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(54) Title: MODIFIED Fc MOLECULES

(57) Abstract: The present invention concerns molecules and a process in which one or more biologically active peptides are incorporated into an Fc domain. In this invention, pharmacologically active compounds may be prepared by a process comprising (a) selecting at least one peptide that modulates the activity of a protein of interest; and (b) preparing a pharmacologic agent comprising an amino acid sequence of the selected peptide in a loop region of an Fc domain. This process may be employed to modify an Fc domain that is already linked through an N- or C-terminus or sidechain to a peptide or to a polypeptide (e.g., etanercept). This process may 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 or an additional binding domain to the precursor molecule's existing epitope. The peptide can be selected, for example, by phage display, *E. coli* display, ribosome display, RNA-peptide screening, yeast-based screening, chemical-peptide screening, rational design, or protein structural analysis.



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Modified Fc Molecules

This application claims the benefit of U.S. Provisional Application No. 60/612,680, filed September 24, 2004, which is hereby incorporated by reference.

Background of the Invention

The success of the drug Enbrel® (etanercept) brought to fruition the promise of therapeutic agents modified with the constant domain of an antibody. 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 an Fab is short-lived. Capon *et al.* (1989), *Nature* 337: 525-31. When constructed together with a therapeutic protein, an Fc domain can provide longer half-life or incorporate such functions as Fc receptor binding, protein A binding, complement fixation and perhaps even placental transfer. *Id.* Table 1 summarizes 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 <i>et al.</i> (1995), <i>J. Immunol.</i> 154: 5590-600
IgG1	TNF receptor	septic shock	Fisher <i>et al.</i> (1996), <i>N. Engl. J. Med.</i> 334: 1697-1702; Van Zee, K. <i>et al.</i> (1996), <i>J. Immunol.</i> 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 <i>et al.</i> (1989), <i>Nature</i> 337: 525-31
IgG1, IgG3	N-terminus of IL-2	anti-cancer, antiviral	Harvill <i>et al.</i> (1995), <i>Immunotech.</i> 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 Gγ1	CTLA-4	autoimmune disorders	Linsley (1991), <i>J. Exp. Med.</i> 174:561-9

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy. Clackson *et al.* (1995), *Science* 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott *et al.* (1990), *Science* 249: 386; Devlin *et al.* (1990), *Science* 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12, 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference). In such libraries, random peptide sequences are displayed by fusion with coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an antibody-immobilized extracellular domain of a receptor. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify key residues within one or more structurally related families of peptides. See, e.g., Cwirla *et al.* (1997), *Science* 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created

and screened to further optimize the sequence of the best binders.

Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor
5 and expressed in E. coli. Another E. coli-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "E. coli display." Another biological approach to screening soluble peptide mixtures uses yeast for expression and secretion. See
10 Smith et al. (1993), Mol. Pharmacol. 43: 741-8. Hereinafter, the method of Smith et al. and related methods are referred to as "yeast-based screening." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively
15 referred to as "ribosome display." Other methods employ chemical linkage of peptides to RNA; see, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized
20 on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be
25 advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62.

In the case of known bioactive peptides, rational design of peptide
30 ligands with favorable therapeutic properties can be completed. In such an approach, one makes stepwise changes to a peptide sequence and

determines the effect of the substitution upon bioactivity or a predictive biophysical property of the peptide (e.g., solution structure). Hereinafter, these techniques are collectively referred to as "rational design." In one such technique, one makes a series of peptides in which one replaces a single residue at a time with alanine. This technique is commonly referred to as an "alanine walk" or an "alanine scan." When two residues (contiguous or spaced apart) are replaced, it is referred to as a "double alanine walk." The resultant amino acid substitutions can be used alone or in combination to result in a new peptide entity with favorable therapeutic properties.

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki *et al.* (1997), *Nature Biotech.* 15: 1266-70. Hereinafter, these and related methods are referred to as "protein structural analysis." These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the peptides to increase binding affinity.

Conceptually, one may discover peptide mimetics of any protein using phage display and the other methods mentioned above. These methods have been used for epitope mapping, for identification of critical amino acids in protein-protein interactions, and as leads for the discovery of new therapeutic agents. E.g., Cortese *et al.* (1996), *Curr. Opin. Biotech.* 7: 616-21. Peptide libraries are now being used most often in immunological studies, such as epitope mapping. Kreeger (1996), *The Scientist* 10(13): 19-20.

Of particular interest here is use of peptide libraries and other techniques in the discovery of pharmacologically active peptides. A number of such peptides identified in the art are summarized in Table 2.

The peptides are described in the listed publications, each of which is hereby incorporated by reference. The pharmacologic activity of the peptides is described, and in many instances is followed by a shorthand term therefore in parentheses. Some of these peptides have been modified (e.g., to form C-terminally cross-linked dimers). Typically, peptide libraries were screened for binding to a receptor for a pharmacologically active protein (e.g., EPO receptor). In at least one instance (CTLA4), the peptide library was screened for binding to a monoclonal antibody.

Table 2—Pharmacologically active peptides

Form of peptide	Binding partner/ protein of interest ^a	Pharmacologic activity	Reference
intrapeptide disulfide-bonded	EPO receptor	EPO-mimetic	Wrighton <i>et al.</i> (1996), <i>Science</i> 273: 458-63; U.S. Pat. No. 5,773,569, issued June 30, 1998 to Wrighton <i>et al.</i>
C-terminally cross-linked dimer	EPO receptor	EPO-mimetic	Livnah <i>et al.</i> (1996), <i>Science</i> 273: 464-71; Wrighton <i>et al.</i> (1997), <i>Nature Biotechnology</i> 15: 1261-5; International patent application WO 96/40772, published Dec. 19, 1996
linear	EPO receptor	EPO-mimetic	Naranda <i>et al.</i> (1999), <i>Proc. Natl. Acad. Sci. USA</i> , 96: 7569-74; WO 99/47151, published September 23, 1999
linear; C-terminally cross-linked dimer	c-Mpl	TPO-mimetic	Cwirla <i>et al.</i> (1997) <i>Science</i> 276: 1696-9; U.S. Pat. No. 5,869,451, issued Feb. 9, 1999; U.S. Pat. No. 5,932,946, issued Aug. 3, 1999; WO 00/24770, published May 4, 2000; U.S. Pat. App. No. 2003/0176352, published Sept. 18, 2003; WO 03/031589, published April 17, 2003
disulfide-linked dimer		stimulation of hematopoiesis ("G-CSF-mimetic")	Paukovits <i>et al.</i> (1984), <i>Hoppe-Seylers Z. Physiol. Chem.</i> 365: 303-

^a The protein listed in this column may be bound by the associated peptide (e.g., EPO receptor, IL-1 receptor) or mimicked by the associated peptide. The references listed for each clarify whether the molecule is bound by or mimicked by the peptides.

			11; Laerum <i>et al.</i> (1988), <i>Exp. Hemat.</i> 16: 274-80
alkylene-linked dimer		G-CSF-mimetic	Bhatnagar <i>et al.</i> (1996), <i>J. Med. Chem.</i> 39: 3814-9; Cuthbertson <i>et al.</i> (1997), <i>J. Med. Chem.</i> 40: 2876-82; King <i>et al.</i> (1991), <i>Exp. Hematol.</i> 19:481; King <i>et al.</i> (1995), <i>Blood</i> 86 (Suppl. 1): 309a
linear	IL-1 receptor	inflammatory and autoimmune diseases ("IL-1 antagonist" or "IL-1ra-mimetic")	U.S. Pat. No. 5,608,035; U.S. Pat. No. 5,786,331; U.S. Pat. No. 5,880,096; Yanofsky <i>et al.</i> (1996), <i>Proc. Natl. Acad. Sci.</i> 93: 7381-6; Akesson <i>et al.</i> (1996), <i>J. Biol. Chem.</i> 271: 30517-23; Wiekzorek <i>et al.</i> (1997), <i>Pol. J. Pharmacol.</i> 49: 107-17; Yanofsky (1996), PNAs, 93:7381-7386.
linear	Facteur thymique serique (FTS)	stimulation of lymphocytes ("FTS-mimetic")	Inagaki-Ohara <i>et al.</i> (1996), <i>Cellular Immunol.</i> 171: 30-40; Yoshida (1984), <i>Int. J. Immunopharmacol.</i> 6:141-6.
intrapeptide disulfide bonded	CTLA4 MAb	CTLA4-mimetic	Fukumoto <i>et al.</i> (1998), <i>Nature Biotech.</i> 16: 267-70
exocyclic	TNF- α receptor	TNF- α antagonist	Takasaki <i>et al.</i> (1997), <i>Nature Biotech.</i> 15:1266-70; WO 98/53842, published December 3, 1998
linear	TNF- α receptor	TNF- α antagonist	Chirinos-Rojas (), <i>J. Imm.</i> , 5621-5626.
intrapeptide disulfide bonded	C3b	inhibition of complement activation; autoimmune diseases ("C3b-antagonist")	Sahu <i>et al.</i> (1996), <i>J. Immunol.</i> 157: 884-91; Morikis <i>et al.</i> (1998), <i>Protein Sci.</i> 7: 619-27
linear	vinculin	cell adhesion processes – cell growth, differentiation, wound healing, tumor metastasis ("vinculin binding")	Adey <i>et al.</i> (1997), <i>Biochem. J.</i> 324: 523-8
linear	C4 binding protein (C4BP)	anti-thrombotic	Linse <i>et al.</i> (1997), <i>J. Biol. Chem.</i> 272: 14658-65
linear	urokinase receptor	processes associated with urokinase interaction with its receptor (e.g., angiogenesis, tumor	Goodson <i>et al.</i> (1994), <i>Proc. Natl. Acad. Sci.</i> 91: 7129-33; International application WO 97/35969, published

		cell invasion and metastasis); ("UKR antagonist")	October 2, 1997
linear	Mdm2, Hdm2	Inhibition of inactivation of p53 mediated by Mdm2 or hdm2; anti-tumor ("Mdm/hdm antagonist")	Picksley <i>et al.</i> (1994), <i>Oncogene</i> 9: 2523-9; Bottger <i>et al.</i> (1997) <i>J. Mol. Biol.</i> 269: 744-56; Bottger <i>et al.</i> (1996), <i>Oncogene</i> 13: 2141-7
linear	p21 ^{WAF1}	anti-tumor by mimicking the activity of p21 ^{WAF1}	Ball <i>et al.</i> (1997), <i>Curr. Biol.</i> 7: 71-80
linear	farnesyl transferase	anti-cancer by preventing activation of ras oncogene	Gibbs <i>et al.</i> (1994), <i>Cell</i> 77:175-178
linear	Ras effector domain	anti-cancer by inhibiting biological function of the ras oncogene	Moodie <i>et al.</i> (1994), <i>Trends Genet</i> 10: 44-48 Rodriguez <i>et al.</i> (1994), <i>Nature</i> 370:527-532
linear	SH2/SH3 domains	anti-cancer by inhibiting tumor growth with activated tyrosine kinases; treatment of SH3-mediated disease states ("SH3 antagonist")	Pawson <i>et al.</i> (1993), <i>Curr. Biol.</i> 3:434-432 Yu <i>et al.</i> (1994), <i>Cell</i> 76:933-945; Rickles <i>et al.</i> (1994), <i>EMBO J.</i> 13: 5598-5604; Sparks <i>et al.</i> (1994), <i>J. Biol. Chem.</i> 269: 23853-6; Sparks <i>et al.</i> (1996), <i>Proc. Natl. Acad. Sci.</i> 93: 1540-4; US Pat. No. 5,886,150, issued March 23, 1999; US Pat. No. 5,888,763, issued March 30, 1999
linear	p16 ^{INK4}	anti-cancer by mimicking activity of p16; e.g., inhibiting cyclin D-Cdk complex ("p16-mimetic")	Fåhræus <i>et al.</i> (1996), <i>Curr. Biol.</i> 6:84-91
linear	Src, Lyn	inhibition of Mast cell activation, IgE-related conditions, type I hypersensitivity ("Mast cell antagonist")	Stauffer <i>et al.</i> (1997), <i>Biochem.</i> 36: 9388-94
linear	Mast cell protease	treatment of inflammatory disorders mediated by release of tryptase-6 ("Mast cell protease inhibitors")	International application WO 98/33812, published August 6, 1998
linear	HBV core antigen (HBcAg)	treatment of HBV viral infections ("anti-HBV")	Dyson & Muray (1995), <i>Proc. Natl. Acad. Sci.</i> 92: 2194-8
linear	selectins	neutrophil adhesion; inflammatory diseases ("selectin antagonist")	Martens <i>et al.</i> (1995), <i>J. Biol. Chem.</i> 270: 21129-36; European patent

