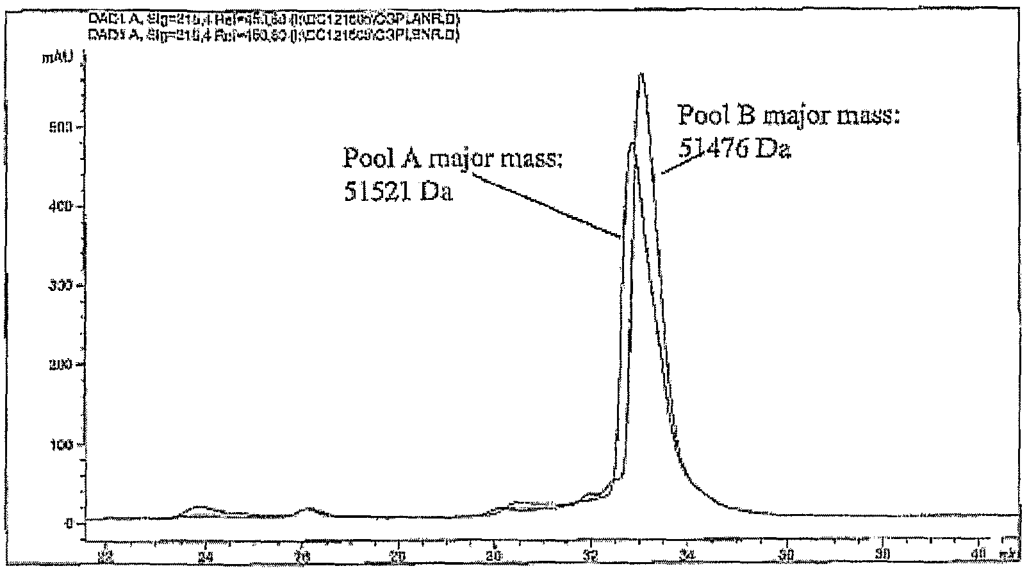


FIGURE 8A

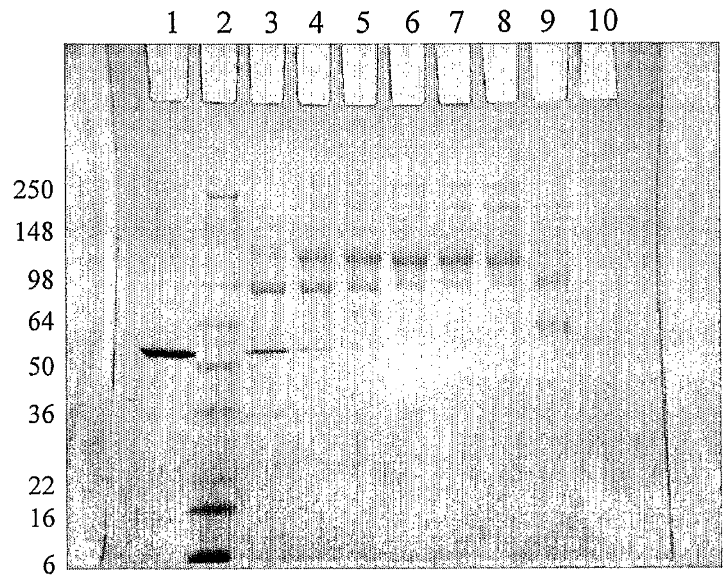


FIGURE 8B

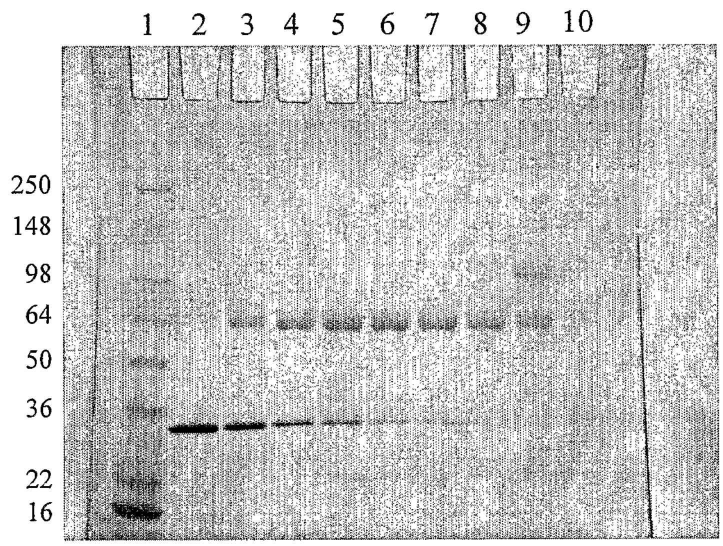
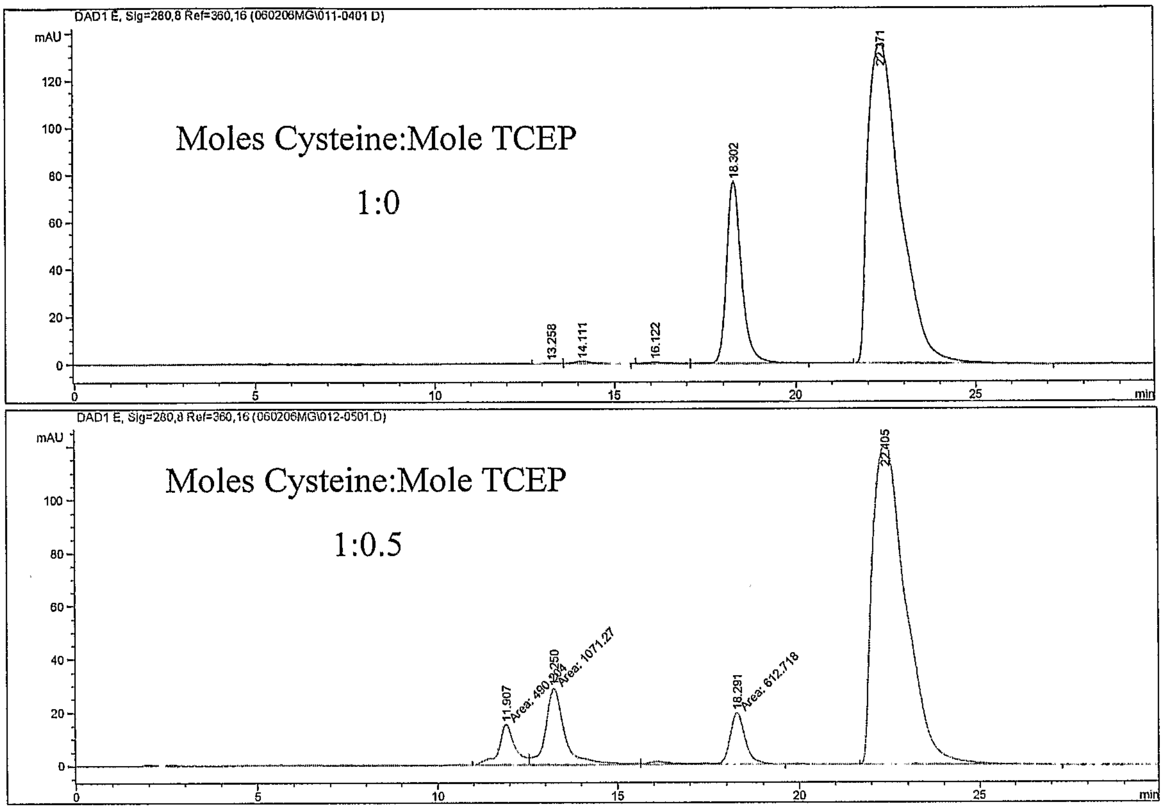


FIGURE 9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mAU
Moles Cysteine:Mole TCEP
1:0
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14.111
16.122
18.302
22.371
min
DAD1 E, Sig=280,8 Ref=360,16 (060206MG\012-0501.D)
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Area: 1071.27
18.291
Area: 612.718
22.405
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Pro Gln Gly Gly
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<400> 3

Gly Gly Asp Tyr His Cys Arg Met Gly Pro Leu Thr Trp Val Cys Lys
1   5   10   15

Pro Leu Gly Gly
            20

<210> 4
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<400> 4

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1   5   10   15

Pro Leu Gly Gly
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1   5   10   15

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1 5 10 15

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Pro Leu Arg Gly

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<210> 13
<211> 22
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Arg Pro Ser Pro Lys Ala
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<400> 16

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1 5 10 15

Tyr Lys Gly Gly

20

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Pro Gln

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Pro Leu Arg Gly
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1 5 10 15

Arg Pro Ser Pro Lys Ala
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Gly Val Arg Glu Val Ile Val Met His Met Leu
1 5 10

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Cys Thr Leu Arg Gln Trp Leu Gln Gly Cys
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<400> 43

Cys Thr Leu Gln Glu Phe Leu Glu Gly Cys
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Cys Thr Leu Arg Glu Trp Leu His Gly Gly Phe Cys
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<400> 47

Cys Thr Leu Arg Gln Trp Leu Ile Leu Leu Gly Met Cys
1 5 10

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Cys Thr Leu Arg Glu Phe Leu Asp Pro Thr Thr Ala Val Cys
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1 5 10

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Arg Glu Gly Pro Thr Leu Arg Gln Trp Met
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Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala
1 5 10

<210> 54
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<400> 54

Glu Arg Gly Pro Phe Trp Ala Lys Ala Cys
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<400> 55

Arg Glu Gly Pro Arg Cys Val Met Trp Met
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<210> 60
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Gly Gly

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Pro Lys Asn

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Arg Asp Thr

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<400> 66

His Gly Arg Val Gly Pro Thr Leu Arg Glu Trp Lys Thr Gln Val Ala
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Thr Lys Lys

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1 5 10 15

Thr Ser

<210> 68
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Ile Ser Asp Gly Pro Thr Leu Lys Glu Trp Leu Ser Val Thr Arg Gly
1 5 10 15

Ala Ser

<210> 69
<211> 18
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Ser Ile Glu Gly Pro Thr Leu Arg Glu Trp Leu Thr Ser Arg Thr Pro
1 5 10 15

His Ser

<210> 70
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Val Gly

<210> 71
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Arg Asp Leu Asp Gly Pro Thr Leu Arg Gln Trp Leu Pro Leu Pro Ser
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Val Gln

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Gln Ala

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1 5 10 15

Met Gly

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Ala Gln

<210> 75

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1 5 10 15

Met Met

<210> 76
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1 5 10 15

Gly Gln

<210> 77
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1 5 10 15

Met Val

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<400> 78

Gln Leu Gly His Gly Pro Thr Leu Arg Gln Trp Leu Ser Trp Tyr Arg

1 5 10 15

Gly Met

<210> 79
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 79

Glu Leu Arg Gln Gly Pro Thr Leu His Glu Trp Leu Gln His Leu Ala
1 5 10 15

Ser Lys

<210> 80
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 80

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

Asn Pro

<210> 81
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 81

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

Val Gly

<210> 82
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 82

Ala Val Pro Gln Gly Pro Thr Leu Lys Gln Trp Leu Leu Trp Arg Arg
1 5 10 15

Cys Ala

<210> 83
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 83

Arg Ile Arg Glu Gly Pro Thr Leu Lys Glu Trp Leu Ala Gln Arg Arg
1 5 10 15

Gly Phe

<210> 84
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 84

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

Leu Val

<210> 85
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 85

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

Ser Val

<210> 86
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 86

Ala Gly Arg Glu Gly Pro Thr Leu Arg Glu Trp Leu Asn Met Arg Val
1 5 10 15

Trp Gln

<210> 87
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 87

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

Trp Gly

<210> 88
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 88

Tyr Cys Asp Glu Gly Pro Thr Leu Lys Gln Trp Leu Val Cys Leu Gly
1 5 10 15

Leu Gln

<210> 89
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 89

Trp Cys Lys Glu Gly Pro Thr Leu Arg Glu Trp Leu Arg Trp Gly Phe
1 5 10 15

Leu Cys

<210> 90
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 90

Cys Ser Ser Gly Gly Pro Thr Leu Arg Glu Trp Leu Gln Cys Arg Arg
1 5 10 15

Met Gln

<210> 91
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 91

Cys Ser Trp Gly Gly Pro Thr Leu Lys Gln Trp Leu Gln Cys Val Arg
1 5 10 15

Ala Lys

<210> 92
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 92

Cys Gln Leu Gly Gly Pro Thr Leu Arg Glu Trp Leu Ala Cys Arg Leu
1 5 10 15

Gly Ala

<210> 93
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 93

Cys Trp Glu Gly Gly Pro Thr Leu Lys Glu Trp Leu Gln Cys Leu Val
1 5 10 15

Glu Arg

<210> 94
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 94

Cys Arg Gly Gly Gly Pro Thr Leu His Gln Trp Leu Ser Cys Phe Arg
1 5 10 15

Trp Gln

<210> 95
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 95

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

Gln Lys

<210> 96
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 96

Glu Leu Arg Ser Gly Pro Thr Leu Lys Glu Trp Leu Val Trp Arg Leu
1 5 10 15

Ala Gln

<210> 97
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 97

Gly Cys Arg Ser Gly Pro Thr Leu Arg Glu Trp Leu Ala Cys Arg Glu
1 5 10 15

Val Gln

<210> 98
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 98

Thr Cys Glu Gln Gly Pro Thr Leu Arg Gln Trp Leu Leu Cys Arg Gln
1 5 10 15

Gly Arg

<210> 99
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic peptide sequence