			application EP 0 714 912, published June 5, 1996
linear, cyclized	calmodulin	calmodulin antagonist	Pierce et al. (1995), <u>Molec. Diversity</u> 1: 259-65; Dedman et al. (1993), <u>J. Biol. Chem.</u> 268: 23025-30; Adey & Kay (1996), <u>Gene</u> 169: 133-4
linear, cyclized-	integrins	tumor-homing; treatment for conditions related to integrin-mediated cellular events, including platelet aggregation, thrombosis, wound healing, osteoporosis, tissue repair, angiogenesis (e.g., for treatment of cancer), and tumor invasion ("integrin-binding")	International applications WO 95/14714, published June 1, 1995; WO 97/08203, published March 6, 1997; WO 98/10795, published March 19, 1998; WO 99/24462, published May 20, 1999; Kraft et al. (1999), <u>J. Biol. Chem.</u> 274: 1979-1985
cyclic, linear	fibronectin and extracellular matrix components of T cells and macrophages	treatment of inflammatory and autoimmune conditions	WO 98/09985, published March 12, 1998
linear	somatostatin and cortistatin	treatment or prevention of hormone-producing tumors, acromegaly, gigantism, dementia, gastric ulcer, tumor growth, inhibition of hormone secretion, modulation of sleep or neural activity	European patent application O 911 393, published April 28, 1999
linear	bacterial lipopolysaccharide	antibiotic; septic shock; disorders modulatable by CAP37	U.S. Pat. No. 5,877,151, issued March 2, 1999
linear or cyclic, including D-amino acids	pardaxin, mellitin	antipathogenic	WO 97/31019, published 28 August 1997
linear, cyclic	VIP	impotence, neurodegenerative disorders	WO 97/40070, published October 30, 1997
linear	CTLs	cancer	EP 0 770 624, published May 2, 1997
linear	THF-gamma2		Burnstein (1988), <u>Biochem.</u> , 27:4066-71.
linear	Amylin		Cooper (1987), <u>Proc. Natl. Acad. Sci.</u> , 84:8628-32.
linear	Adrenomedullin		Kitamura (1993), <u>BBRC</u> ,

			192:553-60.
cyclic, linear	VEGF	anti-angiogenic; cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis ("VEGF antagonist")	Fairbrother (1998), <u>Biochem.</u> , 37:17754-17764.
cyclic	MMP	inflammation and autoimmune disorders; tumor growth ("MMP inhibitor")	Koivunen (1999), <u>Nature Biotech.</u> , 17:768-774.
	HGH fragment	treatment of obesity	U.S. Pat. No. 5,869,452
	Echistatin	inhibition of platelet aggregation	Gan (1988), <u>J. Biol. Chem.</u> , 263:19827-32.
linear	SLE autoantibody	SLE	WO 96/30057, published October 3, 1996
	GD1alpha	suppression of tumor metastasis	Ishikawa et al. (1998), <u>FEBS Lett.</u> 441 (1): 20-4
	antiphospholipid beta-2-glycoprotein-I (α 2GPI) antibodies	endothelial cell activation, antiphospholipid syndrome (APS), thromboembolic phenomena, thrombocytopenia, and recurrent fetal loss	Blank et al. (1999), <u>Proc. Natl. Acad. Sci. USA</u> 96: 5164-8
linear	T Cell Receptor beta chain	diabetes	WO 96/11214, published April 18, 1996.
		Antiproliferative, antiviral	WO 00/01402, published January 13, 2000.
		anti-ischemic, growth hormone-liberating	WO 99/62539, published December 9, 1999.
		anti-angiogenic	WO 99/61476, published December 2, 1999.
linear		Apoptosis agonist; treatment of T cell-associated disorders (e.g., autoimmune diseases, viral infection, T cell leukemia, T cell lymphoma)	WO 99/38526, published Aug. 5, 1999.
linear	MHC class II	treatment of autoimmune diseases	US Pat. No. 5,880,103, issued March 9, 1999.
linear	androgen R, p75, MJD, DCC, huntingtin	proapoptotic, useful in treating cancer	WO 99/45944, published September 16, 1999.
linear	von Willebrand Factor; Factor VIII	inhibition of Factor VIII interaction; anticoagulants	WO 97/41220, published April 29, 1997.
linear	lentivirus LLP1	antimicrobial	US Pat. No. 5,945,507, issued Aug. 31, 1999.
linear	Delta-Sleep Inducing Peptide	sleep disorders	Graf (1986), <u>Peptides</u> 7:1165.
linear	C-Reactive Protein (CRP)	inflammation and cancer	Barna (1994), <u>Cancer Immunol. Immunother.</u> 38:38 (1994).

linear	Sperm-Activating Peptides	infertility	Suzuki (1992), <u>Comp. Biochem. Physiol.</u> 102B:679.
linear	angiotensins	hematopoietic factors for hematocytopenic conditions from cancer, AIDS, etc.	Lundergan (1999), <u>J. Periodontal Res.</u> 34(4):223-228.
linear	HIV-1 gp41	anti-AIDS	Chan (1998), <u>Cell</u> 93:681-684.
linear	PKC	inhibition of bone resorption	Moonga (1998), <u>Exp. Physiol.</u> 83:717-725.
linear	defensins (HNP-1, -2, -3, -4)	antimicrobial	Harvig (1994), <u>Methods Enz.</u> 236:160-172.
linear	p185 ^{HER2/neu} , C-erbB-2	AHNP-mimetic: anti-tumor	Park (2000), <u>Nat. Biotechnol.</u> 18:194-198.
linear	gp130	IL-6 antagonist	WO 99/60013, published Nov. 25, 1999.
linear	collagen, other joint, cartilage, arthritis-related proteins	autoimmune diseases	WO 99/50282, published Oct. 7, 1999.
linear	HIV-1 envelope protein	treatment of neurological degenerative diseases	WO 99/51254, published Oct. 14, 1999.
linear	IL-2	autoimmune disorders (e.g., graft rejection, rheumatoid arthritis)	WO 00/04048, published Jan. 27, 2000; WO 00/11028, published March 2, 2000.
linear, cyclic	various	inflammatory conditions, autoimmune disease, others	U.S. Pat. No. 6,660,843
linear, cyclic	Ang-2	inhibition of angiogenesis (e.g., for treatment of tumor)	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
	NGF	chronic pain, migraine, asthma, hyperactive bladder, psoriasis, cancer, other conditions linked to NGF	WO 04/026329, published April 1, 2004
	myostatin		U.S. Serial No. 10/742,379, filed Dec. 19, 2003; PCT/US03/40781, filed Dec. 19, 2003
	BAFF/TALL-1	B-cell mediated autoimmune diseases and cancers (e.g., lupus, B-cell lymphoma)	U.S. 2003/0195156, published Oct. 16, 2003; WO 02/092620, published Nov. 21, 2002
linear	GLP-1	Diabetes, metabolic syndrome	

Peptides identified by peptide library screening were for a long time regarded simply as "leads" in development of therapeutic agents rather than as therapeutic agents themselves. Like other proteins and peptides, they would be rapidly removed in vivo either by renal filtration, cellular clearance mechanisms in the reticuloendothelial system, or proteolytic degradation. Francis (1992), Focus on Growth Factors 3: 4-11. As a result, the art used the identified peptides to validate drug targets or as scaffolds for design of organic compounds that might not have been as easily or as quickly identified through chemical library screening.

10 Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24; Kay et al. (1998), Drug Disc. Today 3: 370-8.

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 sidechains, 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, 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

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April 8, 2004); U.S. Ser. No. 10/666,480, filed September 18, 2003
(corresponding to WO 04/026329, published April 1, 2004), each of which
is hereby incorporated by reference in its entirety. The art would benefit
from further technology enabling such rational design of polypeptide
5 therapeutic agents.

Summary of the Invention

The present invention concerns a process in which at least one
biologically active peptide is incorporated as an internal sequence into an
10 Fc domain. Such an internal sequence may be added by insertion (i.e.,
between amino acids in the previously existing Fc domain) or by
replacement of amino acids in the previously existing Fc domain (i.e.,
removing amino acids in the previously existing Fc domain and adding
peptide amino acids). In the latter case, the number of peptide amino acids
15 added need not correspond to the number of amino acids removed from
the previously existing Fc domain; for example, this invention concerns a
molecule in which 10 amino acids are removed and 15 amino acids are
added. In this invention, pharmacologically active compounds are
prepared by a process comprising:

- 20 a) selecting at least one peptide that modulates the activity of a
protein of interest; and
- b) preparing a pharmacologic agent comprising an amino acid
sequence of the selected peptide as an internal sequence of
an Fc domain.

25 This process may be employed to modify an Fc domain that is already
linked through an N- or C-terminus or sidechain to a polypeptide (e.g.,
etanercept) or to a peptide (e.g., as described in U.S. Pat. App. Nos.
2003/0195156, 2003/0176352, 2003/0229023, and 2003/0236193; WO
00/24770; WO 04/026329). The process described throughout may also be
30 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 or an additional binding domain to the precursor molecule's existing epitope. The peptide can be selected, for example, by phage display (which is preferred), *E. coli* display, ribosome display, RNA-peptide screening, yeast-based screening, chemical-peptide screening, rational design, or protein structural analysis or may be a naturally occurring peptide (e.g. PTH, GLP-1).

The invention further relates to molecules comprising an Fc domain modified to comprise a peptide as an internal sequence (preferably in a loop region) of the Fc domain. Molecules comprising an internal peptide sequence are referred to throughout as "Fc internal peptibodies" or "Fc internal peptide molecules." These molecules are further described herein below.

The Fc internal peptide molecules may include more than one peptide sequence in tandem in a particular internal region, and they may include further peptides in other internal regions. While the putative loop regions are preferred, insertions in any other non-terminal domains of the Fc are also considered part of this invention. Variants and derivatives of the above compounds (described below) are also encompassed by this invention.

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.

The primary use contemplated for Fc internal peptide molecules is as therapeutic or prophylactic agents. A selected peptide may have activity comparable to—or even greater than—the natural ligand mimicked by the peptide. In addition, certain natural ligand-based therapeutic agents might induce antibodies against the patient's own endogenous ligand. In contrast, the unique sequence of the vehicle-linked peptide avoids this pitfall by having little or typically no sequence identity

with the natural ligand. Furthermore, the Fc internal peptibodies may have advantages in refolding and purification over N- or C-terminally linked Fc molecules. Further still, Fc internal peptibodies may be more stable in both thermodynamically, due to the stabilization of chimeric domains, and chemically, due to increased resistance to proteolytic degradation from amino- and carboxy-peptidases. Fc internal peptibodies may also exhibit improved pharmacokinetic properties.

Although mostly contemplated as therapeutic agents, compounds of this invention may also be useful in screening for such agents. For example, one could use an Fc internal peptibody (e.g., Fc-loop-SH2 domain peptide) in an assay employing anti-Fc coated plates. Fc internal peptibodies may make insoluble peptides soluble and thus useful in a number of assays.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them with appropriate pharmaceutical carrier materials 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 instant invention.

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

Description of the Figures

Figures 1A, 1B and 1C show loop regions of Fc domains that may be modified in accordance with this invention. In these structural representations of the CH2 and CH3 domains of Fc, the loop regions may be considered any part of the model not shown as β -sheet (flat arrows) or α -helix (cylinder).

Figure 1A shows the monomeric rat IgG2a Fc domain (Protein Database file #1I1C, <http://www.rcsb.org/pdb/>). This figure shows a three dimensional model of rat IgG2a Fc domain monomer from x-ray diffraction crystal structure (pdb #1I1C). Potential Fc loop insertion sites

are shown for both CH2 and CH3 domains with the preferred CH3 domain Fc loop insertion site specifically identified.

Figure 1B shows the monomeric murine IgG1 Fc domain (Protein Database file #1IGY). This figure shows a three-dimensional model of murine IgG1 Fc domain monomer from x-ray diffraction crystal structure (pdb #1IGY). Potential Fc loop insertion sites are shown for both CH2 and
5 CH3 domains with the preferred CH3 domain Fc loop insertion site specifically identified.

Figure 1C shows the monomeric human IgG1 Fc domain (Protein Database file #1H3T). This figure shows a three-dimensional model of human IgG1 Fc domain monomer from x-ray diffraction crystal structure (pdb #1H3T). Potential Fc loop insertion sites are shown for both CH2 and CH3 domains with the preferred CH3 domain Fc loop insertion site specifically identified.

These structures illustrate the high degree of homology in the secondary and tertiary structural conformations within the Fc domains of different IgG subtypes and between species. The x-ray crystal structure
10 coordinates for these structures can be found in the RCSB Protein Data Bank (<http://www.rcsb.org/pdb/>).

Figure 2A shows a sequence of human IgG1 Fc sequence (SEQ ID NO: 599) used for peptibody fusions with predicted loop sequences in boldface. Figure 2A shows, in the context of the human IgG1 sequence
15 used for this invention, the Fc loop regions in boldface (SEQ ID NOS: 621, 622, 624, 625, 627, 628, 630, 632, 634, and 636), which are suggested by the structures shown in Figures 1A, 1B and 1C. Any, or all of the sites shown in boldface may be suitable for full or partial replacement by or insertion of peptide sequences and are considered part of this invention. Specifically
20 preferred internal sites are underlined (SEQ ID NOS: 623, 626, 629, 631, 633, 635, and 637). One preferred site is SEQ ID NO: 631, between Leu₁₃₉ and Thr₁₄₀ in the DELTK (SEQ ID NO: 630) loop. Potential loop sites in

other Ig subtypes are understood in the art based on the alignments provided in Figures 2B and 2C.

Figures 2B and 2C show a sequence alignment of human Fc domains from IgA, IgM and IgG subclasses. Figures 2B and 2C show
 5 exemplary amino acid sequences (SEQ ID NOS: 600 to 607) of human Fc regions from IgA, IgM and IgG subtypes that may be useful in this invention. Also shown in Figures 2B and 2C is a consensus sequence (SEQ ID NO: 608).

Figures 2B and 2C also show in boldface the preferred internal sites
 10 for peptide addition that correspond to those of the Fc sequence shown in Figure 2A (SEQ ID NO: 599). In particular, Figures 2B and 2C show as such preferred sites the following:

- SEQ ID NO: 621 as shown in boldface within SEQ ID NOS: 603 to 608;
- SEQ ID NO: 622 within SEQ ID NOS: 603 to 606 and 608;
- 15 • SEQ ID NO: 638 within SEQ ID NO: 607;
- SEQ ID NO: 624 within SEQ ID NO: 603 to 608;
- SEQ ID NO: 625 within SEQ ID NOS: 603 and 604;
- SEQ ID NO: 639 within SEQ ID NOS: 605 to 608;
- SEQ ID NO: 627 within SEQ ID NOS: 603 to 605, 607, and 608;
- 20 • SEQ ID NO: 640 within SEQ ID NO: 606;
- SEQ ID NO: 628 within SEQ ID NOS: 603, 604, and 608;
- SEQ ID NO: 641 within SEQ ID NO: 605;
- SEQ ID NO: 642 within SEQ ID NO: 606;
- SEQ ID NO: 643 within SEQ ID NO: 607;
- 25 • SEQ ID NO: 630 within SEQ ID NO: 603;
- SEQ ID NO: 644 within SEQ ID NOS: 604 to 608;
- SEQ ID NO: 632 within SEQ ID NOS: 603, 604, 606, 607, and 608;
- SEQ ID NO: 645 within SEQ ID NO: 605;
- SEQ ID NO: 634 within SEQ ID NOS: 603, 604, and 607;
- 30 • SEQ ID NO: 646 within SEQ ID NOS: 605, 606 and 608;

- SEQ ID NO: 636 within SEQ ID NOS: 603, 604, 606, and 608;
- SEQ ID NO: 614 within SEQ ID NO: 605; and
- SEQ ID NO: 620 within SEQ ID NO: 607.

5 The sequence alignments of Figures 2B and 2C suggest two more potential insertion sites at Q₁₆₇/P₁₆₈ and/or G₁₈₃/S₁₈₄ (using the numbering of SEQ ID NO: 599 in Figure 2A). These positions correspond to gaps in the IgG sequences where there are 2 and 3 residue insertions found in the aligned IgA and IgM sequences. Other preferred insertion
10 sites correspond to the sequence in Figure 2A. The preferred insertion sites are underlined Figures 2B and 2C and are as follows:

- H₅₃/E₅₄ in SEQ ID NOS: 603 and 604;
- H₁₀₀/E₁₀₁ in SEQ ID NO: 605;
- H₄₉/E₅₀ in SEQ ID NO: 606;
- 15 • Q₅₀/E₅₁ in SEQ ID NO: 607;
- H₁₁₂/E₁₁₃ in SEQ ID NO: 608;
- Y₈₁/N₈₂ in SEQ ID NOS: 603 and 604;
- F₁₂₈/N₁₂₉ in SEQ ID NO: 605;
- F₇₇/N₇₈ in SEQ ID NO: 606;
- 20 • F₇₈/N₇₉ in SEQ ID NO: 607;
- F₁₄₀/N₁₄₁ in SEQ ID NO: 608;
- N₁₁₀/K₁₁₁ in SEQ ID NOS: 603 and 604;
- N₁₅₇/K₁₅₈ in SEQ ID NO: 605;
- N₁₀₆/K₁₀₇ in SEQ ID NO: 606;
- 25 • N₁₀₇/K₁₀₈ in SEQ ID NO: 607;
- N₁₆₉/K₁₇₀ in SEQ ID NO: 608;
- L₁₄₃/T₁₄₄ in SEQ ID NOS: 603 and 604;
- M₁₉₀/T₁₉₁ in SEQ ID NO: 605;
- M₁₃₉/T₁₄₀ in SEQ ID NO: 606;
- 30 • M₁₄₀/T₁₄₁ in SEQ ID NO: 607;

- M₂₀₄/T₂₀₅ in SEQ ID NO: 608;
- Q₁₇₁P₁₇₂ in SEQ ID NOS: 603 and 604;
- Q₂₁₈/P₂₁₉ in SEQ ID NO: 605;
- Q₁₆₇/P₁₆₈ in SEQ ID NO: 606;
- 5 • Q₁₆₈/P₁₆₉ in SEQ ID NO: 607;
- Q₂₃₂/P₂₃₃ in SEQ ID NO: 608;
- E₁₇₃N₁₇₄ in SEQ ID NOS: 603 and 604;
- E₂₂₀/N₂₂₁ in SEQ ID NO: 605;
- E₁₆₉/N₁₇₀ in SEQ ID NO: 606;
- 10 • E₁₇₀/N₁₇₁ in SEQ ID NO: 607;
- E₂₃₄/N₂₃₅ in SEQ ID NO: 608;
- S₁₈₆/D₁₈₇ in SEQ ID NOS: 603 and 604;
- S₂₃₂/D₂₃₃ in SEQ ID NO: 605;
- S₁₈₁/D₁₈₂ in SEQ ID NO: 606;
- 15 • S₁₈₂/D₁₈₃ in SEQ ID NO: 607;
- S₂₄₆/D₂₄₇ in SEQ ID NO: 608;
- G₁₈₈/S₁₈₉ in SEQ ID NOS: 603 and 604;
- G₂₃₄/S₂₃₅ in SEQ ID NO: 605;
- G₁₈₃/S₁₈₄ in SEQ ID NO: 606;
- 20 • G₁₈₄/S₁₈₅ in SEQ ID NO: 607;
- G₂₄₈/S₂₄₉ in SEQ ID NO: 608;
- G₂₀₅/N₂₀₆ in SEQ ID NOS: 603 and 604;
- G₂₅₂/N₂₅₃ in SEQ ID NO: 605;
- G₂₀₁/N₂₀₂ in SEQ ID NO: 606;
- 25 • G₂₀₂/N₂₀₃ in SEQ ID NO: 607; and
- G₂₆₈/N₂₆₉ in SEQ ID NO: 608.

Figure 2D shows an alignment of human IgG1 Fc domain (Amgen Fc, SEQ ID NO: 609) used for the peptibody platform with rat IgG2A from crystal structure of FcRn/Fc complex (1I1A.pdb, SEQ ID NO: 610). The resulting consensus sequence (SEQ ID NO: 611) is also shown.

Figure 3A shows the amino acid sequence (SEQ ID NO: 612) of a human IgG1 Fc domain having insertion of a myostatin binding peptide (SEQ ID NO: 365). Hereinafter, this molecule is referred to as the “myostatin loop peptibody” or “Fc-loop-myo7.” The inserted peptide is shown in boldface and the glycine linkers in italics.

Figure 3B shows the amino acid sequence (SEQ ID NO: 613) of a C-terminally linked peptibody referred to as TN8-19-07. This peptibody incorporates the same peptide sequence as Fc-loop-myo7 (SEQ ID NO: 365). The TN8-19-07 peptide is shown in boldface and the glycine and alanine linkers in italics.

Figure 3C shows the amino acid sequence (SEQ ID NO: 615) of an Fc internal peptibody referred to hereinafter as Fc-loop-EMP. This peptibody incorporates an EPO-mimetic peptide (SEQ ID NO: 2). The inserted peptide is shown in boldface and the glycine linkers in italics. The cysteines that form a disulfide bond are underlined.

Figure 3D shows the amino acid sequence (SEQ ID NO: 616) of an Fc internal peptibody referred to hereinafter as Fc-loop-Amp2. Bioactive peptide (SEQ ID NO: 28) is highlighted in boldface and glycine linkers in italics. There is no disulfide constraint in the AMP-2 peptide insertion.

Figure 3E shows the amino acid sequence (SEQ ID NO: 617) of a C-terminally linked peptibody referred to hereinafter as Fc-loop-AMP2-dimer. This tandem-linked therapeutic peptide dimer shows the therapeutic peptide sequence (SEQ ID NO: 28) in boldface and the linkers in italics. This molecule incorporates a tandem peptide dimer of the same peptide sequence as found in Fc-loop-AMP-2.