<400> 99

Gln Gly Tyr Cys Asp Glu Gly Pro Thr Leu Lys Gln Trp Leu Val Cys
1 5 10 15

Leu Gly Leu Gln His Ser
20

<210> 100
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 100

Trp Asp Pro Trp Thr
1 5

<210> 101
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 101

Trp Asp Pro Trp Thr Cys
1 5

<210> 102
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa in position 2 is an acidic or neutral polar amino acid residue

<400> 102

Cys Xaa Trp Asp Pro Trp Thr
1 5

<210> 103
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa in position 2 is an acidic or neutral polar amino acid residue

<400> 103

Cys Xaa Trp Asp Pro Trp Thr Cys
1 5

<210> 104
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 104

Pro Ile Arg Gln Glu Glu Cys Asp Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Trp Glu Val
20

<210> 105
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 105

Thr Asn Ile Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Asp His
1 5 10 15

Met Pro Gly Lys
20

<210> 106
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 106

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

Met Ala Glu Val
20

<210> 107
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 107

Asn Arg Leu Gln Glu Val Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Glu Asn Val
20

<210> 108
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 108

Ala Ala Thr Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Pro Arg Ser
20

<210> 109
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 109

Leu Arg His Gln Glu Gly Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Phe Asp Trp
20

<210> 110
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 110

Val Pro Arg Gln Lys Asp Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Tyr Val Gly
20

<210> 111
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 111

Ser Ile Ser His Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Gln Val Gly
20

<210> 112
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 112

Trp Ala Ala Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Gly Arg Met
20

<210> 113
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 113

Thr Trp Pro Gln Asp Lys Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Gly Ser Thr
20

<210> 114
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 114

Gly His Ser Gln Glu Glu Cys Gly Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Gly Thr Ser
20

<210> 115
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 115

Gln His Trp Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Asp His
1 5 10 15

Met Pro Ser Lys
20

<210> 116
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 116

Asn Val Arg Gln Glu Lys Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Pro Val Arg
20

<210> 117
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 117

Lys Ser Gly Gln Val Glu Cys Asn Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Pro Arg Asn

20

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

<220>
<223> Ang-2 binding peptide sequence

<400> 118

Val Lys Thr Gln Glu His Cys Asp Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Arg Glu Trp
20

<210> 119
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 119

Ala Trp Gly Gln Glu Gly Cys Asp Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Leu Pro Met
20

<210> 120
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 120

Pro Val Asn Gln Glu Asp Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Pro Pro Met
20

<210> 121
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 121

Arg Ala Pro Gln Glu Asp Cys Glu Trp Asp Pro Trp Thr Cys Ala His
1 5 10 15

Met Asp Ile Lys
20

<210> 122
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 122

His Gly Gln Asn Met Glu Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Phe Arg Tyr
20

<210> 123
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 123

Pro Arg Leu Gln Glu Glu Cys Val Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Pro Leu Arg
20

<210> 124
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 124

Arg Thr Thr Gln Glu Lys Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Glu Ser Gln
20

<210> 125
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 125

Gln Thr Ser Gln Glu Asp Cys Val Trp Asp Pro Trp Thr Cys Asp His
1 5 10 15

Met Val Ser Ser
20

<210> 126
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 126

Gln Val Ile Gly Arg Pro Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Leu Glu Gly Leu
20

<210> 127
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 127

Trp Ala Gln Gln Glu Glu Cys Ala Trp Asp Pro Trp Thr Cys Asp His
1 5 10 15

Met Val Gly Leu
20

<210> 128
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 128

Leu Pro Gly Gln Glu Asp Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Val Arg Ser
20

<210> 129
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 129

Pro Met Asn Gln Val Glu Cys Asp Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Pro Arg Ser
20

<210> 130
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 130

Phe Gly Trp Ser His Gly Cys Glu Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Gly Ser Thr
20

<210> 131
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 131

Lys Ser Thr Gln Asp Asp Cys Asp Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Val Gly Pro
20

<210> 132

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

<220>
<223> Ang-2 binding peptide sequence

<400> 132

Gly Pro Arg Ile Ser Thr Cys Gln Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Asp Gln Leu
20

<210> 133
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 133

Ser Thr Ile Gly Asp Met Cys Glu Trp Asp Pro Trp Thr Cys Ala His
1 5 10 15

Met Gln Val Asp
20

<210> 134
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 134

Val Leu Gly Gly Gln Gly Cys Glu Trp Asp Pro Trp Thr Cys Arg Leu
1 5 10 15

Leu Gln Gly Trp
20

<210> 135
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 135

Val Leu Gly Gly Gln Gly Cys Gln Trp Asp Pro Trp Thr Cys Ser His

1 5 10 15

Leu Glu Asp Gly
20

<210> 136
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 136

Thr Thr Ile Gly Ser Met Cys Glu Trp Asp Pro Trp Thr Cys Ala His
1 5 10 15

Met Gln Gly Gly
20

<210> 137
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 137

Thr Lys Gly Lys Ser Val Cys Gln Trp Asp Pro Trp Thr Cys Ser His
1 5 10 15

Met Gln Ser Gly
20

<210> 138
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 138

Thr Thr Ile Gly Ser Met Cys Gln Trp Asp Pro Trp Thr Cys Ala His
1 5 10 15

Met Gln Gly Gly
20

<210> 139
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 139

Trp Val Asn Glu Val Val Cys Glu Trp Asp Pro Trp Thr Cys Asn His
1 5 10 15

Trp Asp Thr Pro
20

<210> 140
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 140

Val Val Gln Val Gly Met Cys Gln Trp Asp Pro Trp Thr Cys Lys His
1 5 10 15

Met Arg Leu Gln
20

<210> 141
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 141

Ala Val Gly Ser Gln Thr Cys Glu Trp Asp Pro Trp Thr Cys Ala His
1 5 10 15

Leu Val Glu Val
20

<210> 142
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 142

Gln Gly Met Lys Met Phe Cys Glu Trp Asp Pro Trp Thr Cys Ala His
1 5 10 15

Ile Val Tyr Arg
20

<210> 143
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 143

Thr Thr Ile Gly Ser Met Cys Gln Trp Asp Pro Trp Thr Cys Glu His
1 5 10 15

Met Gln Gly Gly
20

<210> 144
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 144

Thr Ser Gln Arg Val Gly Cys Glu Trp Asp Pro Trp Thr Cys Gln His
1 5 10 15

Leu Thr Tyr Thr
20

<210> 145
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 145

Gln Trp Ser Trp Pro Pro Cys Glu Trp Asp Pro Trp Thr Cys Gln Thr
1 5 10 15

Val Trp Pro Ser
20

<210> 146
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 146

Gly Thr Ser Pro Ser Phe Cys Gln Trp Asp Pro Trp Thr Cys Ser His
1 5 10 15

Met Val Gln Gly
20

<210> 147
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 147

Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr Cys Glu His Met
1 5 10

<210> 148
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 148

Gln Asn Tyr Lys Pro Leu Asp Glu Leu Asp Ala Thr Leu Tyr Glu His
1 5 10 15

Phe Ile Phe His Tyr Thr
20

<210> 149
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 149

Leu Asn Phe Thr Pro Leu Asp Glu Leu Glu Gln Thr Leu Tyr Glu Gln
1 5 10 15

Trp Thr Leu Gln Gln Ser
20

<210> 150

<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 150

Thr Lys Phe Asn Pro Leu Asp Glu Leu Glu Gln Thr Leu Tyr Glu Gln
1 5 10 15

Trp Thr Leu Gln His Gln
20

<210> 151
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 151

Val Lys Phe Lys Pro Leu Asp Ala Leu Glu Gln Thr Leu Tyr Glu His
1 5 10 15

Trp Met Phe Gln Gln Ala
20

<210> 152
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 152

Val Lys Tyr Lys Pro Leu Asp Glu Leu Asp Glu Ile Leu Tyr Glu Gln
1 5 10 15

Gln Thr Phe Gln Glu Arg
20

<210> 153
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 153

Thr Asn Phe Met Pro Met Asp Asp Leu Glu Gln Arg Leu Tyr Glu Gln

1 5 10 15

Phe Ile Leu Gln Gln Gly
20

<210> 154
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 154

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

Trp Thr Leu Gln His Ala
20

<210> 155
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 155

Gln Lys Phe Gln Pro Leu Asp Glu Leu Glu Gln Thr Leu Tyr Glu Gln
1 5 10 15

Phe Met Leu Gln Gln Ala
20

<210> 156
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 156

Gln Asn Phe Lys Pro Met Asp Glu Leu Glu Asp Thr Leu Tyr Lys Gln
1 5 10 15

Phe Leu Phe Gln His Ser
20

<210> 157
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 157

Tyr Lys Phe Thr Pro Leu Asp Asp Leu Glu Gln Thr Leu Tyr Glu Gln
1 5 10 15

Trp Thr Leu Gln His Val
20

<210> 158
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 158

Gln Glu Tyr Glu Pro Leu Asp Glu Leu Asp Glu Thr Leu Tyr Asn Gln
1 5 10 15

Trp Met Phe His Gln Arg
20

<210> 159
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 159

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

Phe Met Leu Gln His Gln
20

<210> 160
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 160

Gln Lys Tyr Gln Pro Leu Asp Glu Leu Asp Lys Thr Leu Tyr Asp Gln
1 5 10 15

Phe Met Leu Gln Gln Gly
20

<210> 161
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 161

Gln Lys Phe Gln Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Lys Gln
1 5 10 15

Trp Thr Leu Gln Gln Arg
20

<210> 162
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 162

Val Lys Tyr Lys Pro Leu Asp Glu Leu Asp Glu Trp Leu Tyr His Gln
1 5 10 15

Phe Thr Leu His His Gln
20

<210> 163
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 163

Gln Lys Phe Met Pro Leu Asp Glu Leu Asp Glu Ile Leu Tyr Glu Gln
1 5 10 15

Phe Met Phe Gln Gln Ser
20

<210> 164
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 164

Gln Thr Phe Gln Pro Leu Asp Asp Leu Glu Glu Tyr Leu Tyr Glu Gln
1 5 10 15

Trp Ile Arg Arg Tyr His
20

<210> 165
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 165

Glu Asp Tyr Met Pro Leu Asp Ala Leu Asp Ala Gln Leu Tyr Glu Gln
1 5 10 15

Phe Ile Leu Leu His Gly
20

<210> 166
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 166

His Thr Phe Gln Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Tyr Gln
1 5 10 15

Trp Leu Tyr Asp Gln Leu
20

<210> 167
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 167

Tyr Lys Phe Asn Pro Met Asp Glu Leu Glu Gln Thr Leu Tyr Glu Glu
1 5 10 15

Phe Leu Phe Gln His Ala

20

<210> 168
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 168

Thr Asn Tyr Lys Pro Leu Asp Glu Leu Asp Ala Thr Leu Tyr Glu His
1 5 10 15

Trp Ile Leu Gln His Ser
20

<210> 169
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 169

Gln Lys Phe Lys Pro Leu Asp Glu Leu Glu Gln Thr Leu Tyr Glu Gln
1 5 10 15

Trp Thr Leu Gln Gln Arg
20

<210> 170
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 170

Thr Lys Phe Gln Pro Leu Asp Glu Leu Asp Gln Thr Leu Tyr Glu Gln
1 5 10 15

Trp Thr Leu Gln Gln Arg
20

<210> 171
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 171

Thr Asn Phe Gln Pro Leu Asp Glu Leu Asp Gln Thr Leu Tyr Glu Gln
1 5 10 15

Trp Thr Leu Gln Gln Arg
20

<210> 172
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 172

Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln Phe
1 5 10 15

Thr Phe Gln Gln
20

<210> 173
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 173

Ala Gly Gly Met Arg Pro Tyr Asp Gly Met Leu Gly Trp Pro Asn Tyr
1 5 10 15

Asp Val Gln Ala
20

<210> 174
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 174

Gln Thr Trp Asp Asp Pro Cys Met His Ile Leu Gly Pro Val Thr Trp
1 5 10 15

Arg Arg Cys Ile
20

<210> 175
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 175

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

Gln Arg Ile Val
20

<210> 176
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 176

Ser Gly Gln Leu Arg Pro Cys Glu Glu Ile Phe Gly Cys Gly Thr Gln
1 5 10 15

Asn Leu Ala Leu
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<210> 177
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 177