Figures 4A and 4B shows the expression in E. coli of Fc-loop-myo7 and TN8-19-07 by SDS-PAGE (4-20%). Samples of the crude cell lysate (lys), the insoluble fraction (insol) and the soluble (sol) fraction for both the Fc-loop-Myo7 (#6951) and TN8-19-07 (#6826) are shown in reducing gels. SeeBlue and molecular weight markers (lane 1), whole cell lysate (lane 2), insoluble fraction (lane 3) and insoluble fraction (lane 4).

Figure 5 shows a reverse phase, high performance liquid chromatography (RP-HPLC) comparison of the unpurified refold reactions of the Fc-loop-Myo7 (#6951) and TN8-19-07 (#6826). Approximately 10 µg of peptibody was loaded directly from a refold reaction to a Vydak C4 column (5 µM, 300 angstrom, 4.6 x 250 mm) and eluted with a linear 40-50% ACN gradient at 0.5 %/min.

Figure 6 shows reversed-phase high performance liquid chromatography (RP-HPLC) comparison of the final, purified pools of Fc-loop TN8-19-07 (#6951) and carboxy-terminal Fc TN8-19-07 (#6826). Loaded 10 µg purified peptibody to Vydak C4 column (5 µM, 300 angstrom, 4.6 x 250 mm) and eluted with a linear 40-50% ACN gradient at 0.5 %/min.

Figure 7 shows the analyses of final purified pools of Fc-loop TN8-19-07 (#6951) and carboxy-terminal Fc TN8-19-07 (#6826) by SDS-PAGE (4-20% gel). Five µg of each sample was loaded as follows: #6951 (lane 1), #6826 (lane 2), SeeBlue + markers (lane M), #6951 reduced (lane 3), #6826 reduced (lane 4).

Figure 8 shows an in vitro cell-based bioassay for measuring myostatin inhibitory compounds. Fc-loop TN8-19-07 (#6951) retains full inhibitory activity relative to the carboxy-terminal TN8-19-07 peptibody (#6826).

Figure 9 shows a western blot analysis of an in vivo stability study for Fc-loop TN8-19-07 (#6951) and the carboxy-terminal TN8-19-07 peptibody (#6826). Sera pools from five mice were evaluated for each time point (0, 4, 24 and 48 hours). Lanes 1-3 are Fc-loop TN8-19-07 standards at 2 ng, 5 ng and 10 ng respectively. Lanes 4 & 5 are the Fc-loop vs. carboxy terminal peptibodies, respectively, at 4 hours. Lanes 6 & 7 are the Fc-loop vs. carboxy terminal peptibodies respectively at 24 hours. Lanes 8 & 9 are the Fc-loop vs. carboxy terminal peptibodies respectively at 48 hours. Lanes 10-12 are the carboxy-terminal peptibody standard at 2 ng, 5 ng and 10 ng, respectively. The gel was a 1 mm 4-12% SDS-PAGE gel

run in MES reducing buffer and the western blot was developed using a goat anti-human IgG Fc-HRP conjugate.

Figure 10A shows the amino acid sequence (SEQ ID NO: 618) of a human IgG1 Fc domain having insertion of an Ang2 binding peptide (SEQ ID NO: 147). Hereinafter, this molecule is referred to as "Ang2 loop peptibody" or "Fc-loop-Ang2." Bioactive peptide is highlighted in boldface and Glycine linkers in italics.

Figure 10B shows the amino acid sequence (SEQ ID NO: 619) of a C-terminally linked peptibody referred to herein as TN8-Con4. This molecule incorporates the same peptide sequence as Fc-loop-ang2 (SEQ ID NO: 147). The bioactive peptide is highlighted in boldface and the glycine and alanine linkers in italics.

Figure 11 shows the expression and distribution in *E. coli* of the Fc-loop TN8-Con4 (#6888) and carboxy-terminal TN8-Con4 (#5564) peptibodies by SDS-PAGE. Samples of the crude cell lysate (lys), the insoluble fraction (insol) and the soluble (sol) fraction for both the Fc-loop-Tn8-Con4 (#6888) and TN8-Con4 (#5564) are shown in reducing gels.

Figure 12 shows a RP-HPLC comparison of Fc-loop Ang2 (#6888) and carboxy-terminal Fc TN8-19-07 (#5564) refold reactions. Loaded 20 μ l refold reaction to Vydak C4 column (5 μ M, 300 angstrom, 4.6 x 250 mm) and eluted with a linear 40-50% ACN gradient at 0.5 %/min.

Figure 13 shows a RP-HPLC comparison of the final purified pools of Fc-loop Ang2 (#6888) and carboxy-terminal Fc TN8-Con4 (#5564). Ten μ g purified peptibody was loaded to a Vydak C4 column (5 μ M, 300 angstrom, 4.6 x 250 mm) and eluted with a linear 40-50% ACN gradient at 0.5 %/min.

Figure 14 shows purified Fc-loop-myo7 and TN8-19-7.

Figure 15 shows Biacore binding analysis of Fc-loop-ang2 and Fc-ang2-tandem.

Figure 16 shows the results of an in vitro enzyme-linked immunosorbent assay (ELISA) for Fc-loop-ang2, TN8-Con4, and Fc-ang2-tandem.

Figure 17 shows the results of a UT7 erythropoietin proliferation assay for Fc-loop-EMP. In the assay, the activity of two different of Fc-loop-EMP molecules is compared to that of epoetin alfa.

Figure 18 shows the expression and distribution in E. coli of the Fc-loop TN8-Amp2 (#6875) peptibody by SDS-PAGE. Samples of the crude cell lysate (lys), the insoluble fraction (insol) and the soluble (sol) fraction for the Fc-loop-Amp2 (#6888) are shown in reducing gels.

Figure 19 shows an analysis of the final purified pool of Fc-loop AMP 2 (#6875) by SDS-PAGE (4-20% gel). Lane 2 was loaded with 5 µg Fc-loop AMP 2 peptibody; lane 4 with 5 µg reduced Fc-loop AMP 2 peptibody; lanes 1 and 3 with SeeBlue and two molecular weight markers.

Figure 20 shows an RP-HPLC analysis of the final purified pool of Fc-loop AMP 2 (#6875). Ten µg purified peptibody was loaded to Vydak C4 column (5 µM, 300 angstrom, 4.6 x 250 mm) and eluted with a linear 40-50% ACN gradient at 0.5 %/min.

Figure 21 shows a murine in vivo bioassay of Fc-loop AMP 2 and AMG 531 peptibodies. Mice dosed with a single subcutaneous injection of 50 µg/kg peptibody or carrier alone. See example 9 for assay methodology.

Figure 22 shows several strategies for incorporating 2 bioactive peptides into an Fc-loop peptibody.

Figure 23 shows SDS-PAGE Gels of purified Fc-loop constructs. Samples (2ug/lane) were run +/- reducing buffer on a 4-20% Tris-Glycine SDS-PAGE gel.

Figure 24 shows RP-HPLC of Fc-loop constructs.

Detailed Description of the Invention

Definition of Terms

The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

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

 "Antibody" or "antibody peptide(s)" refer to an intact antibody, or a binding fragment thereof that competes with the intact antibody for
10 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,
15 Fab', F(ab')₂, Fv, and single-chain antibodies.

 The term "native Fc" refers to a molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form, into which a peptide sequence may be added by insertion into or replacement of a
20 loop region. The original immunoglobulin source of the native Fc is preferably of human origin and may be any of the immunoglobulins, although IgG1 and IgG2 are preferred. Native Fc's 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
25 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
30 "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

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 the fusion 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 "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. 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.

The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more 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,
5 which is hereby incorporated by reference.

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
10 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 -NRR¹, NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR, a succinimide group, or substituted or unsubstituted
15 benzyloxycarbonyl-NH-, wherein R and R¹ and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by -C(O)R² or -NR³R⁴ wherein R², R³ and R⁴ 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
20 residues. Derivatives are further described hereinafter.

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 IL-1ra, leptin, soluble TNF receptors type 1 and type 2 (sTNF-R1, sTNF-R2),
25 KGF, EPO, TPO, G-CSF, darbepoietin, Fab fragments and the like.

The term "peptide" refers to molecules of 2 to 40 amino acids, with molecules of 3 to 20 amino acids preferred and those of 6 to 15 amino acids most preferred. Exemplary peptides may be randomly generated by any of the methods cited above, carried in a peptide library (e.g., a phage
30 display library), or derived by digestion of proteins.

The term "randomized" as used to refer to peptide sequences refers to fully 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.

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). Thus, pharmacologically active peptides comprise agonistic or mimetic and antagonistic peptides as defined below.

The terms "-mimetic peptide" and "-agonist peptide" refer to a peptide having biological activity comparable to a protein (e.g., EPO, TPO, G-CSF) that interacts with a protein of interest. These terms further include peptides 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 G-CSF-mimetic peptides listed in Table 2 hereof and in Table 7 of U.S. Pat. No. 6,660,843, which is hereby incorporated by reference. Thus, the term "EPO-mimetic peptide" comprises any peptides 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 2 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 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 "TNF-antagonist peptide" comprises peptides that can be identified or derived as described in Takasaki et al. (1997), Nature Biotech. 15: 1266-70 or any of the references in Table 2 identified as having TNF-antagonistic subject matter. 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.

10 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; U.S. Pat. App. No. 2003/0176352, published Sept. 18, 2003; WO 03/031589, published April 17, 2003 and any other reference in Table 2 identified as having TPO-mimetic subject matter, as well as WO 00/24770, published May 4, 2000, which is hereby incorporated by reference. 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.

20 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; and any other reference in Table 2 identified as having subject matter related to ang-2. 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 other reference in Table 2 identified as having subject matter related to NGF. 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 "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 and any other reference in Table 2 identified as having subject matter related to myostatin. 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.

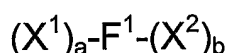
Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. By "physiologically acceptable salts" is meant any salts that are known or later discovered to be pharmaceutically acceptable. Some specific examples are: acetate; trifluoroacetate; hydrohalides,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

Structure of compounds

In General

In the compositions of matter prepared in accordance with this invention, the peptide may be attached to the vehicle through the peptide's N-terminus or C-terminus. Thus, the vehicle-peptide molecules of this invention may be described by the following formula I:

I



wherein:

F^1 is an Fc domain modified so that it comprises at least one X^3 in a loop region;

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

X^3 is independently selected from $-(L^5)_c-P^5$, $-(L^5)_c-P^5-(L^6)_d-P^6$, $-(L^5)_c-P^5-(L^6)_d-P^6-(L^7)_e-P^7$, and $-(L^5)_c-P^5-(L^6)_d-P^6-(L^7)_e-P^7-(L^8)_f-P^8$;

P¹, P², P³, and P⁴ are each independently sequences of pharmacologically active polypeptides or pharmacologically active peptides;

P⁵, P⁶, P⁷, and P⁸ are each independently sequences of
 5 pharmacologically active peptides;

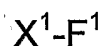
L¹, L², L³, L⁴, L⁵, L⁶, L⁷, and L⁸ are each independently linkers; and
 a, b, c, d, e, and f are each independently 0 or 1.

In preferred embodiments, a and b are both zero--i.e., neither X¹ nor X² groups appear at the N-terminus or C-terminus of the Fc domain.

10 Those of ordinary skill in the art will appreciate that more than one X³ substituent may be present in the Fc domain, and that the multiple X³ substituents may be different; for example, comprising different P⁵ peptides, different linkers attached to the same peptide sequence, and so on. Likewise, X¹ and X² may be the same or different, and the integers c
 15 through f may be different for X¹, X², and X³.

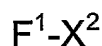
Thus, compound I comprises compounds of the formulae

II



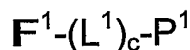
and multimers thereof wherein F¹ is attached at the C-terminus of X¹;

20 III



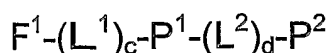
and multimers thereof wherein F¹ is attached at the N-terminus of X²;

IV



25 and multimers thereof wherein F¹ is attached at the N-terminus of -(L¹)_c-P¹; and

V



and multimers thereof wherein F¹ is attached at the N-terminus of -L¹-P¹-
 30 L²-P².

Peptides

Any number of peptides may be used in conjunction with the present invention. Preferred peptides 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 may be discovered by methods described in the references cited in this specification and other references.

Phage display, in particular, 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 3). The receptor classification appears in Table 3.

Table 3—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	I. Cytokine R (CKR)	1. shared γ Cr, IL-9R, IL-4R
	2.	IL-3, IL-5, GM-CSF		2. shared GP 140 β R
	3.	IL-6, IL-11, IL-		3. 3.shared RP

	12, LIF, OSM, CNTF, Leptin (OB)		130, IL-6 R, Leptin R
	4. G-CSF, EPO, TPO, PRL, GH		4. "single chain" R, GCSF-R, TPO-R, GH-R
	5. IL-17, HVS-IL-17		5. other R ^b
II. IL-10 ligands	IL-10, BCRF-1, HSV-IL-10	II. IL-10 R	
III. Interferons	1. IFN- α 1, α 2, α 4, m, t, IFN- β^c	III. Interferon R	1. IFNAR
	2. IFN- γ		2. IFNGR
IV. IL-1 and IL-1 like ligands	1. IL-1 α , IL-1 β , IL-1Ra	IV. IL-1R	1. IL-1R, IL-1RAcP
	2. IL-18, IL-18BP		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, Neutrokin- α	3. NGF/TNF R ^d	TNF-RI, AGP-3R, DR4, DR5, OX40, OPG, TACI, CD40, FAS, ODR
VI. Chemokines	1. α chemokines: IL-8, GRO α , β , γ , IF-10, PF-4, SDF-1	4. Chemokine R	1. CXCR
	2. β chemokines: MIP1 α , MIP1 β , MCP-1,2,3,4, RANTES, eotaxin		2. CCR
	3. γ chemokines: lymphotactin		3. CR
			4. DARC ^e
VII. Growth factors	1.1 SCF, M-CSF, PDGF-AA, AB, BB, KDR, FLT-1, FLT-3L,	VII. RKF	1. TK sub-family
			1.1 IgTK III R, VEGF-RI, VEGF-RII

¹ IL-17R - belongs to CKR family but is unassigned to 4 indicated subfamilies.

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- α 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.

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.

VEGF, SSV- PDGF, HGF, SF	
1.2 FGF α , FGF β	1.2 IgTK IV R
1.3 EGF, TGF- α , VV-F19 (EGF- like)	1.3 Cysteine-rich TK-I
1.4 IGF-I, IGF-II, Insulin	1.4 Cysteine rich TK-II, IGF-RI
1.5 NGF, BDNF, NT-3, NT-4 ^f	1.5 Cysteine knot TK V
2. TGF- β 1, β 2, β 3	2. Serine- threonine kinase subfamily (STKS) ^g

Particular proteins of interest as targets for peptide generation in the present invention include the following:

α v β 3
 α V β 1
 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

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.

matrix metalloproteinases (MMPs), both secreted and
 membrane-bound (e.g., MMP-9)
 Cathepsins
 angiopoietin-2
 5 TIE-2 receptor
 heparanase
 urokinase plasminogen activator (UPA), UPA receptor
 parathyroid hormone (PTH), parathyroid hormone-related
 protein (PTHrP), PTH-RI, PTH-RII
 10 Her2
 Her3
 Insulin

15 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
 25 prepared by methods disclosed in the art.

Particularly preferred peptides appear in the tables 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-
 30 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 4 – EPO-mimetic peptide sequences

SEQUENCE	SEQ ID NO:
YXCXXGPXTWXCXP	1
GGTYSCHFGPLTWVCKPQGG	2
GGDYHCRMGPLTWVCKPLGG	3
GGVYACRMGPITWVCSPLGG	4
VGNYMCHFGPITWVCRPGGG	5
GGLYLCRFGPVTWDCGYKGG	6
GGTYSCHFGPLTWVCKPQGGSSK	7
GGTYSCHGPLTWVCKPQGG	8
VGNYMAHMGPITWVCRPGG	9
GGPHHVYACRMGPLTWIC	10
GGTYSCHFGPLTWVCKPQ	11
GGLYACHMGPMTWVCQPLRG	12
TIAQYICYMGPETWECRPSKA	13
YSCHFGPLTWVCK	14
YCHFGPLTWVC	15
GGLYLCRFGPVTWDCGYKGG	16
GGTYSCHFGPLTWVCKPQGG	17
GGDYHCRMGPLTWVCKPLGG	18
VGNYMCHFGPITWVCRPGGG	19
GGVYACRMGPITWVCSPLGG	20
VGNYMAHMGPITWVCRPGG	21
GGTYSCHFGPLTWVCKPQ	22
GGLYACHMGPMTWVCQPLRG	23
TIAQYICYMGPETWECRPSKA	24
YSCHFGPLTWVCK	25
YCHFGPLTWVC	26
SCHFGPLTWVCK	27

Table 5 – TPO-mimetic peptide sequences

SEQUENCE	SEQ ID NO:
IEGPTLRQWLAARA	28
IEGPTLRQWLAACA	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
AGREGPTLREWLNMVRVWQ	86
ALQEGPTLRQWLGWGQWG	87
YCDEGPTLKQWLVCGLQ	88
WCKEGPTLREWLRWGFLC	89
CSSGGPTLREWLQCRRMQ	90
CSWGGPTLKQWLQCVRAK	91
CQLGGPTLREWLACRLGA	92
CWEGGPTLKEWLQCLVER	93
CRGGGPTLHQWLSCFRWQ	94
CRDGGPTLRQWLACLQOK	95
ELRSGPTLKEWLVRRLAQ	96
GCRSGPTLREWLACREVQ	97
TCEQGPTLRQWLLCRQGR	98
QGYCDEGPTLKQWLVCGLQHS	99

Table 6 – Ang-2 binding peptide sequences

SEQUENCE	SEQ ID NO.
WDPWT	100
WDPWTC	101
Cz ² WDPWT (wherein z ² is an acidic or neutral polar amino acid residue)	102
Cz ² WDPWTC (wherein z ² is an acidic or neutral polar amino acid residue)	103
PIRQEECDWDPWTCEHMWEV	104
TNIQEECEWDPWTCDHMPGK	105
WYEQDACEWDPWTCEHMAEV	106
NRLQEVCEWDPWTCEHMENV	107
AATQEECEWDPWTCEHMPRS	108
LRHQEGCEWDPWTCEHMFWD	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
HGQNMECEWDPWTCEHMFY	122
PRLQEECVWDPWTCEHMPLR	123
RTTQEKCEWDPWTCEHMESQ	124
QTSQEDCVWDPWTCDHMOVSS	125
QVIGRPCEWDPWTCEHLEGL	126
WAQQEECAWDPWTCDHMOVGL	127
LPGQEDCEWDPWTCEHMOVRS	128
PMNQVECDWDPWTCEHMVPRS	129
FGWSHGCEWDPWTCEHMGST	130
KSTQDDCDWDPWTCEHMOVGP	131
GPRISTCQWDPWTCEHMDQL	132
STIGDMCEWDPWTCAHMQVD	133
VLGGQGCEWDPWTCRLLQGW	134
VLGGQGCQWDPWTCSHLEDG	135
TTIGSMCEWDPWTCAHMQGG	136
TKGKSVCQWDPWTCSHMQSG	137
TTIGSMCQWDPWTCAHMQGG	138
WNNEVVCEWDPWTCNHWDTP	139
VVQVGMCCQWDPWTCKHMLRQ	140
AVGSQTCEWDPWTCAHLVEV	141
QGMKMFCEWDPWTCAHIVYR	142
TTIGSMCQWDPWTCEHMQGG	143
TSQRVGCEWDPWTCQHLYT	144
QWSWPPCEWDPWTCQTVWPS	145
GTSPSFCQWDPWTCSHMOVQG	146
QEECEWDPWTCEHM	147
QNYKPLDELDAITLYEHFIFHYT	148
LNFTPLDELEQTLYEQWTLQQS	149
TKFNPLDELEQTLYEQWTLQHQ	150
VKFKPLDALEQTLYEHWMFQQA	151
VKYKPLDELDEILYEQQTFQER	152
TNFMPPMDDLEQRLYEQFILQQG	153
SKFKPLDELEQTLYEQWTLQHA	154
QKFQPLDELEQTLYEQFMLQQA	155
QNFKPMDELEDITLYKQFLFQHS	156
YKFTPLDDLEQTLYEQWTLQHV	157
QEYEPLDELDETLYNQWMFHQR	158
SNFMPLDELEQTLYEQFMLQHQ	159
QKYQPLDELDKITLYDQFMLQQG	160
QKFQPLDELEETLYKQWTLQQR	161
VKYKPLDELDEWLYHQFTLHHQ	162

QKFMPLDELDEILYEQFMFQQS	163
QTFQPLDDLEEYLYEQWIRRYH	164
EDYMPLDALDAQLYEQFILLHG	165
HTFQPLDELEETLYYQWLYDQL	166
YKFNPMDLEEQTLYEFLFQHA	167
TNYKPLDELDAATLYEHWILQHS	168
QKFKPLDELEQTLYEQWTLQQR	169
TKFQPLDELDQTLYEQWTLQQR	170
TNFQPLDELDQTLYEQWTLQQR	171
KFNPLDELEETLYEQFTFQQ	172
AGGMRPYDGM LGWPNYDVQA	173
QWDDPCMHILGPVTWRRCI	174
APGQRPYDGM LGWPTYQRIV	175
SGQLRPC EEIFGCGTQNLAL	176
FGDKRPLECMFGGPQLCPR	177
GQDLRPCEDMFGCGTKDWYG	178
KRPC EEIFGGCTYQ	179
GFEYCDGMEDPFTFGCDKQT	180
KLEYCDGMEDPFTQGC DNQS	181
LQEWCEGVDPFTFGCEKQR	182
AQDYCEGMEDPFTFGCEMQK	183
LLDYCEGVQDPFTFGCENLD	184
HQEYCEGMEDPFTFGCEYQG	185
MLDYCEGMDDPFTFGCDKQM	186
LQDYCEGVDPFTFGCENQR	187
LQDYCEGVDPFTFGCEKQR	188
FDYCEGVDPFTFGCDNH	189

Table 7--NGF-Binding Peptide Sequences

SEQUENCE	SEQ ID NO.
TGYTEYTEEWPMGFGYQWSF	190
TDWLSDFPFYEQYFGLMPPG	191
FMRFNPWKLVEPPQGWYYG	192
VVKAPHFEFLAPPHFHEFPF	193
FSYIWIDETPSNIDRYMLWL	194
VNFPKVPEDVEPWPSLKLY	195
TWHPKTYEEFALPFFVPEAP	196
WHFGTPYIQQQPGVYWLQAP	197
VWNYGPFFMNFDPSTYFLHE	198
WRIHSKPLDYSHVWFFPADF	199
FWDGNQPPDILVDWPWNPPV	200