Phe Gly Asp Lys Arg Pro Leu Glu Cys Met Phe Gly Gly Pro Ile Gln
1 5 10 15

Leu Cys Pro Arg
20

<210> 178
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 178

Gly Gln Asp Leu Arg Pro Cys Glu Asp Met Phe Gly Cys Gly Thr Lys
1 5 10 15

Asp Trp Tyr Gly
20

<210> 179
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 179

Lys Arg Pro Cys Glu Glu Ile Phe Gly Gly Cys Thr Tyr Gln
1 5 10

<210> 180
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 180

Gly Phe Glu Tyr Cys Asp Gly Met Glu Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Asp Lys Gln Thr
20

<210> 181
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 181

Lys Leu Glu Tyr Cys Asp Gly Met Glu Asp Pro Phe Thr Gln Gly Cys
1 5 10 15

Asp Asn Gln Ser
20

<210> 182
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 182

Leu Gln Glu Trp Cys Glu Gly Val Glu Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Glu Lys Gln Arg
20

<210> 183
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 183

Ala Gln Asp Tyr Cys Glu Gly Met Glu Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Glu Met Gln Lys
20

<210> 184
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 184

Leu Leu Asp Tyr Cys Glu Gly Val Gln Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Glu Asn Leu Asp
20

<210> 185
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 185

His Gln Glu Tyr Cys Glu Gly Met Glu Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Glu Tyr Gln Gly

20

<210> 186
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 186

Met Leu Asp Tyr Cys Glu Gly Met Asp Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Asp Lys Gln Met
20

<210> 187
<211> 20
<212> PRT
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<220>
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<400> 187

Leu Gln Asp Tyr Cys Glu Gly Val Glu Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Glu Asn Gln Arg
20

<210> 188
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 188

Leu Gln Asp Tyr Cys Glu Gly Val Glu Asp Pro Phe Thr Phe Gly Cys
1 5 10 15

Glu Lys Gln Arg
20

<210> 189
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 189

Phe Asp Tyr Cys Glu Gly Val Glu Asp Pro Phe Thr Phe Gly Cys Asp
1 5 10 15

Asn His

<210> 190
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 190

Thr Gly Tyr Thr Glu Tyr Thr Glu Glu Trp Pro Met Gly Phe Gly Tyr
1 5 10 15

Gln Trp Ser Phe
20

<210> 191
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 191

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

Met Pro Pro Gly
20

<210> 192
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 192

Phe Met Arg Phe Pro Asn Pro Trp Lys Leu Val Glu Pro Pro Gln Gly
1 5 10 15

Trp Tyr Tyr Gly
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<210> 193
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 193

Val Val Lys Ala Pro His Phe Glu Phe Leu Ala Pro Pro His Phe His
1 5 10 15

Glu Phe Pro Phe
20

<210> 194
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 194

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

Met Leu Trp Leu
20

<210> 195
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 195

Val Asn Phe Pro Lys Val Pro Glu Asp Val Glu Pro Trp Pro Trp Ser
1 5 10 15

Leu Lys Leu Tyr
20

<210> 196
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 196

Thr Trp His Pro Lys Thr Tyr Glu Glu Phe Ala Leu Pro Phe Phe Val
1 5 10 15

Pro Glu Ala Pro
20

<210> 197
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 197

Trp His Phe Gly Thr Pro Tyr Ile Gln Gln Gln Pro Gly Val Tyr Trp
1 5 10 15

Leu Gln Ala Pro
20

<210> 198
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 198

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

Phe Leu His Glu
20

<210> 199
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 199

Trp Arg Ile His Ser Lys Pro Leu Asp Tyr Ser His Val Trp Phe Phe
1 5 10 15

Pro Ala Asp Phe
20

<210> 200

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

<220>
<223> NGF-Binding Peptide Sequences

<400> 200

Phe Trp Asp Gly Asn Gln Pro Pro Asp Ile Leu Val Asp Trp Pro Trp
1 5 10 15

Asn Pro Pro Val
20

<210> 201
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 201

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

Val Thr Glu Trp
20

<210> 202
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 202

Gln Phe Met Glu Leu Leu Lys Phe Phe Asn Ser Pro Gly Asp Ser Ser
1 5 10 15

His His Phe Leu
20

<210> 203
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 203

Thr Asn Val Asp Trp Ile Ser Asn Asn Trp Glu His Met Lys Ser Phe

1 5 10 15

Phe Thr Glu Asp
20

<210> 204
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 204

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

Pro Val Pro Tyr
20

<210> 205
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 205

Trp Ser His Thr Glu Trp Val Pro Gln Val Trp Trp Lys Pro Pro Asn
1 5 10 15

His Phe Tyr Val
20

<210> 206
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 206

Trp Gly Glu Trp Ile Asn Asp Ala Gln Val His Met His Glu Gly Phe
1 5 10 15

Ile Ser Glu Ser
20

<210> 207
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 207

Val Pro Trp Glu His Asp His Asp Leu Trp Glu Ile Ile Ser Gln Asp
1 5 10 15

Trp His Ile Ala
20

<210> 208
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 208

Val Leu His Leu Gln Asp Pro Arg Gly Trp Ser Asn Phe Pro Pro Gly
1 5 10 15

Val Leu Glu Leu
20

<210> 209
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> NGF-Binding Peptide Sequences

<400> 209

Ile His Gly Cys Trp Phe Thr Glu Glu Gly Cys Val Trp Gln
1 5 10

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

<220>
<223> NGF-Binding Peptide Sequences

<400> 210

Tyr Met Gln Cys Gln Phe Ala Arg Asp Gly Cys Pro Gln Trp
1 5 10

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

<213> Artificial Sequence

<220>
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<400> 211

Lys Leu Gln Cys Gln Tyr Ser Glu Ser Gly Cys Pro Thr Ile
1 5 10

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

<220>
<223> NGF-Binding Peptide Sequences

<400> 212

Phe Leu Gln Cys Glu Ile Ser Gly Gly Ala Cys Pro Ala Pro
1 5 10

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

<220>
<223> NGF-Binding Peptide Sequences

<400> 213

Lys Leu Gln Cys Glu Phe Ser Thr Ser Gly Cys Pro Asp Leu
1 5 10

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

<220>
<223> NGF-Binding Peptide Sequences

<400> 214

Lys Leu Gln Cys Glu Phe Ser Thr Gln Gly Cys Pro Asp Leu
1 5 10

<210> 215
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 215

Lys Leu Gln Cys Glu Phe Ser Thr Ser Gly Cys Pro Trp Leu

1 5 10

<210> 216
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 216

Ile Gln Gly Cys Trp Phe Thr Glu Glu Gly Cys Pro Trp Gln
1 5 10

<210> 217
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 217

Ser Phe Asp Cys Asp Asn Pro Trp Gly His Val Leu Gln Ser Cys Phe
1 5 10 15

Gly Phe

<210> 218
<211> 18
<212> PRT
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<220>
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<400> 218

Ser Phe Asp Cys Asp Asn Pro Trp Gly His Lys Leu Gln Ser Cys Phe
1 5 10 15

Gly Phe

<210> 219
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 219

Lys Asp Leu Cys Ala Met Trp His Trp Met Cys Lys Pro Pro

1 5 10

<210> 220
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 220

Lys Asp Leu Cys Lys Met Trp Lys Trp Met Cys Lys Pro Pro
1 5 10

<210> 221
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 221

Lys Asp Leu Cys Lys Met Trp His Trp Met Cys Lys Pro Lys
1 5 10

<210> 222
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 222

Trp Tyr Pro Cys Tyr Glu Phe His Phe Trp Cys Tyr Asp Leu
1 5 10

<210> 223
<211> 14
<212> PRT
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<220>
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<400> 223

Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu
1 5 10

<210> 224
<211> 14
<212> PRT
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<220>
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<400> 224

Ile Phe Gly Cys Lys Trp Trp Asp Val Gln Cys Tyr Gln Phe
1 5 10

<210> 225
<211> 14
<212> PRT
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<220>
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<400> 225

Ile Phe Gly Cys Lys Trp Trp Asp Val Asp Cys Tyr Gln Phe
1 5 10

<210> 226
<211> 14
<212> PRT
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<220>
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<400> 226

Ala Asp Trp Cys Val Ser Pro Asn Trp Phe Cys Met Val Met
1 5 10

<210> 227
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 227

His Lys Phe Cys Pro Trp Trp Ala Leu Phe Cys Trp Asp Phe
1 5 10

<210> 228
<211> 14
<212> PRT
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<220>
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<400> 228

Lys Asp Leu Cys Lys Met Trp His Trp Met Cys Lys Pro Pro
1 5 10

<210> 229
<211> 14
<212> PRT
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<220>
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<400> 229

Ile Asp Lys Cys Ala Ile Trp Gly Trp Met Cys Pro Pro Leu
1 5 10

<210> 230
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<220>
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<400> 230

Trp Tyr Pro Cys Gly Glu Phe Gly Met Trp Cys Leu Asn Val
1 5 10

<210> 231
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<400> 231

Trp Phe Thr Cys Leu Trp Asn Cys Asp Asn Glu
1 5 10

<210> 232
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<400> 232

His Thr Pro Cys Pro Trp Phe Ala Pro Leu Cys Val Glu Trp
1 5 10

<210> 233
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<220>
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<400> 233

Lys Glu Trp Cys Trp Arg Trp Lys Trp Met Cys Lys Pro Glu
1 5 10

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<400> 234

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

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<400> 235

Ala Tyr Lys Cys Glu Ala Asn Asp Trp Gly Cys Trp Trp Leu
1 5 10

<210> 236
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<400> 236

Asn Ser Trp Cys Glu Asp Gln Trp His Arg Cys Trp Trp Leu
1 5 10

<210> 237
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<400> 237

Trp Ser Ala Cys Tyr Ala Gly His Phe Trp Cys Tyr Asp Leu
1 5 10

<210> 238

<211> 14
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<400> 238

Ala Asn Trp Cys Val Ser Pro Asn Trp Phe Cys Met Val Met
1 5 10

<210> 239
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<400> 239

Trp Thr Glu Cys Tyr Gln Gln Glu Phe Trp Cys Trp Asn Leu
1 5 10

<210> 240
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<400> 240

Glu Asn Thr Cys Glu Arg Trp Lys Trp Met Cys Pro Pro Lys
1 5 10

<210> 241
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<400> 241

Trp Leu Pro Cys His Gln Glu Gly Phe Trp Cys Met Asn Phe
1 5 10

<210> 242
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Ser Thr Met Cys Ser Gln Trp His Trp Met Cys Asn Pro Phe
1 5 10

<210> 243
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<400> 243

Ile Phe Gly Cys His Trp Trp Asp Val Asp Cys Tyr Gln Phe
1 5 10

<210> 244
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<220>
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<400> 244

Ile Tyr Gly Cys Lys Trp Trp Asp Ile Gln Cys Tyr Asp Ile
1 5 10

<210> 245
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<400> 245

Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys Phe Trp
1 5 10

<210> 246
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<220>
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<400> 246

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr
1 5 10

<210> 247
<211> 14
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<220>
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<400> 247

Trp Gln Glu Cys Tyr Arg Glu Gly Phe Trp Cys Leu Gln Thr
1 5 10

<210> 248
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<400> 248

Trp Phe Asp Cys Tyr Gly Pro Gly Phe Lys Cys Trp Ser Pro
1 5 10

<210> 249
<211> 14
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<400> 249

Gly Val Arg Cys Pro Lys Gly His Leu Trp Cys Leu Tyr Pro
1 5 10

<210> 250
<211> 14
<212> PRT
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<220>
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<400> 250

His Trp Ala Cys Gly Tyr Trp Pro Trp Ser Cys Lys Trp Val
1 5 10

<210> 251
<211> 14
<212> PRT
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<220>
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<400> 251

Gly Pro Ala Cys His Ser Pro Trp Trp Trp Cys Val Phe Gly

1 5 10

<210> 252
<211> 14
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<220>
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<400> 252

Thr Thr Trp Cys Ile Ser Pro Met Trp Phe Cys Ser Gln Gln
1 5 10

<210> 253
<211> 14
<212> PRT
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<400> 253

His Lys Phe Cys Pro Pro Trp Ala Ile Phe Cys Trp Asp Phe
1 5 10

<210> 254
<211> 14
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<400> 254

Pro Asp Trp Cys Val Ser Pro Arg Trp Tyr Cys Asn Met Trp
1 5 10

<210> 255
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<400> 255

Val Trp Lys Cys His Trp Phe Gly Met Asp Cys Glu Pro Thr
1 5 10

<210> 256
<211> 14
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<400> 256

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys
1 5 10

<210> 257
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<400> 257

Trp Phe Gln Cys Gly Ser Thr Leu Phe Trp Cys Tyr Asn Leu
1 5 10

<210> 258
<211> 14
<212> PRT
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<400> 258