FYSLEWLKDHSEFFQTVTEW	201
QFMELLKFFNSPGDSSHFL	202
TNVDWISNNWEHMKSFTEW	203
PNEKPYQMOSWFPPDWVPY	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
SFDCDNPWGHVLOSCFGF	217
SFDCDNPWGHKLQSCFGF	218

Table 8 – Myostatin binding peptide sequences

SEQUENCE	SEQ ID NO:
KDKCKMWHWMCKPP	647
KDLCAMWHWMCKPP	219
KDLCKMWKWMCKPP	220
KDLCKMWHWMCKPK	221
WYPCYEFHFWCYDL	222
WYPCYEGHFWCYDL	223
IFGCKWWDVQCYQF	224
IFGCKWWDVDCYQF	225
ADWCVSPNWFCMVM	226
HKFCPWWALFCWDF	227
KDLCKMWHWMCKPP	228
IDKCAIWGWMCPL	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
WFDCYGPFGKCWSP	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
LKTCNLWPWMCPL	261
VVGCKWYEAWCYNK	262
PIHCTQWAWMCPPT	263
DSNCPWYFLSCVIF	264
HIWCNLAMMKCVEM	265
NLQCIYFLGKCIYF	266
AWRCMWFSDVCTPG	267
WFRCLDADWCTSV	268
EKICQMWSWMCAPP	269
WFYCHLNKSECTEP	270
FWRCAIGIDKCKRV	271
NLGCKWYEVWCFTY	272
IDLCNMWDGMCYPP	273
EMPCNIWGWMCPPV	274
WFRCVLTGIVDWSECFGL	275
GFSCTFGLDEFYVDCSPF	276
LPWCHDQVNADWGFCMLW	277
YPTCSEKFWIYGQTCVLW	278
LGPCPIHHGPWPQYCVYW	279
PFPCEHQISWLGHCLSF	280
HWGCEDLMWSWHPLCRRP	281
LPLCDADMPTIGFCVAY	282
SHWCETTFWMNYAKCVHA	283

LPKCTHVFPDQGGFCLWY	284
FSSCWSPVSRQDMFCVFY	285
SHKCEYSGWLQPLCYRP	286
PWWCQDNYVQHMLHCDSP	287
WFRCLMNSFDAFQCVSY	288
PDACRDQPWYMFMGCM LG	289
FLACFVEFELCFDS	290
SAYCIITESDPYVLCVPL	291
PSICESYSTMWLPMCQHIN	292
WLDCHDDSWAWTKMCRSH	293
YLNCVMMNTSPFVECVFN	294
YPWCDGFM IQQGITCMFY	295
FDYCTWLNGFKDWKCWSR	296
LPLCNLKEISHVQACVLF	297
SPECAFARWLGIEQCQRD	298
YPQCFNLHLLWTECDWF	299
RWRCEIYDSEFLPKCWFF	300
LVGCDNVWHRCKLF	301
AGWCHVWGEMFGMGCSAL	302
HHECEWMARWMSLDCVGL	303
FPMCGLIAGMKDFDFCVWY	304
RDDCTFWPEWLWKLCEP	305
YNFCSYLFGVSKEACQLP	306
AHWCEQGPWRYGNICMAY	307
NLVC GKISAWGDEACARA	308
HNVCTIMGPSMKWFCWND	309
NDLCAMWGW RNTIWCQNS	310
PPFCQNDNDMLQSLCKLL	311
WYDCNVPNELLSGLCRLF	312
YGDCDQNHWMWPFTCLSL	313
GWMCHFDLHDWGATCQPD	314
YFHCMFGGHEFEVHCESE	315
AYWCWHGQCVR	316
SEHWTFTDWDGNEWVVRPF	317
MEMLDSL FELKDMVPISKA	318
SPPEEALMEWLGWQYGKFT	319
SPENLLNDLYILMTKQEWYG	320
FHWEEGIPFHVVT PYSYDRM	321
KRLLEQFMNDLAE LVSGHS	322
DTRDALFQEFYEFVRSRLVI	323
RMSAAPRPLTYRDIMDQYWH	324
NDKAHFFEMFMFDVHNFVES	325
QTQAQKIDGLWELLQSI RNQ	326
MLSEFEEFLGNLVHRQEA	327

YTPKMGSEWTSFWHNRIHYL	328
LNDTLLRELKMVLNLSDMK	329
FDVERDLMRWLEGFMQSAAT	330
HHGWNLYLRKGSAPQWFEAWV	331
VESLHQLQMWLDQKLASGPH	332
RATLLKDFWQLVEGYGDN	333
EELLREFYRFVSAFDY	334
GLLDEFSHFIAEQFYQMPGG	335
YREMSMLEGLLDVLERLQHY	336
HNSSQMLLSELIMLVGSM MQ	337
WREHFLNSDYIRDKLIADG	338
QFPFYVFDDLPAQLEYWIA	339
EFFHWLHNHRSEVNHWLD MN	340
EALFQNFFRDVLTLSEREY	341
QYWEQQWMTYFRENGLHVQY	342
NQRMMLLEDLWRIMTPMFGRS	343
FLDELKAELSRHYALDDLDE	344
GKLIEGLLNELMQLETMPD	345
ILLDEYKKDWKSWF	346
QGHCTRWPWMCPPYGSGSATGSGSGST ASSGSGSATGQGHCTRWPWMCPPY	347
WYPCYEGHFWCYDLGSGSTASSGSGSA TGWYPCYEGHFWCYDL	348
HTPCPWFAPLCVEWGSGSATGSGSGSTA SSGSGSATGHTPCPWFAPLCVEW	349
PDWCIDPDWWCKFWGSGSATGSGSGST ASSGSGSATGPDWCIDPDWWCKFW	350
ANWCVSPNWFCMVMGSGSATGSGSGST ASSGSGSATGANWCVSPNWFCMVM	351
PDWCIDPDWWCKFWGSGSATGSGSGST ASSGSGSATGPDWCIDPDWWCKFW	352
HWACGYWPWSCKWVGSGSATGSGSGST ASSGSGSATGHWACGYWPWSCKWV	353
KKHCQIWTWMCAPKSGSATGSGSGST ASSGSGSATGQGHCTRWPWMCPPY	354
QGHCTRWPWMCPPYGSGSATGSGSGST ASSGSGSATGKKHCQIWTWMCAPK	355
KKHCQIWTWMCAPKSGSATGSGSGST ASSGSGSATGQGHCTRWPWMCPPY	356
KKHCQIWTWMCAPKGGGGGGGGQGH CTRWPWMCPPY	357
QGHCTRWPWMCPPYGGGGGGGKKHCQ IWTWMCAPK	358
VALHGQCTRWPWMCPPOREG	359
YPEQGLCTRWPWMCPPQTLA	360

GLNQGHCTRWPWMCPPQDSN	361
MITQGGCTRWPWMCPPQPSG	362
AGAQEHCTRWPWMCAPNDWI	363
GVNQGGCTRWRWMCPPNGWE	364
LADHGGCIRWPWMCPPEGWE	365
ILEQAQCTRWPWMCPPQRGG	366
TQTHAQCTRWPWMCPPQWEG	367
VVTQGHCTLWPWMCPPQRWR	368
IYPHDQCTRWPWMCPPQPYP	369
SYWQGGCTRWPWMCPPQWRG	370
MWQQGHCTRWPWMCPPQGWG	371
EFTQWHCTRWPWMCPPQRSQ	372
LDDQWQCTRWPWMCPPQGFS	373
YQTQGLCTRWPWMCPPQSQR	374
ESNQGGCTRWPWMCPPQGGW	375
WTDRGPCTRWPWMCPPQANG	376
VGTQGGCTRWPWMCPPYETG	377
PYEQGKCTRWPWMCPPYEVE	378
SEYQGLCTRWPWMCPPQGWK	379
TFSQGHCTRWPWMCPPQGWG	380
PGAHDHCTRWPWMCPPQSR	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
VATQGGCTRWPWMCPPQGWG	399
VATQGGCTRWPWMCPPQRWG	400
QREWYPCYGGHLWCYDLHKA	401
ISAWYSCYAGHFWCWDLKQK	402
WTGWYQCYGGHLWCYDLRRK	403
KTFWYPCYDGHFWCYNLKSS	404

ESRWYPCYEGHLWCFDLTET	405
MEMLDSLFELLKDMVPISKA	406
RMEMLESLELLKEIVPMSKAG	407
RMEMLESLELLKEIVPMSKAR	408
RMEMLESLELLKDIVPMSKPS	409
GMEMLESLELLQEIVPMSKAP	410
RMEMLESLELLKDIVPISNPP	411
RIEMLESLELLQEIVPISKA	412
RMEMLQSLLELLKDIVPMSNAR	413
RMEMLESLELLKEIVPTSNGT	414
RMEMLESLELLKEIVPMSKAG	415
RMEMLGSLLELLKEIVPMSKAR	416
QMELLDLSLFELLKEIVPKSQPA	417
RMEMLDSLELLKEIVPMSNAR	418
RMEMLESLELLHEIVPMSQAG	419
QMEMLESLLQLLKEIVPMSKAS	420
RMEMLDSLELLKDMVPMITTGA	421
RIEMLESLELLKDMVPMANAS	422
RMEMLESLLQLLNEIVPMSRAR	423
RMEMLESLELLKELVPMSKGV	424
RIEMLESLELLKDIVPIQKAR	425
RMELLESLELLKDMVPMSDSS	426
RMEMLESLELLQEIVPRAKGA	427
RMEMLDSLLQLLNEIVPMSHAR	428
RMEMLESLELLKDIVPMSNAG	429
RMEMLQSLFELLKGMVPISKAG	430
RMEMLESLELLKEIVPNSTAA	431
RMEMLQSLLELLKEIVPISKAG	432
RIEMLDSLELLNELVPMSKAR	433
HHGWNLYLRKGSAPQWFEAWV	434
QVESLQQLLMWLDQKLASGPQG	435
RMELLESLELLKEMVPRSKAV	436
QAVSLQHLLMWLDQKLASGPQH	437
DEDSLQQLLMWLDQKLASGPQL	438
PVASLQQLLIWLDQKLAQGPHA	439
EVDELQQLLNWLDHKLASGPLQ	440
DVESLEQLLMWLDHQLASGPHG	441
QVDSLQQVLLWLEHKLALGPQV	442
GDESLQHLLMWLEQKLALGPHG	443
QIEMLESLLDLLRDMVPMSNAF	444
EVDSLQQLLMWLDQKLASGPQA	445
EDESLQQLLIYLDKMLSSGPQV	446
AMDQLHQLLIWLDHKLASGPQA	447
RIEMLESLELLDEIALIPKAW	448

EVVSLQHLLMWLEHKLASGPDG	449
GGESLQQLLMWLDQQLASGPQR	450
GVESLQQLLIFLDHMLVSGPHD	451
NVESLEHLMMWLERLLASGPYA	452
QVDSLQQLLIWLDHQLASGPKR	453
EVESLQQLLMWLEHKLAAQGPQG	454
EVDSLQQLLMWLDQKLASGPHA	455
EVDSLQQLLMWLDQQLASGPQK	456
GVEQLPQLLMWLEQKLASGPQR	457
GEDSLQQLLMWLDQQLAAGPQV	458
ADDSLQQLLMWLDRLKASGPHV	459
PVDSLQQLLIWLDQKLASGPQG	460
RATLLKDFWQQLVEGYGDN	461
DWRATLLKEFWQLVEGLGDNLV	462
QSRATLLKEFWQLVEGLGDKQA	463
DGRATLLTEFWQLVQGLGQKEA	464
LARATLLKEFWQLVEGLGEKVV	465
GSRDTLLKEFWQLVVGLGDMQT	466
DARATLLKEFWQLVDAYGDRMV	467
NDRAQLLRDFWQLVDGLGVKSW	468
GVRETLLYELWYLLKGLGANQG	469
QARATLLKEFCQLVGCQGDKLS	470
QERATLLKEFWQLVAGLGQNMR	471
SGRATLLKEFWQLVQGLGEYRW	472
TMRATLLKEFWLFDVGQREMQW	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
WNRDMRMLESLEFVLDGLRQQV	496
GYRDMSMLEGLLAVLDRLGPQL	497
TQRDMSMLEGLLEVLDRLGQQR	498
WYRDMSMLEGLLEVLDRLGQQR	499
HNSSQMLLSELIIMLVGSMMQ	500
TQNSRQMLLSDFMMLVGSMIQQ	501
MQTSRHILLSEFMMLVGSIHMG	502
HDNSRQMLLSDLLHLVGTMIQQ	503
MENSRQNLLRELIMLVGNMSHQ	504
QDTSRHMLLREFMMLVGEMIQQ	505
DQNSRQMLLSLDMILVGSMIQQ	506
EFFHWLHNHRSEVNHWLDMN	507
NVFFQWVQKHGRVVYQWLDINV	508
FDFLQWLQNHRSEVEHWLVMDV	509

Table 9--BAFF binding peptide sequences

SEQUENCE	SEQ ID NO:
PGTCFPPWECTHA	510
WGACWPFPWECFKE	511
VPFCDLLTKHCFEA	512
GSRCKYKWDVLTKQCFHH	513
LPGCKWDLLIKQWVCDPL	514
SADCYFDILTKSDVCTSS	515
SDDCMYDQLTRMFICSNL	516
DLNCKYDELTYKEWCQFN	517
FHDCKYDLLTRQMVCHGL	518
RNHCFWDHLLKQDICPSP	519
ANQCWWDSLTKKNVCEFF	520
YKGRQQMWDLTRSWVSL	521
QQDVGLWWDILTRAWMPNI	522
QQNAQRVWDLLIRTWVYPQ	523
GWNEAWWDELTKIWVLEQQ	524
RITCDTWDSLKKCVPPQS	525
GAIMQQFWDSLTKTWLRQS	526
WLHSGWWDPLTKHWLQQKV	527
SEWFFWFDPLTRAQQLKFR	528
GVWFWWFDPLTKQWTQQAG	529
MQQCKGYDILTKWCVTNG	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
QAAAAATWDLLTKQWLVP	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
GQIGWKWDLLTKQWIIQQTR	565
VWLDWKWDLLTKQWIHPQQ	566
QQEWEYKWDLLTKQWGWLR	567
HWDSWKWDLLTKQWVVQQA	568
TRPLQQKWDLLTKQWLRVG	569
SDQWQQKWDLLTKQWFWDV	570
QQQTFMKWDLLTKQWIRRH	571
QQGECRKWDLLTKQCFPGQ	572
GQQMGWRWDPLIKMCLGPS	573
QQLDGCKWDLLTKQKVCIP	574
HGYWQQKWDLLTKQWVSSE	575
HQQGQCGWDLLTRYLPCH	576

LHKACKWDL LTKQCWPMQQ	577
GPPGSVWDL LTKIWIQQTG	578
ITQQDWRFD TLRWLPLR	579
QQGGFAAWD VLT KMWITVP	580
GHGTPWWDA LTRI WILGV	581
VWPWQQKWDL LTKQFVFQD	582
WQQWSWKWDL LTRQYISSS	583
NQQTLWKWDL LTKQFITYM	584
PVYQQGWWD TLT KLYIWDG	585
WLDGGWRDPL IKRSVQQLG	586
GHQQQFKWDL LTKQWVQSN	587
QQRVGQFWD VLT KMFITGS	588
QQAQGWSYD ALIKTWIRWP	589
GWMHWKWDPL TKQQALPWM	590
GHPTYKWDL LTKQWILQQM	591
WNNWSLWDPL TKLWLQQQN	592
WQWGWKWDL LTKQWVQQQ	593
GQMGWRWDPL TKMWLGTS	594

Fc Domains

This invention requires the presence of at least one Fc domain modified to comprise a peptide sequence.

- 5 As noted above, both native Fc's and Fc variants are suitable Fc domains for use within the scope of this invention. 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 such Fc variants, one may
- 10 remove one or more sites of a native Fc that provide structural features or functional activity not required by the fusion molecules of this invention. One may remove these sites by, for example, substituting or deleting residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted residues may also be altered amino
- 15 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). In particular, one may truncate the N-terminal 20-amino acid segment of SEQ ID NO: 599 or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 599. 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 SEQ ID NO: 599 (Figure 2A) is one such Fc variant.
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 of the first 20 amino acid residues at the N-terminus, particularly those at positions 1, 2, 3, 4 and 5.
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.
- 5 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
10 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 SEQ ID NO: 599
15 (Figure 2A) 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 phenylalanine residues.

Additional vehicles

20 The invention further embraces molecules covalently modified to include one or more water soluble polymer attachments, such as 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
25 include monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of these polymers. Particularly preferred are
30 peptibodies covalently modified with polyethylene glycol (PEG) subunits. Water-soluble polymers may be bonded at specific positions, for example

at the amino terminus of the peptibodies, or randomly attached to one or more side chains of the polypeptide. The use of PEG for improving the therapeutic capacity for specific binding agents, e.g. peptibodies, and for humanized antibodies in particular, is described in US Patent No. 6, 133, 426 to Gonzales et al., issued October 17, 2000.

Various means for attaching chemical moieties useful as vehicles are currently available, see, e.g., Patent Cooperation Treaty ("PCT") International Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

A preferred polymer vehicle 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).

A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis (see, for example, Figures 5 and 6 and the accompanying text herein). The 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 peptide with PEG usually takes place in aqueous phase and can be

easily monitored by reverse phase analytical HPLC. The PEGylated peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

5 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 α 1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1
10 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention as a vehicle by itself or in combination with another vehicle (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
15 315 456, which is hereby incorporated by reference. Dextran of about 1 kD to about 20 kD is preferred when dextran is used as a vehicle in accordance with the present invention.

An additional vehicle may also be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic
20 compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta et al. Peptides could 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
25 "vehicle" in this invention. Such vehicles should be selected 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).

Linkers

30 Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker is

preferably made up of amino acids linked together by peptide bonds.

Thus, in preferred embodiments, the linker is made up of from 1 to 20 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. In a more preferred embodiment, the 1 to 20 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 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);

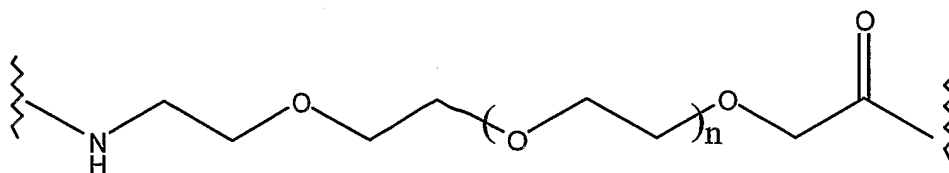
(Gly)₃Cys(Gly)₄ (SEQ ID NO: 597); and

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.

Non-peptide linkers are also possible. For example, alkyl linkers such as -NH-(CH₂)_s-C(O)-, where in 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., C₁-C₆) lower acyl, halogen (e.g., Cl, Br), CN, NH₂, phenyl, etc. An exemplary non-peptide linker is a PEG linker,

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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.

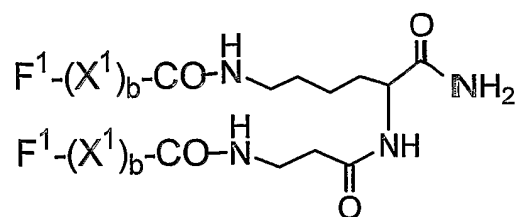
Derivatives

5 The invention also provides "derivatives" that include molecules 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
 10 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:

- 15 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. For citations to references on preparation of cyclized derivatives, see Table 2.
- 20 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
 25 shown below.

VII



3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH₂-carbamate [-CH₂-OC(O)NR-], phosphonate, -CH₂-sulfonamide [-CH₂-S(O)₂NR-], urea [-NHC(O)NH-], -CH₂-secondary amine, and alkylated peptide [-C(O)NR⁶- wherein R⁶ 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 -NRR¹ (other than -NH₂), -NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR¹, succinimide, or benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R¹ 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 C₁-C₄ alkyl, C₁-C₄ 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-CH₂-CH₂-NH₂)₂ to compounds of this invention. Likewise, one may use methods described in the art to add -NH₂ to compounds of this invention. Exemplary C-terminal derivative groups include, for example, -C(O)R² wherein R² is lower alkoxy or -NR³R⁴ wherein R³ and R⁴ are independently hydrogen or C₁-C₈ alkyl (preferably C₁-C₄ 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 sidechains 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 picolinimide; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

5 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
10 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
15 commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl sidechain 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-
20 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
25 are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Cysteiny 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.

30 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'-
5 dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimide 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
10 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.
15 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
20 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
25 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
30 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 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 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:

- 5 • radioisotopes, such as ⁹⁰Yttrium, ¹³¹Iodine, ²²⁵Actinium, and ²¹³Bismuth;
- ricin A toxin, microbially derived toxins such as Pseudomonas endotoxin (e.g., PE38, PE40), and the like;
- partner molecules in capture systems (see below);
- 10 • 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.

A process for preparing conjugation derivatives is also contemplated. 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 vehicle (Fc domain preferred), (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 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 variants. Insertional and substitutional variants may contain natural amino acids, unconventional amino acids (as set forth below), or both.

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 peptibody amino acid sequence. Insertions may be located at either or both termini of the protein, or may

be positioned within internal regions of the peptibody 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
5 peptibodies wherein one or more amino acid residues are added to the peptide or peptibody amino acid sequence, or fragment thereof.

Variants of the invention also include mature peptides and peptibodies wherein leader or signal sequences are removed, and the resulting proteins having additional amino terminal residues, which
10 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). Variants having additional Met, Met-Lys, Lys residues (or
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 systems include but are not limited to the glutathione-S-transferase (GST) system (Pharmacia), the maltose binding protein system (NEB, Beverly, 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
25 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
30 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
5 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, Beverly, MA).

10 The invention also provides fusion polypeptides which comprises all or part of a peptibody or peptide of the present invention, 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.
15 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 another aspect, the invention provides deletion variants wherein
20 one or more amino acid residues in a peptide or peptibody are removed. Deletions can be effected at one or both termini of the peptibody, or from removal of one or more residues within the peptibody amino acid sequence. Deletion variants necessarily include all fragments of a peptide or peptibody.

25 In still another aspect, the invention provides substitution variants of peptides and peptibodies of the invention. Substitution variants include those peptides and peptibodies 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.
30 Substitutional variants generate peptides or peptibodies that are "similar" to the original peptide or peptibody, in that the two molecules have 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
5 peptibody. In one aspect, the substitutions are conservative in nature, however, the invention embraces substitutions that are also non-conservative and also includes unconventional amino acids.