Trp Ser Pro Cys Tyr Asp His Tyr Phe Tyr Cys Tyr Thr Ile
1 5 10

<210> 259
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 259

Ser Trp Met Cys Gly Phe Phe Lys Glu Val Cys Met Trp Val
1 5 10

<210> 260
<211> 14
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<400> 260

Glu Met Leu Cys Met Ile His Pro Val Phe Cys Asn Pro His
1 5 10

<210> 261
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<400> 261

Leu Lys Thr Cys Asn Leu Trp Pro Trp Met Cys Pro Pro Leu
1 5 10

<210> 262
<211> 14
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<400> 262

Val Val Gly Cys Lys Trp Tyr Glu Ala Trp Cys Tyr Asn Lys
1 5 10

<210> 263
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<400> 263

Pro Ile His Cys Thr Gln Trp Ala Trp Met Cys Pro Pro Thr
1 5 10

<210> 264
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<400> 264

Asp Ser Asn Cys Pro Trp Tyr Phe Leu Ser Cys Val Ile Phe
1 5 10

<210> 265
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<400> 265

His Ile Trp Cys Asn Leu Ala Met Met Lys Cys Val Glu Met
1 5 10

<210> 266
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<400> 266

Asn Leu Gln Cys Ile Tyr Phe Leu Gly Lys Cys Ile Tyr Phe
1 5 10

<210> 267
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<400> 267

Ala Trp Arg Cys Met Trp Phe Ser Asp Val Cys Thr Pro Gly
1 5 10

<210> 268
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<400> 268

Trp Phe Arg Cys Phe Leu Asp Ala Asp Trp Cys Thr Ser Val
1 5 10

<210> 269
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<400> 269

Glu Lys Ile Cys Gln Met Trp Ser Trp Met Cys Ala Pro Pro
1 5 10

<210> 270

<211> 14
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<400> 270

Trp Phe Tyr Cys His Leu Asn Lys Ser Glu Cys Thr Glu Pro
1 5 10

<210> 271
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<400> 271

Phe Trp Arg Cys Ala Ile Gly Ile Asp Lys Cys Lys Arg Val
1 5 10

<210> 272
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 272

Asn Leu Gly Cys Lys Trp Tyr Glu Val Trp Cys Phe Thr Tyr
1 5 10

<210> 273
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 273

Ile Asp Leu Cys Asn Met Trp Asp Gly Met Cys Tyr Pro Pro
1 5 10

<210> 274
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 274

Glu Met Pro Cys Asn Ile Trp Gly Trp Met Cys Pro Pro Val
1   5   10

<210> 275
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 275

Trp Phe Arg Cys Val Leu Thr Gly Ile Val Asp Trp Ser Glu Cys Phe
1   5   10   15

Gly Leu

<210> 276
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 276

Gly Phe Ser Cys Thr Phe Gly Leu Asp Glu Phe Tyr Val Asp Cys Ser
1   5   10   15

Pro Phe

<210> 277
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 277

Leu Pro Trp Cys His Asp Gln Val Asn Ala Asp Trp Gly Phe Cys Met
1   5   10   15

Leu Trp

<210> 278
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 278

Tyr Pro Thr Cys Ser Glu Lys Phe Trp Ile Tyr Gly Gln Thr Cys Val
1 5 10 15

Leu Trp

<210> 279
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 279

Leu Gly Pro Cys Pro Ile His His Gly Pro Trp Pro Gln Tyr Cys Val
1 5 10 15

Tyr Trp

<210> 280
<211> 18
<212> PRT
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<220>
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<400> 280

Pro Phe Pro Cys Glu Thr His Gln Ile Ser Trp Leu Gly His Cys Leu
1 5 10 15

Ser Phe

<210> 281
<211> 18
<212> PRT
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<220>
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<400> 281

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

Arg Pro

<210> 282
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 282

Leu Pro Leu Cys Asp Ala Asp Met Met Pro Thr Ile Gly Phe Cys Val
1 5 10 15

Ala Tyr

<210> 283
<211> 18
<212> PRT
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<220>
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<400> 283

Ser His Trp Cys Glu Thr Thr Phe Trp Met Asn Tyr Ala Lys Cys Val
1 5 10 15

His Ala

<210> 284
<211> 18
<212> PRT
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<220>
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<400> 284

Leu Pro Lys Cys Thr His Val Pro Phe Asp Gln Gly Gly Phe Cys Leu
1 5 10 15

Trp Tyr

<210> 285
<211> 18
<212> PRT
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<220>
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<400> 285

Phe Ser Ser Cys Trp Ser Pro Val Ser Arg Gln Asp Met Phe Cys Val
1 5 10 15

Phe Tyr

<210> 286
<211> 17
<212> PRT
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<220>
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<400> 286

Ser His Lys Cys Glu Tyr Ser Gly Trp Leu Gln Pro Leu Cys Tyr Arg
1 5 10 15

Pro

<210> 287
<211> 18
<212> PRT
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<220>
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<400> 287

Pro Trp Trp Cys Gln Asp Asn Tyr Val Gln His Met Leu His Cys Asp
1 5 10 15

Ser Pro

<210> 288
<211> 18
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<220>
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<400> 288

Trp Phe Arg Cys Met Leu Met Asn Ser Phe Asp Ala Phe Gln Cys Val
1 5 10 15

Ser Tyr

<210> 289
<211> 18
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<220>
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<400> 289

Pro Asp Ala Cys Arg Asp Gln Pro Trp Tyr Met Phe Met Gly Cys Met
1 5 10 15

Leu Gly

<210> 290
<211> 14
<212> PRT
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<220>
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<400> 290

Phe Leu Ala Cys Phe Val Glu Phe Glu Leu Cys Phe Asp Ser
1 5 10

<210> 291
<211> 18
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<220>
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<400> 291

Ser Ala Tyr Cys Ile Ile Thr Glu Ser Asp Pro Tyr Val Leu Cys Val
1 5 10 15

Pro Leu

<210> 292
<211> 18
<212> PRT
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<220>
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<400> 292

Pro Ser Ile Cys Glu Ser Tyr Ser Thr Met Trp Leu Pro Met Cys Gln
1 5 10 15

His Asn

<210> 293
<211> 18
<212> PRT
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<220>
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<400> 293

Trp Leu Asp Cys His Asp Asp Ser Trp Ala Trp Thr Lys Met Cys Arg
1 5 10 15

Ser His

<210> 294
<211> 18
<212> PRT
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<220>
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<400> 294

Tyr Leu Asn Cys Val Met Met Asn Thr Ser Pro Phe Val Glu Cys Val
1 5 10 15

Phe Asn

<210> 295
<211> 18
<212> PRT
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<220>
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<400> 295

Tyr Pro Trp Cys Asp Gly Phe Met Ile Gln Gln Gly Ile Thr Cys Met
1 5 10 15

Phe Tyr

<210> 296
<211> 18
<212> PRT
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<220>
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<400> 296

Phe Asp Tyr Cys Thr Trp Leu Asn Gly Phe Lys Asp Trp Lys Cys Trp
1 5 10 15

Ser Arg

<210> 297
<211> 18
<212> PRT
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<220>
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<400> 297

Leu Pro Leu Cys Asn Leu Lys Glu Ile Ser His Val Gln Ala Cys Val
1 5 10 15

Leu Phe

<210> 298
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 298

Ser Pro Glu Cys Ala Phe Ala Arg Trp Leu Gly Ile Glu Gln Cys Gln
1 5 10 15

Arg Asp

<210> 299
<211> 18
<212> PRT
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<220>
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<400> 299

Tyr Pro Gln Cys Phe Asn Leu His Leu Leu Glu Trp Thr Glu Cys Asp
1 5 10 15

Trp Phe

<210> 300
<211> 18
<212> PRT
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<220>
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<400> 300

Arg Trp Arg Cys Glu Ile Tyr Asp Ser Glu Phe Leu Pro Lys Cys Trp
1 5 10 15

Phe Phe

<210> 301
<211> 14
<212> PRT
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<220>
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<400> 301

Leu Val Gly Cys Asp Asn Val Trp His Arg Cys Lys Leu Phe
1 5 10

<210> 302
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 302

Ala Gly Trp Cys His Val Trp Gly Glu Met Phe Gly Met Gly Cys Ser
1 5 10 15

Ala Leu

<210> 303
<211> 18
<212> PRT
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<220>
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<400> 303

His His Glu Cys Glu Trp Met Ala Arg Trp Met Ser Leu Asp Cys Val

1 5 10 15

Gly Leu

<210> 304
<211> 18
<212> PRT
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<220>
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<400> 304

Phe Pro Met Cys Gly Ile Ala Gly Met Lys Asp Phe Asp Phe Cys Val
1 5 10 15

Trp Tyr

<210> 305
<211> 18
<212> PRT
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<220>
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<400> 305

Arg Asp Asp Cys Thr Phe Trp Pro Glu Trp Leu Trp Lys Leu Cys Glu
1 5 10 15

Arg Pro

<210> 306
<211> 18
<212> PRT
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<220>
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<400> 306

Tyr Asn Phe Cys Ser Tyr Leu Phe Gly Val Ser Lys Glu Ala Cys Gln
1 5 10 15

Leu Pro

<210> 307
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
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<400> 307

Ala His Trp Cys Glu Gln Gly Pro Trp Arg Tyr Gly Asn Ile Cys Met
1 5 10 15

Ala Tyr

<210> 308
<211> 18
<212> PRT
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<220>
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<400> 308

Asn Leu Val Cys Gly Lys Ile Ser Ala Trp Gly Asp Glu Ala Cys Ala
1 5 10 15

Arg Ala

<210> 309
<211> 18
<212> PRT
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<220>
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<400> 309

His Asn Val Cys Thr Ile Met Gly Pro Ser Met Lys Trp Phe Cys Trp
1 5 10 15

Asn Asp

<210> 310
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 310

Asn Asp Leu Cys Ala Met Trp Gly Trp Arg Asn Thr Ile Trp Cys Gln
1 5 10 15

Asn Ser

<210> 311
<211> 18
<212> PRT
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<220>
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<400> 311

Pro Pro Phe Cys Gln Asn Asp Asn Asp Met Leu Gln Ser Leu Cys Lys
1 5 10 15

Leu Leu

<210> 312
<211> 18
<212> PRT
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<220>
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<400> 312

Trp Tyr Asp Cys Asn Val Pro Asn Glu Leu Leu Ser Gly Leu Cys Arg
1 5 10 15

Leu Phe

<210> 313
<211> 18
<212> PRT
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<220>
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<400> 313

Tyr Gly Asp Cys Asp Gln Asn His Trp Met Trp Pro Phe Thr Cys Leu
1 5 10 15

Ser Leu

<210> 314
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 314

Gly Trp Met Cys His Phe Asp Leu His Asp Trp Gly Ala Thr Cys Gln
1 5 10 15

Pro Asp

<210> 315
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 315

Tyr Phe His Cys Met Phe Gly Gly His Glu Phe Glu Val His Cys Glu
1 5 10 15

Ser Phe

<210> 316
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 316

Ala Tyr Trp Cys Trp His Gly Gln Cys Val Arg Phe
1 5 10

<210> 317
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 317

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

Arg Pro Phe

<210> 318

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

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 318

Met Glu Met Leu Asp Ser Leu Phe Glu Leu Leu Lys Asp Met Val Pro
1 5 10 15

Ile Ser Lys Ala
20

<210> 319
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 319

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

Lys Phe Thr

<210> 320
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 320

Ser Pro Glu Asn Leu Leu Asn Asp Leu Tyr Ile Leu Met Thr Lys Gln
1 5 10 15

Glu Trp Tyr Gly
20

<210> 321
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 321

Phe His Trp Glu Glu Gly Ile Pro Phe His Val Val Thr Pro Tyr Ser

1 5 10 15

Tyr Asp Arg Met
20

<210> 322
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 322

Lys Arg Leu Leu Glu Gln Phe Met Asn Asp Leu Ala Glu Leu Val Ser
1 5 10 15

Gly His Ser

<210> 323
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 323

Asp Thr Arg Asp Ala Leu Phe Gln Glu Phe Tyr Glu Phe Val Arg Ser
1 5 10 15

Arg Leu Val Ile
20

<210> 324
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 324

Arg Met Ser Ala Ala Pro Arg Pro Leu Thr Tyr Arg Asp Ile Met Asp
1 5 10 15

Gln Tyr Trp His
20

<210> 325
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
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<400> 325

Asn Asp Lys Ala His Phe Phe Glu Met Phe Met Phe Asp Val His Asn
1 5 10 15

Phe Val Glu Ser
20

<210> 326
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 326

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

Ile Arg Asn Gln
20

<210> 327
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 327

Met Leu Ser Glu Phe Glu Glu Phe Leu Gly Asn Leu Val His Arg Gln
1 5 10 15

Glu Ala

<210> 328
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 328

Tyr Thr Pro Lys Met Gly Ser Glu Trp Thr Ser Phe Trp His Asn Arg
1 5 10 15

Ile His Tyr Leu
20

<210> 329
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 329

Leu Asn Asp Thr Leu Leu Arg Glu Leu Lys Met Val Leu Asn Ser Leu
1 5 10 15

Ser Asp Met Lys
20

<210> 330
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 330

Phe Asp Val Glu Arg Asp Leu Met Arg Trp Leu Glu Gly Phe Met Gln
1 5 10 15

Ser Ala Ala Thr
20

<210> 331
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 331

His His Gly Trp Asn Tyr Leu Arg Lys Gly Ser Ala Pro Gln Trp Phe
1 5 10 15

Glu Ala Trp Val
20

<210> 332
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 332

Val Glu Ser Leu His Gln Leu Gln Met Trp Leu Asp Gln Lys Leu Ala
1 5 10 15

Ser Gly Pro His
20

<210> 333
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 333

Arg Ala Thr Leu Leu Lys Asp Phe Trp Gln Leu Val Glu Gly Tyr Gly
1 5 10 15

Asp Asn

<210> 334
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 334

Glu Glu Leu Leu Arg Glu Phe Tyr Arg Phe Val Ser Ala Phe Asp Tyr
1 5 10 15

<210> 335
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 335

Gly Leu Leu Asp Glu Phe Ser His Phe Ile Ala Glu Gln Phe Tyr Gln
1 5 10 15

Met Pro Gly Gly
20

<210> 336

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

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 336

Tyr Arg Glu Met Ser Met Leu Glu Gly Leu Leu Asp Val Leu Glu Arg
1 5 10 15

Leu Gln His Tyr
20

<210> 337
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 337

His Asn Ser Ser Gln Met Leu Leu Ser Glu Leu Ile Met Leu Val Gly
1 5 10 15

Ser Met Met Gln
20

<210> 338
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 338

Trp Arg Glu His Phe Leu Asn Ser Asp Tyr Ile Arg Asp Lys Leu Ile
1 5 10 15

Ala Ile Asp Gly
20

<210> 339
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 339

Gln Phe Pro Phe Tyr Val Phe Asp Asp Leu Pro Ala Gln Leu Glu Tyr

1 5 10 15

Trp Ile Ala

<210> 340
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 340

Glu Phe Phe His Trp Leu His Asn His Arg Ser Glu Val Asn His Trp
1 5 10 15

Leu Asp Met Asn
20

<210> 341
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 341

Glu Ala Leu Phe Gln Asn Phe Phe Arg Asp Val Leu Thr Leu Ser Glu
1 5 10 15

Arg Glu Tyr

<210> 342
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 342

Gln Tyr Trp Glu Gln Gln Trp Met Thr Tyr Phe Arg Glu Asn Gly Leu
1 5 10 15

His Val Gln Tyr
20

<210> 343
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 343

Asn Gln Arg Met Met Leu Glu Asp Leu Trp Arg Ile Met Thr Pro Met
1 5 10 15

Phe Gly Arg Ser
20

<210> 344
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 344

Phe Leu Asp Glu Leu Lys Ala Glu Leu Ser Arg His Tyr Ala Leu Asp
1 5 10 15

Asp Leu Asp Glu
20

<210> 345
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 345

Gly Lys Leu Ile Glu Gly Leu Leu Asn Glu Leu Met Gln Leu Glu Thr
1 5 10 15

Phe Met Pro Asp
20

<210> 346
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<400> 346

Ile Leu Leu Leu Asp Glu Tyr Lys Lys Asp Trp Lys Ser Trp Phe
1 5 10 15

<210> 347
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 347

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro
35 40 45

Pro Tyr
50

<210> 348
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
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<400> 348

Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu Gly Ser
1 5 10 15

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Trp Tyr Pro
20 25 30

Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu
35 40

<210> 349
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
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<400> 349

His Thr Pro Cys Pro Trp Phe Ala Pro Leu Cys Val Glu Trp Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly

20 25 30

Ser Ala Thr Gly His Thr Pro Cys Pro Trp Phe Ala Pro Leu Cys Val
35 40 45

Glu Trp
50

<210> 350
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
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<400> 350

Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys Phe Trp Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys
35 40 45

Phe Trp
50

<210> 351
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 351

Ala Asn Trp Cys Val Ser Pro Asn Trp Phe Cys Met Val Met Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Ala Asn Trp Cys Val Ser Pro Asn Trp Phe Cys Met
35 40 45

Val Met
50

<210> 352

<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 352

Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys Phe Trp Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys
35 40 45

Phe Trp
50

<210> 353
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 353

His Trp Ala Cys Gly Tyr Trp Pro Trp Ser Cys Lys Trp Val Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly His Trp Ala Cys Gly Tyr Trp Pro Trp Ser Cys Lys
35 40 45

Trp Val
50

<210> 354
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 354

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro
35 40 45

Pro Tyr
50

<210> 355
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 355

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala
35 40 45

Pro Lys
50

<210> 356
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 356

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys Gly Ser
1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
20 25 30

Ser Ala Thr Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro
35 40 45

Pro Tyr
50

<210> 357
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 357

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys Gly Gly
1   5   10   15

Gly Gly Gly Gly Gly Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met
            20   25   30

Cys Pro Pro Tyr
        35

<210> 358
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 358

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr Gly Gly
1   5   10   15

Gly Gly Gly Gly Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala
            20   25   30

Pro Lys

<210> 359
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 359

Val Ala Leu His Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1   5   10   15

Gln Arg Glu Gly
            20

<210> 360

<211> 20
<212> PRT
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<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 360

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

Gln Thr Leu Ala
20

<210> 361
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 361

Gly Leu Asn Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Asp Ser Asn
20

<210> 362
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 362

Met Ile Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Pro Ser Gly
20

<210> 363
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 363

Ala Gly Ala Gln Glu His Cys Thr Arg Trp Pro Trp Met Cys Ala Pro

1 5 10 15

Asn Asp Trp Ile
20

<210> 364
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 364

Gly Val Asn Gln Gly Gln Cys Thr Arg Trp Arg Trp Met Cys Pro Pro
1 5 10 15

Asn Gly Trp Glu
20

<210> 365
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 365

Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Glu Gly Trp Glu
20

<210> 366
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 366

Ile Leu Glu Gln Ala Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Gly Gly
20

<210> 367
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 367

Thr Gln Thr His Ala Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Trp Glu Gly
20

<210> 368
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 368

Val Val Thr Gln Gly His Cys Thr Leu Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Arg
20

<210> 369
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 369

Ile Tyr Pro His Asp Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Pro Tyr Pro
20

<210> 370
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 370

Ser Tyr Trp Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Trp Arg Gly
20

<210> 371
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 371

Met Trp Gln Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
20

<210> 372
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 372

Glu Phe Thr Gln Trp His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Ser Gln
20

<210> 373
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 373

Leu Asp Asp Gln Trp Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Phe Ser
20

<210> 374
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 374

Tyr Gln Thr Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Ser Gln Arg
20

<210> 375
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 375

Glu Ser Asn Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Gly Trp
20

<210> 376
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 376

Trp Thr Asp Arg Gly Pro Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Ala Asn Gly
20

<210> 377
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 377

Val Gly Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Tyr Glu Thr Gly

20

<210> 378
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 378

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

Tyr Glu Val Glu
20

<210> 379
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 379

Ser Glu Tyr Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Lys
20

<210> 380
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 380

Thr Phe Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
20

<210> 381
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 381

Pro Gly Ala His Asp His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Ser Arg Tyr
20

<210> 382
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 382

Val Ala Glu Glu Trp His Cys Arg Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Asp Trp Arg
20

<210> 383
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 383

Val Gly Thr Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Pro Ala Gly
20

<210> 384
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 384

Glu Glu Asp Gln Ala His Cys Arg Ser Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Val
20

<210> 385
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 385

Ala Asp Thr Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln His Trp Phe
20

<210> 386
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 386

Ser Gly Pro Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Ala Pro
1 5 10 15

Gln Gly Trp Phe
20

<210> 387
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 387

Thr Leu Val Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Val
20

<210> 388
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 388

Gly Met Ala His Gly Lys Cys Thr Arg Trp Ala Trp Met Cys Pro Pro
1 5 10 15

Gln Ser Trp Lys
20

<210> 389
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 389

Glu Leu Tyr His Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Ser Trp Ala
20

<210> 390
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 390

Val Ala Asp His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
20

<210> 391
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 391

Pro Glu Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
20

<210> 392

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

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 392

Ile Pro Ala His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Arg
20

<210> 393
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 393

Phe Thr Val His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Tyr Gly Trp Val
20

<210> 394
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 394

Pro Asp Phe Pro Gly His Cys Thr Arg Trp Arg Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Glu
20

<210> 395
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 395

Gln Leu Trp Gln Gly Pro Cys Thr Gln Trp Pro Trp Met Cys Pro Pro

1 5 10 15

Lys Gly Arg Tyr
20

<210> 396
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 396

His Ala Asn Asp Gly His Cys Thr Arg Trp Gln Trp Met Cys Pro Pro
1 5 10 15

Gln Trp Gly Gly
20

<210> 397
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 397

Glu Thr Asp His Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Tyr Gly Ala Arg
20

<210> 398
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 398

Gly Thr Trp Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gln
20

<210> 399
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 399

Val Ala Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
20

<210> 400
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 400

Val Ala Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Gly
20

<210> 401
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 401

Gln Arg Glu Trp Tyr Pro Cys Tyr Gly Gly His Leu Trp Cys Tyr Asp
1 5 10 15

Leu His Lys Ala
20

<210> 402
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 402

Ile Ser Ala Trp Tyr Ser Cys Tyr Ala Gly His Phe Trp Cys Trp Asp
1 5 10 15

Leu Lys Gln Lys
20

<210> 403
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 403

Trp Thr Gly Trp Tyr Gln Cys Tyr Gly Gly His Leu Trp Cys Tyr Asp
1 5 10 15

Leu Arg Arg Lys
20

<210> 404
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 404

Lys Thr Phe Trp Tyr Pro Cys Tyr Asp Gly His Phe Trp Cys Tyr Asn
1 5 10 15

Leu Lys Ser Ser
20

<210> 405
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 405

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

Leu Thr Glu Thr
20

<210> 406
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 406

Met Glu Met Leu Asp Ser Leu Phe Glu Leu Leu Lys Asp Met Val Pro
1 5 10 15

Ile Ser Lys Ala
20

<210> 407
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 407

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Gly
20

<210> 408
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 408

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Arg
20

<210> 409
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 409

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Met Ser Lys Pro Ser

20

<210> 410
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 410

Gly Met Glu Met Leu Glu Ser Leu Phe Glu Leu Leu Gln Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Pro
20

<210> 411
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 411

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Ile Ser Asn Pro Pro
20

<210> 412
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 412

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Gln Glu Ile Val
1 5 10 15

Pro Ile Ser Lys Ala Glu
20

<210> 413
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 413

Arg Met Glu Met Leu Gln Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Met Ser Asn Ala Arg
20

<210> 414
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 414

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Thr Ser Asn Gly Thr
20

<210> 415
<211> 22
<212> PRT
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<220>
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<400> 415

Arg Met Glu Met Leu Glu Ser Leu Phe Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Gly
20

<210> 416
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 416

Arg Met Glu Met Leu Gly Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Arg
20

<210> 417
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 417

Gln Met Glu Leu Leu Asp Ser Leu Phe Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Lys Ser Gln Pro Ala
20

<210> 418
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 418

Arg Met Glu Met Leu Asp Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Asn Ala Arg
20

<210> 419
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 419

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu His Glu Ile Val
1 5 10 15

Pro Met Ser Gln Ala Gly
20

<210> 420
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 420

Gln Met Glu Met Leu Glu Ser Leu Leu Gln Leu Leu Lys Glu Ile Val
1   5   10   15

Pro Met Ser Lys Ala Ser
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<210> 421
<211> 22
<212> PRT
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<220>
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<400> 421

Arg Met Glu Met Leu Asp Ser Leu Leu Glu Leu Leu Lys Asp Met Val
1   5   10   15

Pro Met Thr Thr Gly Ala
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<210> 422
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<212> PRT
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<220>
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<400> 422

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Met Val
1   5   10   15

Pro Met Ala Asn Ala Ser
            20

<210> 423
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<212> PRT
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<220>
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<400> 423

Arg Met Glu Met Leu Glu Ser Leu Leu Gln Leu Leu Asn Glu Ile Val
1   5   10   15

Pro Met Ser Arg Ala Arg
            20

<210> 424

<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 424

Arg Met Glu Met Leu Glu Ser Leu Phe Asp Leu Leu Lys Glu Leu Val
1 5 10 15

Pro Met Ser Lys Gly Val
20

<210> 425
<211> 22
<212> PRT
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<220>
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<400> 425

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Ile Gln Lys Ala Arg
20

<210> 426
<211> 22
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<220>
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<400> 426

Arg Met Glu Leu Leu Glu Ser Leu Phe Glu Leu Leu Lys Asp Met Val
1 5 10 15

Pro Met Ser Asp Ser Ser
20

<210> 427
<211> 22
<212> PRT
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<220>
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<400> 427

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Val Leu Gln Glu Ile Val

1 5 10 15

Pro Arg Ala Lys Gly Ala
20

<210> 428
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 428

Arg Met Glu Met Leu Asp Ser Leu Leu Gln Leu Leu Asn Glu Ile Val
1 5 10 15

Pro Met Ser His Ala Arg
20

<210> 429
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 429

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Met Ser Asn Ala Gly
20

<210> 430
<211> 22
<212> PRT
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<220>
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<400> 430

Arg Met Glu Met Leu Gln Ser Leu Phe Glu Leu Leu Lys Gly Met Val
1 5 10 15

Pro Ile Ser Lys Ala Gly
20

<210> 431
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
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<400> 431

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Asn Ser Thr Ala Ala
20

<210> 432
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 432

Arg Met Glu Met Leu Gln Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Ile Ser Lys Ala Gly
20

<210> 433
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 433

Arg Ile Glu Met Leu Asp Ser Leu Leu Glu Leu Leu Asn Glu Leu Val
1 5 10 15

Pro Met Ser Lys Ala Arg
20

<210> 434
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 434

His His Gly Trp Asn Tyr Leu Arg Lys Gly Ser Ala Pro Gln Trp Phe
1 5 10 15

Glu Ala Trp Val
20

<210> 435
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 435

Gln Val Glu Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Gly
20

<210> 436
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 436

Arg Met Glu Leu Leu Glu Ser Leu Phe Glu Leu Leu Lys Glu Met Val
1 5 10 15

Pro Arg Ser Lys Ala Val
20

<210> 437
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 437

Gln Ala Val Ser Leu Gln His Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln His
20

<210> 438
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 438

Asp Glu Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1   5   10   15

Ala Ser Gly Pro Gln Leu
            20

<210> 439
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 439

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

Ala Gln Gly Pro His Ala
            20

<210> 440
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 440

Glu Val Asp Glu Leu Gln Gln Leu Leu Asn Trp Leu Asp His Lys Leu
1   5   10   15

Ala Ser Gly Pro Leu Gln
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<210> 441
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 441

Asp Val Glu Ser Leu Glu Gln Leu Leu Met Trp Leu Asp His Gln Leu
1   5   10   15

Ala Ser Gly Pro His Gly

20

<210> 442
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 442

Gln Val Asp Ser Leu Gln Gln Val Leu Leu Trp Leu Glu His Lys Leu
1 5 10 15

Ala Leu Gly Pro Gln Val
20

<210> 443
<211> 22
<212> PRT
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<220>
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<400> 443

Gly Asp Glu Ser Leu Gln His Leu Leu Met Trp Leu Glu Gln Lys Leu
1 5 10 15

Ala Leu Gly Pro His Gly
20

<210> 444
<211> 22
<212> PRT
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<220>
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<400> 444

Gln Ile Glu Met Leu Glu Ser Leu Leu Asp Leu Leu Arg Asp Met Val
1 5 10 15

Pro Met Ser Asn Ala Phe
20

<210> 445
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 445

Glu Val Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Ala
20

<210> 446
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 446

Glu Asp Glu Ser Leu Gln Gln Leu Leu Ile Tyr Leu Asp Lys Met Leu
1 5 10 15

Ser Ser Gly Pro Gln Val
20

<210> 447
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 447

Ala Met Asp Gln Leu His Gln Leu Leu Ile Trp Leu Asp His Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Ala
20

<210> 448
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 448

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Asp Glu Ile Ala
1 5 10 15

Leu Ile Pro Lys Ala Trp
20

<210> 449
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 449

Glu Val Val Ser Leu Gln His Leu Leu Met Trp Leu Glu His Lys Leu
1 5 10 15

Ala Ser Gly Pro Asp Gly
20

<210> 450
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 450

Gly Gly Glu Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Gln Leu
1 5 10 15

Ala Ser Gly Pro Gln Arg
20

<210> 451
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 451

Gly Val Glu Ser Leu Gln Gln Leu Leu Ile Phe Leu Asp His Met Leu
1 5 10 15

Val Ser Gly Pro His Asp
20

<210> 452
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 452

Asn Val Glu Ser Leu Glu His Leu Met Met Trp Leu Glu Arg Leu Leu
1 5 10 15

Ala Ser Gly Pro Tyr Ala
20

<210> 453
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 453

Gln Val Asp Ser Leu Gln Gln Leu Leu Ile Trp Leu Asp His Gln Leu
1 5 10 15

Ala Ser Gly Pro Lys Arg
20

<210> 454
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 454

Glu Val Glu Ser Leu Gln Gln Leu Leu Met Trp Leu Glu His Lys Leu
1 5 10 15

Ala Gln Gly Pro Gln Gly
20

<210> 455
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 455

Glu Val Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro His Ala
20

<210> 456

<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 456

Glu Val Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Gln Leu
1 5 10 15

Ala Ser Gly Pro Gln Lys
20

<210> 457
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 457

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

Ala Ser Gly Pro Gln Arg
20

<210> 458
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 458

Gly Glu Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Gln Leu
1 5 10 15

Ala Ala Gly Pro Gln Val
20

<210> 459
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 459

Ala Asp Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Arg Lys Leu

1 5 10 15

Ala Ser Gly Pro His Val
20

<210> 460
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 460

Pro Val Asp Ser Leu Gln Gln Leu Leu Ile Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Gly
20

<210> 461
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 461

Arg Ala Thr Leu Leu Lys Asp Phe Trp Gln Leu Val Glu Gly Tyr Gly
1 5 10 15

Asp Asn

<210> 462
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 462

Asp Trp Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Glu Gly
1 5 10 15

Leu Gly Asp Asn Leu Val
20

<210> 463
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 463

Gln Ser Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Glu Gly
1 5 10 15

Leu Gly Asp Lys Gln Ala
20

<210> 464
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 464

Asp Gly Arg Ala Thr Leu Leu Thr Glu Phe Trp Gln Leu Val Gln Gly
1 5 10 15

Leu Gly Gln Lys Glu Ala
20

<210> 465
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 465

Leu Ala Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Glu Gly
1 5 10 15

Leu Gly Glu Lys Val Val
20

<210> 466
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 466

Gly Ser Arg Asp Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Val Gly
1 5 10 15

Leu Gly Asp Met Gln Thr
20

<210> 467
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 467

Asp Ala Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Asp Ala
1 5 10 15

Tyr Gly Asp Arg Met Val
20

<210> 468
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 468

Asn Asp Arg Ala Gln Leu Leu Arg Asp Phe Trp Gln Leu Val Asp Gly
1 5 10 15

Leu Gly Val Lys Ser Trp
20

<210> 469
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 469

Gly Val Arg Glu Thr Leu Leu Tyr Glu Leu Trp Tyr Leu Leu Lys Gly
1 5 10 15

Leu Gly Ala Asn Gln Gly
20

<210> 470
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 470

Gln Ala Arg Ala Thr Leu Leu Lys Glu Phe Cys Gln Leu Val Gly Cys
1 5 10 15

Gln Gly Asp Lys Leu Ser
20

<210> 471
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 471

Gln Glu Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Ala Gly
1 5 10 15

Leu Gly Gln Asn Met Arg
20

<210> 472
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 472

Ser Gly Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Gln Gly
1 5 10 15

Leu Gly Glu Tyr Arg Trp
20

<210> 473
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 473

Thr Met Arg Ala Thr Leu Leu Lys Glu Phe Trp Leu Phe Val Asp Gly
1 5 10 15

Gln Arg Glu Met Gln Trp

20

<210> 474
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 474

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

Gln Gly Asp Asn Thr Gly
20

<210> 475
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 475

Asp Glu Arg Glu Thr Leu Leu Lys Glu Phe Trp Gln Leu Val His Gly
1 5 10 15

Trp Gly Asp Asn Val Ala
20

<210> 476
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 476

Gly Gly Arg Ala Thr Leu Leu Lys Glu Leu Trp Gln Leu Leu Glu Gly
1 5 10 15

Gln Gly Ala Asn Leu Val
20

<210> 477
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 477

Thr Ala Arg Ala Thr Leu Leu Asn Glu Leu Val Gln Leu Val Lys Gly
1 5 10 15

Tyr Gly Asp Lys Leu Val
20

<210> 478
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 478

Gly Met Arg Ala Thr Leu Leu Gln Glu Phe Trp Gln Leu Val Gly Gly
1 5 10 15

Gln Gly Asp Asn Trp Met
20

<210> 479
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 479

Ser Thr Arg Ala Thr Leu Leu Asn Asp Leu Trp Gln Leu Met Lys Gly
1 5 10 15

Trp Ala Glu Asp Arg Gly
20

<210> 480
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 480

Ser Glu Arg Ala Thr Leu Leu Lys Glu Leu Trp Gln Leu Val Gly Gly
1 5 10 15

Trp Gly Asp Asn Phe Gly
20

<210> 481
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 481

Val Gly Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Glu Gly
1 5 10 15

Leu Val Gly Gln Ser Arg
20

<210> 482
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 482

Glu Ile Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Asp Glu
1 5 10 15

Trp Arg Glu Gln Pro Asn
20

<210> 483
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 483

Gln Leu Arg Ala Thr Leu Leu Lys Glu Phe Leu Gln Leu Val His Gly
1 5 10 15

Leu Gly Glu Thr Asp Ser
20

<210> 484
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 484

Thr Gln Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Ile Glu Gly
1   5   10   15

Leu Gly Gly Lys His Val
            20

<210> 485
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 485

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

Leu Arg Glu Gln Gly Val
            20

<210> 486
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 486

Gln Ser Arg Val Thr Leu Leu Arg Glu Phe Trp Gln Leu Val Glu Ser
1   5   10   15

Tyr Arg Pro Ile Val Asn
            20

<210> 487
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 487

Leu Ser Arg Ala Thr Leu Leu Asn Glu Phe Trp Gln Phe Val Asp Gly
1   5   10   15

Gln Arg Asp Lys Arg Met
            20

<210> 488

<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 488

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

Leu Ser Gln Lys Pro Gly
20

<210> 489
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 489

Gln Glu Arg Ala Thr Leu Leu Lys Glu Phe Trp Arg Met Val Glu Gly
1 5 10 15

Leu Gly Lys Asn Arg Gly
20

<210> 490
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 490

Asn Glu Arg Ala Thr Leu Leu Arg Glu Phe Trp Gln Leu Val Gly Gly
1 5 10 15

Tyr Gly Val Asn Gln Arg
20

<210> 491
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 491

Tyr Arg Glu Met Ser Met Leu Glu Gly Leu Leu Asp Val Leu Glu Arg

1 5 10 15

Leu Gln His Tyr
20

<210> 492
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 492

His Gln Arg Asp Met Ser Met Leu Trp Glu Leu Leu Asp Val Leu Asp
1 5 10 15

Gly Leu Arg Gln Tyr Ser
20

<210> 493
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 493

Thr Gln Arg Asp Met Ser Met Leu Asp Gly Leu Leu Glu Val Leu Asp
1 5 10 15

Gln Leu Arg Gln Gln Arg
20

<210> 494
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 494

Thr Ser Arg Asp Met Ser Leu Leu Trp Glu Leu Leu Glu Glu Leu Asp
1 5 10 15

Arg Leu Gly His Gln Arg
20

<210> 495
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 495

Met Gln His Asp Met Ser Met Leu Tyr Gly Leu Val Glu Leu Leu Glu
1 5 10 15

Ser Leu Gly His Gln Ile
20

<210> 496
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 496

Trp Asn Arg Asp Met Arg Met Leu Glu Ser Leu Phe Glu Val Leu Asp
1 5 10 15

Gly Leu Arg Gln Gln Val
20

<210> 497
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 497

Gly Tyr Arg Asp Met Ser Met Leu Glu Gly Leu Leu Ala Val Leu Asp
1 5 10 15

Arg Leu Gly Pro Gln Leu
20

<210> 498
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 498

Thr Gln Arg Asp Met Ser Met Leu Glu Gly Leu Leu Glu Val Leu Asp
1 5 10 15

Arg Leu Gly Gln Gln Arg
20

<210> 499
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 499

Trp Tyr Arg Asp Met Ser Met Leu Glu Gly Leu Leu Glu Val Leu Asp
1 5 10 15

Arg Leu Gly Gln Gln Arg
20

<210> 500
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 500

His Asn Ser Ser Gln Met Leu Leu Ser Glu Leu Ile Met Leu Val Gly
1 5 10 15

Ser Met Met Gln
20

<210> 501
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 501

Thr Gln Asn Ser Arg Gln Met Leu Leu Ser Asp Phe Met Met Leu Val
1 5 10 15

Gly Ser Met Ile Gln Gly
20

<210> 502
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 502

Met Gln Thr Ser Arg His Ile Leu Leu Ser Glu Phe Met Met Leu Val
1 5 10 15

Gly Ser Ile Met His Gly
20

<210> 503
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 503

His Asp Asn Ser Arg Gln Met Leu Leu Ser Asp Leu Leu His Leu Val
1 5 10 15

Gly Thr Met Ile Gln Gly
20

<210> 504
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 504

Met Glu Asn Ser Arg Gln Asn Leu Leu Arg Glu Leu Ile Met Leu Val
1 5 10 15

Gly Asn Met Ser His Gln
20

<210> 505
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 505

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

Gly Glu Met Ile Gln Gly

20

<210> 506
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 506

Asp Gln Asn Ser Arg Gln Met Leu Leu Ser Asp Leu Met Ile Leu Val
1 5 10 15

Gly Ser Met Ile Gln Gly
20

<210> 507
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 507

Glu Phe Phe His Trp Leu His Asn His Arg Ser Glu Val Asn His Trp
1 5 10 15

Leu Asp Met Asn
20

<210> 508
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide or polypeptide sequence

<400> 508

Asn Val Phe Phe Gln Trp Val Gln Lys His Gly Arg Val Val Tyr Gln
1 5 10 15

Trp Leu Asp Ile Asn Val
20

<210> 509
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 509

Phe Asp Phe Leu Gln Trp Leu Gln Asn His Arg Ser Glu Val Glu His
1 5 10 15

Trp Leu Val Met Asp Val
20

<210> 510
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 510

Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala
1 5 10

<210> 511
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 511

Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu
1 5 10

<210> 512
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 512

Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala
1 5 10

<210> 513
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 513

Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys Phe

1 5 10 15

His His

<210> 514
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 514

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu

<210> 515
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 515

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser

<210> 516
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 516

Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys Ser
1 5 10 15

Asn Leu

<210> 517
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
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<400> 517

Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys Gln
1 5 10 15

Phe Asn

<210> 518
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 518

Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys His
1 5 10 15

Gly Leu

<210> 519
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 519

Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys Pro
1 5 10 15

Ser Pro

<210> 520
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 520

Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys Glu
1 5 10 15

Phe Phe

<210> 521
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 521

Tyr Lys Gly Arg Gln Gln Met Trp Asp Ile Leu Thr Arg Ser Trp Val
1 5 10 15

Val Ser Leu

<210> 522
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 522

Gln Gln Asp Val Gly Leu Trp Trp Asp Ile Leu Thr Arg Ala Trp Met
1 5 10 15

Pro Asn Ile

<210> 523
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 523

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

Tyr Pro Gln

<210> 524
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 524

Gly Trp Asn Glu Ala Trp Trp Asp Glu Leu Thr Lys Ile Trp Val Leu
1 5 10 15

Glu Gln Gln

<210> 525
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 525

Arg Ile Thr Cys Asp Thr Trp Asp Ser Leu Ile Lys Lys Cys Val Pro
1 5 10 15

Gln Gln Ser

<210> 526
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 526

Gly Ala Ile Met Gln Gln Phe Trp Asp Ser Leu Thr Lys Thr Trp Leu
1 5 10 15

Arg Gln Ser

<210> 527
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 527

Trp Leu His Ser Gly Trp Trp Asp Pro Leu Thr Lys His Trp Leu Gln
1 5 10 15

Gln Lys Val

<210> 528
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 528

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

Lys Phe Arg

<210> 529
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 529

Gly Val Trp Phe Trp Trp Phe Asp Pro Leu Thr Lys Gln Trp Thr Gln
1 5 10 15

Gln Ala Gly

<210> 530
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 530

Met Gln Gln Cys Lys Gly Tyr Tyr Asp Ile Leu Thr Lys Trp Cys Val
1 5 10 15

Thr Asn Gly

<210> 531
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 531

Leu Trp Ser Lys Glu Val Trp Asp Ile Leu Thr Lys Ser Trp Val Ser
1 5 10 15

Gln Gln Ala

<210> 532
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 532

Lys Ala Ala Gly Trp Trp Phe Asp Trp Leu Thr Lys Val Trp Val Pro
1 5 10 15

Ala Pro

<210> 533
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 533

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

Ser Thr Thr

<210> 534
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 534

Ser Gly Gln Gln His Phe Trp Trp Asp Leu Leu Thr Arg Ser Trp Thr
1 5 10 15

Pro Ser Thr

<210> 535
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 535

Leu Gly Val Gly Gln Gln Lys Trp Asp Pro Leu Thr Lys Gln Trp Val
1 5 10 15

Ser Arg Gly

<210> 536
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 536

Val Gly Lys Met Cys Gln Gln Trp Asp Pro Leu Ile Lys Arg Thr Val
1 5 10 15

Cys Val Gly

<210> 537
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 537

Cys Arg Gln Gly Ala Lys Phe Asp Leu Leu Thr Lys Gln Cys Leu Leu
1 5 10 15

Gly Arg

<210> 538
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 538

Gly Gln Ala Ile Arg His Trp Asp Val Leu Thr Lys Gln Trp Val Asp
1 5 10 15

Ser Gln Gln

<210> 539
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 539

Arg Gly Pro Cys Gly Ser Trp Asp Leu Leu Thr Lys His Cys Leu Asp
1 5 10 15

Ser Gln Gln

<210> 540
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 540

Trp Gln Trp Lys Gln Gln Gln Trp Asp Leu Leu Thr Lys Gln Met Val
1 5 10 15

Trp Val Gly

<210> 541
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 541

Pro Ile Thr Ile Cys Arg Lys Asp Leu Leu Thr Lys Gln Val Val Cys
1 5 10 15

Leu Asp

<210> 542

<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 542

Lys Thr Cys Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln
1 5 10 15

Gln Gln Ala

<210> 543
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 543

Lys Cys Leu Lys Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Thr
1 5 10 15

Glu Val

<210> 544
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 544

Arg Cys Trp Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile His
1 5 10 15

Pro Trp

<210> 545
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 545

Asn Arg Asp Met Arg Lys Trp Asp Pro Leu Ile Lys Gln Trp Ile Val

1 5 10 15

Arg Pro

<210> 546
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 546

Gln Gln Ala Ala Ala Ala Thr Trp Asp Leu Leu Thr Lys Gln Trp Leu
1 5 10 15

Val Pro Pro

<210> 547
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 547

Pro Glu Gly Gly Pro Lys Trp Asp Pro Leu Thr Lys Gln Gln Phe Leu
1 5 10 15

Pro Pro Val

<210> 548
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 548

Gln Gln Thr Pro Gln Gln Lys Lys Trp Asp Leu Leu Thr Lys Gln Trp
1 5 10 15

Phe Thr Arg Asn
20

<210> 549
<211> 19
<212> PRT

<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 549

Ile Gly Ser Pro Cys Lys Trp Asp Leu Leu Thr Lys Gln Met Ile Cys
1 5 10 15

Gln Gln Thr

<210> 550
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 550

Cys Thr Ala Ala Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile Gln
1 5 10 15

Gln Glu Lys

<210> 551
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 551

Val Ser Gln Cys Met Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln
1 5 10 15

Gln Gly Trp

<210> 552
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 552

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

Pro Gln Gln

<210> 553
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 553

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

Pro Gln Gln

<210> 554
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 554

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

Pro Leu Ala

<210> 555
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 555

Gln Leu Trp Gly Thr Lys Trp Asp Leu Leu Thr Lys Gln Tyr Ile Gln
1 5 10 15

Gln Ile Met

<210> 556
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 556

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

Gln Asn Met

<210> 557
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 557

Gln Gln Arg Gln Cys Ala Lys Trp Asp Leu Leu Thr Lys Gln Cys Val
1 5 10 15

Leu Phe Tyr

<210> 558
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 558

Lys Thr Thr Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Arg Ile Cys
1 5 10 15

Gln Gln Val

<210> 559
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 559

Leu Leu Cys Gln Gln Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu
1 5 10 15

Lys Leu Arg

<210> 560
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 560

Leu Met Trp Phe Trp Lys Trp Asp Leu Leu Thr Lys Gln Leu Val Pro
1 5 10 15

Thr Phe

<210> 561
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 561

Gln Gln Thr Trp Ala Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile
1 5 10 15

Gly Pro Met

<210> 562
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 562

Asn Lys Glu Leu Leu Lys Trp Asp Leu Leu Thr Lys Gln Cys Arg Gly
1 5 10 15

Arg Ser

<210> 563
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 563

Gly Gln Gln Lys Asp Leu Lys Trp Asp Leu Leu Thr Lys Gln Tyr Val
1 5 10 15

Arg Gln Ser

<210> 564
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 564

Pro Lys Pro Cys Gln Gln Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu
1 5 10 15

Gly Ser Val

<210> 565
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 565

Gly Gln Ile Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gln
1 5 10 15

Gln Thr Arg

<210> 566
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 566

Val Trp Leu Asp Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile His
1 5 10 15

Pro Gln Gln

<210> 567
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 567

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

Trp Leu Arg

<210> 568
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 568

His Trp Asp Ser Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Val
1 5 10 15

Gln Gln Ala

<210> 569
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 569

Thr Arg Pro Leu Gln Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Leu
1 5 10 15

Arg Val Gly

<210> 570
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 570

Ser Asp Gln Trp Gln Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe
1 5 10 15

Trp Asp Val

<210> 571
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 571

Gln Gln Gln Thr Phe Met Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile
1 5 10 15

Arg Arg His

<210> 572
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 572

Gln Gln Gly Glu Cys Arg Lys Trp Asp Leu Leu Thr Lys Gln Cys Phe
1 5 10 15

Pro Gly Gln

<210> 573
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 573

Gly Gln Gln Met Gly Trp Arg Trp Asp Pro Leu Ile Lys Met Cys Leu
1 5 10 15

Gly Pro Ser

<210> 574

<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 574

Gln Gln Leu Asp Gly Cys Lys Trp Asp Leu Leu Thr Lys Gln Lys Val
1 5 10 15

Cys Ile Pro

<210> 575
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 575

His Gly Tyr Trp Gln Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val
1 5 10 15

Ser Ser Glu

<210> 576
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 576

His Gln Gln Gly Gln Cys Gly Trp Asp Leu Leu Thr Arg Ile Tyr Leu
1 5 10 15

Pro Cys His

<210> 577
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 577

Leu His Lys Ala Cys Lys Trp Asp Leu Leu Thr Lys Gln Cys Trp Pro

1 5 10 15

Met Gln Gln

<210> 578
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 578

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

Gln Thr Gly

<210> 579
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 579

Ile Thr Gln Gln Asp Trp Arg Phe Asp Thr Leu Thr Arg Leu Trp Leu
1 5 10 15

Pro Leu Arg

<210> 580
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 580

Gln Gln Gly Gly Phe Ala Ala Trp Asp Val Leu Thr Lys Met Trp Ile
1 5 10 15

Thr Val Pro

<210> 581
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 581

Gly His Gly Thr Pro Trp Trp Asp Ala Leu Thr Arg Ile Trp Ile Leu
1 5 10 15

Gly Val

<210> 582
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 582

Val Trp Pro Trp Gln Gln Lys Trp Asp Leu Leu Thr Lys Gln Phe Val
1 5 10 15

Phe Gln Asp

<210> 583
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 583

Trp Gln Gln Trp Ser Trp Lys Trp Asp Leu Leu Thr Arg Gln Tyr Ile
1 5 10 15

Ser Ser Ser

<210> 584
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 584

Asn Gln Gln Thr Leu Trp Lys Trp Asp Leu Leu Thr Lys Gln Phe Ile
1 5 10 15

Thr Tyr Met

<210> 585
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 585

Pro Val Tyr Gln Gln Gly Trp Trp Asp Thr Leu Thr Lys Leu Tyr Ile
1 5 10 15

Trp Asp Gly

<210> 586
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 586

Trp Leu Asp Gly Gly Trp Arg Asp Pro Leu Ile Lys Arg Ser Val Gln
1 5 10 15

Gln Leu Gly

<210> 587
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 587

Gly His Gln Gln Gln Phe Lys Trp Asp Leu Leu Thr Lys Gln Trp Val
1 5 10 15

Gln Ser Asn

<210> 588
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 588

Gln Gln Arg Val Gly Gln Phe Trp Asp Val Leu Thr Lys Met Phe Ile
1 5 10 15

Thr Gly Ser

<210> 589
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 589

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

Arg Trp Pro

<210> 590
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 590

Gly Trp Met His Trp Lys Trp Asp Pro Leu Thr Lys Gln Gln Ala Leu
1 5 10 15

Pro Trp Met

<210> 591
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 591

Gly His Pro Thr Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Leu
1 5 10 15

Gln Gln Met

<210> 592
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 592

Trp Asn Asn Trp Ser Leu Trp Asp Pro Leu Thr Lys Leu Trp Leu Gln
1 5 10 15

Gln Gln Asn

<210> 593
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 593

Trp Gln Trp Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Gln Gln

<210> 594
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> BAFF binding peptide sequence

<400> 594

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Thr Lys Met Trp Leu Gly
1 5 10 15

Thr Ser

<210> 595
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 595

Gly Gly Gly Lys Gly Gly Gly Gly
1 5

<210> 596
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 596

Gly Gly Gly Asn Gly Ser Gly Gly
1 5

<210> 597
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 597

Gly Gly Gly Cys Gly Gly Gly Gly
1 5

<210> 598
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 598

Gly Pro Asn Gly Gly
1 5

<210> 599
<211> 228
<212> PRT
<213> Homo sapiens

<400> 599

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
130 135 140

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

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly Lys
225

<210> 600
<211> 227
<212> PRT
<213> Homo sapiens

<400> 600

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140

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

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

<210> 601
<211> 2
<212> PRT
<213> Homo sapiens

<400> 601

Pro Pro
1

<210> 602
<211> 8
<212> PRT
<213> Homo sapiens

<400> 602

Asp Val Ser His Glu Asp Pro Glu
1 5

<210> 603
<211> 232
<212> PRT
<213> Homo sapiens

<400> 603

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 604
<211> 4
<212> PRT
<213> Homo sapiens

<400> 604

Val His Asn Ala
1

<210> 605
<211> 7
<212> PRT
<213> Homo sapiens

<400> 605

Glu Glu Gln Tyr Asn Ser Thr
1 5

<210> 606
<211> 11
<212> PRT
<213> Homo sapiens

<400> 606

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
1 5 10

<210> 607
<211> 22
<212> PRT
<213> Homo sapiens

<400> 607

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
1 5 10 15

Gly Gln Pro Arg Glu Pro
20

<210> 608
<211> 5
<212> PRT
<213> Homo sapiens

<400> 608

Asp Glu Leu Thr Lys
1 5

<210> 609
<211> 7
<212> PRT
<213> Homo sapiens

<400> 609

Asn Gly Gln Pro Glu Asn Asn
1 5

<210> 610
<211> 11
<212> PRT
<213> Homo sapiens

<400> 610

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
1 5 10

<210> 611
<211> 9
<212> PRT
<213> Homo sapiens

<400> 611

Lys Ser Arg Trp Gln Gln Gly Asn Val
1 5

<210> 612
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Ang-2 binding peptide sequence

<400> 612

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Gln Glu Glu
130 135 140

Cys Glu Trp Asp Pro Trp Thr Cys Glu His Met Gly Gly Thr Lys Asn
145 150 155 160

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
165 170 175

Ala Val Glu Tyr Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
180 185 190

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
195 200 205

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
210 215 220

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
225 230 235 240

Ser Leu Ser Pro Gly Lys
245

<210> 613
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding polypeptide sequence

<400> 613

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Leu Ala Asp
130 135 140

His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro Glu Gly Trp
145 150 155 160

Glu Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 614
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> EPO-mimetic polypeptide

<400> 614

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Gly Gly Thr
130 135 140

Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly
145 150 155 160

Gly Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 615
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> TPO-mimetic polypeptide sequence

<400> 615

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Gly Gly Ile Glu Gly
130 135 140

Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Gly Gly Thr Lys Asn
145 150 155 160

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
165 170 175

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
180 185 190

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
195 200 205

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
210 215 220

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
225 230 235 240

Ser Leu Ser Pro Gly Lys
245

<210> 616
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin binding peptide sequence

<400> 616

Lys Asp Lys Cys Lys Met Trp His Trp Met Cys Lys Pro Pro
1 5 10

<210> 617
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> sTNF-R2 sequence

<400> 617

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
1 5 10 15

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

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
35 40 45

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
50 55 60

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Phe Ala Leu Pro Val
65 70 75 80

Gly Leu Ile Val Gly Val Thr Ala Leu Gly Leu Leu Ile Ile Gly Val
85 90 95

Val Asn Cys Val Ile Met Thr Gln Val Lys Lys Lys Pro Leu Cys Leu
100 105 110

Gln Arg Glu Ala Lys Val Pro His Leu Pro Ala Asp Lys Ala Arg Gly
115 120 125

Thr Gln Gly Pro Glu Gln Gln His Leu Leu Ile Thr Ala Pro Ser Ser
130 135 140

Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser Ala Leu Asp Arg Arg Ala
145 150 155 160

Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly Val Glu Ala Ser Gly Ala
165 170 175

Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser Asp Ser Ser Pro Gly Gly
180 185 190

His Gly Thr Gln Val Asn Val Thr Cys Ile Val Asn Val Cys Ser Ser
195 200 205

Ser Asp His Ser Ser Gln Cys Ser Ser Gln Ala Ser Ser Thr Met Gly
210 215 220

Asp Thr Asp Ser Ser Pro Ser Glu Ser Pro Lys Asp Glu Gln Val Pro
225 230 235 240

Phe Ser Lys Glu Glu Cys Ala Phe Arg Ser Gln Leu Glu Thr Pro Glu
245 250 255

Thr Leu Leu Gly Ser Thr Glu Glu Lys Pro Leu Pro Leu Gly Val Pro
260 265 270

Asp Ala Gly Met Lys Pro Ser
275

<210> 618
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<223> Etanercept-Fc domain fusion

<400> 618

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

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Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
            20                  25                  30

Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
        35                  40                  45

Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
    50                  55                  60

Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
65                  70                  75                  80

Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
                85                  90                  95

Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys
            100                 105                 110

Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
        115                 120                 125

Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro
    130                 135                 140

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
145                 150                 155                 160

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
                165                 170                 175

Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
            180                 185                 190

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
        195                 200                 205

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
    210                 215                 220

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Glu Pro Lys Ser Cys
225                 230                 235                 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270
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Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
355 360 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
370 375 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 619
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker sequence

<220>

<221> misc_feature
<222> (1)..(2)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (4)..(5)
<223> Xaa can be any naturally occurring amino acid

<400> 619

Xaa Xaa Asn Xaa Xaa Gly
1 5

<210> 620
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> L5 linker sequence

<400> 620

Gly Gly Gly Gly Ser
1 5

<210> 621
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> L10 linker sequence

<400> 621

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 622
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> L25 linker sequence

<400> 622

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 623
<211> 6
<212> PRT

<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 623

Gly Gly Glu Gly Gly Gly
1 5

<210> 624
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 624

Gly Gly Glu Glu Glu Gly Gly Gly
1 5

<210> 625
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 625

Gly Glu Glu Glu Gly
1 5

<210> 626
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 626

Gly Glu Glu Glu
1

<210> 627
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 627

Gly Gly Asp Gly Gly Gly

1 5

<210> 628
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 628

Gly Gly Asp Asp Asp Gly Gly
1 5

<210> 629
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 629

Gly Asp Asp Asp Gly
1 5

<210> 630
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 630

Gly Asp Asp Asp
1

<210> 631
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 631

Gly Gly Gly Gly Ser Asp Asp Ser Asp Glu Gly Ser Asp Gly Glu Asp
1 5 10 15

Gly Gly Gly Gly Ser
20

<210> 632

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 632

Trp Glu Trp Glu Trp
1 5

<210> 633
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 633

Phe Glu Phe Glu Phe
1 5

<210> 634
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 634

Glu Glu Glu Trp Trp Trp
1 5

<210> 635
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 635

Glu Glu Glu Phe Phe Phe
1 5

<210> 636
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 636

Trp Trp Glu Glu Glu Trp Trp
1 5

<210> 637
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<400> 637

Phe Phe Glu Glu Glu Phe Phe
1 5

<210> 638
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<220>
<221> MISC_FEATURE
<222> (1)..(2)
<223> Xaa are each independently any amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(5)
<223> Xaa are each independently any amino acid

<400> 638

Xaa Xaa Tyr Xaa Xaa Gly
1 5

<210> 639
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<220>
<221> MISC_FEATURE
<222> (1)..(2)
<223> Xaa are each independently any amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(5)
<223> Xaa are each independently any amino acid

<400> 639

Xaa Xaa Ser Xaa Xaa Gly
1 5

<210> 640
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide linker sequence

<220>
<221> MISC_FEATURE
<222> (1)..(2)
<223> Xaa are each independently any amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(5)
<223> Xaa are each independently any amino acid

<400> 640

Xaa Xaa Thr Xaa Xaa Gly
1 5

<210> 641
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (3430-37)

<400> 641
gaggaataac atatggacaa aactcacaca tgtccacct 39

<210> 642
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (4220-28)

<400> 642
ggtcaggctg acgcagttct tggtcag 27

<210> 643
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (4220-27)

<400> 643
ctgaccaaga actgcgtcag cctgacc 27

<210> 644
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (3421-87)

<400> 644
ccgcggcgtc tcgagattat ttacccggag acagggagag gct 43

<210> 645
<211> 688
<212> DNA
<213> Artificial Sequence

<220>
<223> Strain 13300 sequence

<220>
<221> CDS
<222> (1)..(687)

<400> 645
atg gac aaa act cac aca tgt cca cct tgc cca gca cct gaa ctc ctg 48
Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa ccc aag gac acc ctc 96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc 144
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag 192
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg 240
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat 288
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc 336
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag 384
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac tgc gtc 432
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Cys Val
130 135 140

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agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg        480
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145                 150                 155                 160

gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct        528
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                165                 170                 175

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc        576
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg        624
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg        672
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

tct ccg ggt aaa taa t                                                  688
Ser Pro Gly Lys
225


<210>  646
<211>  228
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Construct

<400>  646

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1               5                   10                  15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65                  70                  75                  80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                85                  90                  95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            100                 105                 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
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115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Cys Val
130 135 140

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

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly Lys
225

<210> 647
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (4220-26)

<400> 647
ctggttcttg gtgcactcat cccggga 27

<210> 648
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (4220-25)

<400> 648
tcccgggatg agtgcaccaa gaaccag 27

<210> 649
<211> 688
<212> DNA
<213> Artificial Sequence

<220>
<223> Strain 13322 sequence

<220>
<221> CDS
<222> (1)..(687)

<400> 649
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atg gac aaa act cac aca tgt cca cct tgc cca gca cct gaa ctc ctg      48
Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1               5                   10                  15

ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa ccc aag gac acc ctc      96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc     144
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

cac gaa gac cct gag gtc aag ttt aac tgg tac gtg gac ggc gtg gag     192
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg     240
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65                  70                  75                  80

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat     288
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                85                  90                  95

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc     336
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            100                 105                 110

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag     384
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

gtg tac acc ctg ccc cca tcc cgg gat gag tgc acc aag aac cag gtc     432
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Cys Thr Lys Asn Gln Val
    130                 135                 140

agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg     480
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145                 150                 155                 160

gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct     528
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                165                 170                 175

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc     576
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg     624
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg     672
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

tct ccg ggt aaa taa t                                               688
Ser Pro Gly Lys
225
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<210> 650
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 650

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Cys Thr Lys Asn Gln Val
130 135 140

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

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly Lys
225

<210> 651
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (4220-30)

<400> 651
caggcaggtc aggcagacct ggttctt 27

<210> 652
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer sequence (4220-29)

<400> 652
aagaaccagg tctgcctgac ctgcctg 27

<210> 653
<211> 688
<212> DNA
<213> Artificial Sequence

<220>
<223> Strain 13323 sequence

<220>
<221> CDS
<222> (1)..(687)

<400> 653
atg gac aaa act cac aca tgt cca cct tgc cca gca cct gaa ctc ctg 48
Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1 5 10 15

ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa ccc aag gac acc ctc 96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc 144
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag 192
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg 240
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

```
65                  70                  75                  80

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat      288
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                85                  90                  95

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc      336
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            100                 105                 110

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag      384
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc      432
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    130                 135                 140

tgc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg      480
Cys Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145                 150                 155                 160

gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct      528
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                165                 170                 175

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc      576
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg      624
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg      672
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

tct ccg ggt aaa taa t                                                688
Ser Pro Gly Lys
225
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<210> 654
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 654

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Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1               5                   10                  15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

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

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
130 135 140

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

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly Lys
225

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Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1               5                   10                  15

ggg gga ccg tca gtt ttc ctc ttc ccc cca aaa ccc aag gac acc ctc      96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc     144
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag     192
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg     240
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65                  70                  75                  80

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat     288
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                85                  90                  95

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc     336
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            100                 105                 110

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag     384
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc     432
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    130                 135                 140

agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg     480
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145                 150                 155                 160

gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct     528
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Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                165                 170                 175

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc      576
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

gtg gac aag tgc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg      624
Val Asp Lys Cys Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg      672
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

tct ccg ggt aaa taa t                                                688
Ser Pro Gly Lys
225


&lt;210&gt;  658
&lt;211&gt;  228
&lt;212&gt;  PRT
&lt;213&gt;  Artificial Sequence

&lt;220&gt;
&lt;223&gt;  Synthetic Construct

&lt;400&gt;  658

Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1               5                   10                  15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65                  70                  75                  80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                85                  90                  95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            100                 105                 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    130                 135                 140
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Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Cys Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly Lys
225