Identity and similarity of related peptides and peptibodies can be readily calculated by known methods. Such methods include, but are not
10 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
15 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
20 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
25 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
30 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, a standard comparison matrix (see Dayhoff et al., Atlas of Protein Sequence and Structure, 5(3)(1978) for the PAM 250 comparison matrix; Henikoff et al., Proc. Natl. Acad. Sci USA, 89:10915-

10919 (1992) for the BLOSUM 62 comparison matrix) is also used by the algorithm.

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

- 5 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

- 10 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:

- 15 Algorithm: Needleman et al., supra (1970);
- Comparison matrix: matches = +10, mismatch = 0
- Gap Penalty: 50
- 20 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.

- 25 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).

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Immunology--A Synthesis (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference for any purpose.

The amino acids may have either L or D stereochemistry (except for Gly, which is neither L nor D) and the polypeptides and compositions of the present invention may 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 conventional amino acids, unnatural amino acids such as α -, α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include, without limitation: aminoadipic acid, beta-alanine, beta-aminopropionic acid, aminobutyric acid, piperidinic acid, aminocaproic acid, aminoheptanoic acid, aminoisobutyric acid, aminopimelic acid, diaminobutyric acid,

desmosine, diaminopimelic acid, diaminopropionic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, allo-hydroxylysine, hydroxyproline, isodesmosine, allo-isoleucine, N-methylglycine, sarcosine, N-methylisoleucine, N-methylvaline, norvaline, norleucine, orithine, 4-
 5 hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and amino acids (e.g., 4-hydroxyproline).

Similarly, unless specified otherwise, the left-hand end of single-
 10 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
 15 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".

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

- 20 1. Neutral Hydrophobic: 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),
 25 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
5 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 hydrophobic index of amino acids may be considered. Each amino acid
10 has been assigned a hydrophobic 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 (-
15 3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydrophobic 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
20 may be substituted for other amino acids having a similar hydrophobic index or score and still retain a similar biological activity. In making changes based upon the hydrophobic index, in certain embodiments, the substitution of amino acids whose hydrophobic indices are within ± 2 is included. In certain embodiments, those which are within ± 1 are included,
25 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
30 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 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 $\pm$ 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 10 below.

Table 10
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 the polypeptide 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, even areas that may be important for biological activity or for structure may be subject 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 Moulton 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 which 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.

5 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. Thus, all modifications, substitution, derivitizations, etc. discussed herein apply equally to all
10 aspects of the present invention, including but not limited to peptides, peptide dimers and multimers, linkers, and vehicles.

Affinity Maturation

One embodiment of the present invention includes "affinity
15 matured" peptides and peptibodies. This procedure contemplates increasing the affinity or the bio-activity of the peptides and peptibodies of the present invention 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
20 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
25 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 contemplated. Peptide mimetic analogs can be prepared based on a selected inhibitory
30 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

5 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.

10 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.

15 In particular, it is anticipated that 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

20 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

25 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

30 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.

Methods of Making

The compounds of this invention largely may 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 may be performed using methods well known in the art.

Any of a large number of available and well-known host cells may 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 hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines,

useful microbial hosts 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 is cultured and purified. Host cells may
5 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 may also be made by synthetic methods. For
10 example, solid phase synthesis techniques may be used. Suitable techniques are well known in the art, and include those described in 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
15 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. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides.

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

Uses of the Compounds

In general. The compounds of this invention have pharmacologic
25 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. The utility of specific compounds is shown in Table 2. The activity of these compounds can be measured by assays known in the art. For the TPO-mimetic and EPO-mimetic compounds, in vivo assays are further
30 described in the Examples section herein.

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. 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 diagnostic 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". In vivo assays also appear in the Examples hereinafter.

The conditions to be treated are generally those that involve an existing megakaryocyte/platelet deficiency or an expected
5 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
10 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
15 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
20 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
25 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
30 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.

5 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.

10 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
15 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."

20 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
25 glandular structures. Another broad category of 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
30 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;
5 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,
10 basosquamous, Brown-Pearce, ductal, Ehrlich tumor, Krebs 2, merkel cell, mucinous, non-small cell lung, oat cell, papillary, scirrhus, bronchiolar, bronchogenic, squamous cell, and transitional cell); malignant carcinoid syndrome; immunoproliferative small lung cell carcinoma; cementoma; cervical cancer; chondroblastoma; chondroma; chondrosarcoma;
15 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;
20 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;
25 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;
30 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
 5 tumor; leiomyoma; leiomyosarcoma; myoblastoma; myoma; myosarcoma;
 rhabdomyoma; rhabdomyosarcoma; ependymoma; ganglioneuroma;
 glioma; medulloblastoma; meningioma; neurilemmoma; neuroblastoma;
 neuroepithelioma; neurofibroma; neuroma; paraganglioma;
 paraganglioma nonchromaffin; angiokeratoma; angiolymphoid
 10 hyperplasia with eosinophilia; angioma sclerosing; angiomatosis;
 glomangioma; hemangioendothelioma; hemangioma;
 hemangiopericytoma; hemangiosarcoma; lymphangioma;
 lymphangiomyoma; lymphangiosarcoma; pinealoma; carcinosarcoma;
 chondrosarcoma; cystosarcoma phyllodes; fibrosarcoma;
 15 hemangiosarcoma; leiomyosarcoma; leukosarcoma; liposarcoma;
 lymphangiosarcoma; myosarcoma; myxosarcoma; ovarian carcinoma;
 rhabdomyosarcoma; sarcoma; neoplasms; neurofibromatosis; and cervical
 dysplasia.

Therapeutic uses of NGF binding molecules

20 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
 25 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,
 30 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
5 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.

10 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.

15 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
20 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
25 (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
30 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.

5 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
10 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
15 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.

20 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 myostatin-binding molecules of the present invention are useful for detecting and quantitating myostatin in a number
25 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,
30 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.

Pharmaceutical Compositions

In General

The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions 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., Thimerosal, 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 may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may 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. The compositions may be prepared in liquid form, or may be in

dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

Oral dosage forms

Contemplated for use herein are oral solid dosage forms, which are
5 described generally in Chapter 89 of Remington's Pharmaceutical Sciences
(1990), 18th Ed., Mack Publishing Co. Easton PA 18042, which is herein
incorporated by reference. Solid dosage forms include tablets, capsules,
pills, troches or lozenges, cachets or pellets. Also, liposomal or proteinoid
encapsulation may be used to formulate the present compositions (as, for
10 example, proteinoid microspheres reported in U.S. Patent No. 4,925,673).
Liposomal encapsulation may be used and the liposomes may 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
Chapter 10 of Marshall, K., Modern Pharmaceutics (1979), edited by G. S.
15 Banker and C. T. Rhodes, herein incorporated by reference. In general, the
formulation will include the inventive compound, and inert ingredients
which allow for protection against the stomach environment, and release
of the biologically active material in the intestine.

Also specifically contemplated are oral dosage forms of the above
20 inventive compounds. If necessary, the compounds may be chemically
modified so that oral delivery is efficacious. Generally, the chemical
modification contemplated is the attachment of at least one moiety to the
compound molecule itself, where said moiety permits (a) inhibition of
proteolysis; and (b) uptake into the blood stream from the stomach or
25 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 vehicles in this invention may also be used for this purpose.
Examples of such moieties include: PEG, copolymers of ethylene glycol
and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol,
30 polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and
Davis, Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (1981),

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.

5 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
10 conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods".

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

 One may 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,
25 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.

 Disintegrants may be included in the formulation of the therapeutic
30 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 may all be used. Another form of the disintegrants are the insoluble cationic
5 exchange resins. Powdered gums may 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 may be used to hold the therapeutic agent together to form
10 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.

15 An antifrictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may 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,
20 vegetable oils and waxes. Soluble lubricants may 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
25 added. The glidants may 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 may include anionic detergents such as sodium lauryl sulfate,
30 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 laurmacrogol 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.

Additives may also be included in the formulation to enhance uptake of the compound. Additives potentially having this property are for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Controlled release formulation may be desirable. The compound of this invention could be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms e.g., gums. Slowly degrading matrices may also be incorporated into the formulation, e.g., alginates, polysaccharides. Another form of a controlled release of the compounds 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 may be used for the formulation. These include a variety of sugars which 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 methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl 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 may be carried out in a pan coater or in a fluidized bed or by compression coating.

Pulmonary delivery forms

5 Also contemplated herein is pulmonary delivery of the present protein (or derivatives thereof). 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.
10 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 (α 1-antitrypsin); Smith et al. (1989), J. Clin. Invest. 84: 1145-6 (α 1-proteinase); Oswein et al. (March 1990), "Aerosolization of Proteins", Proc. Symp. Resp. Drug Delivery II,
15 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).

Contemplated for use in the practice of this invention are a wide
20 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
25 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.

30 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 may 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
5 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
10 ingredients for use in formulations may include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog). Dextran, such as cyclodextran, may be used. Bile salts and other related enhancers may be used. Cellulose and cellulose derivatives may be used. Amino
15 acids may 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
20 water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by
25 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 may be any conventional material employed for this purpose,
30 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 may also be useful as a surfactant.

5 Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing the inventive compound and may 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.

10 Other delivery forms

Nasal delivery of the inventive compound is also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for
15 nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

Buccal delivery of the inventive compound is also contemplated. Buccal delivery formulations are known in the art for use with peptides.

Dosages

20 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
25 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.

Specific preferred embodiments

The inventors have determined preferred peptide sequences for molecules having many different kinds of activity. The inventors have
30 further determined preferred structures of these preferred peptides combined with preferred linkers and vehicles. Preferred structures for

these preferred peptides listed in Table 11 below. Linker sequences are shown in bold. Active peptide sequences are shown in bold and are underlined.

Table 11 – Preferred embodiments

5

Sequence/structure						SEQ ID NO:	Activ-ity
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	616	Fc-loop-Amp2
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVSVLTVL	HQDWLNGKEY		
1 01	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GIEGPTLRQW</u>		
1 51	<u>LAARAGG</u> TKN	QVSLTCLVKG	FYPSPDIAVEW	ESNGQPENNY	KTPPVLDSD		
2 01	GSFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGK*		
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	648	Fc-Loop-EMP1 (1 Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVSVLTVL	HQDWLNGKEY		
1 01	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDEL	<u>GGGTYSCHFGPL</u>		
1 51	<u>TWVCKPQGGG</u>	TKNQVSLTCLV	KGFYPDIAV	EWESNGQEN	NYKTPPVLD		
2 01	SDGSFFLYSK	LTVDKSRWQQ	GNVFSCSVMH	EALHNHYTQK	SLSLSPGK*		
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	649	Fc-loop-EMP1 (2Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVSVLTVL	HQDWLNGKEY		
1 01	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GTYSCHFGPL</u>		
1 51	<u>TWVCKPQGGT</u>	KNQVSLTCLV	KGFYPDIAV	EWESNGQEN	NYKTPPVLD		
2 01	SDGSFFLYSK	LTVDKSRWQQ	GNVFSCSVMH	EALHNHYTQK	SLSLSPGK*		
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	650	Fc-loop-EMP1 (3Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVSVLTVL	HQDWLNGKEY		
1 01	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GGTYSCHFGP</u>		
1 51	<u>LTWVCKPQGG</u>	GTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTPPV		
2 01	LDSDGSFFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK		
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	651	Fc-loop-EMP1 (4Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVSVLTVL	HQDWLNGKEY		
1 01	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GGGTYSCHFG</u>		
1 51	<u>PLTWVCKPQG</u>	GGGTKNQVSL	TCLVKGFYPS	DIAVEWESNG	QPENNYKTPP		
2 01	PVLDSDGSFF	LYSKLTVDKS	RWQQGNVFSC	SVMHEALHNN	YTQKSLSLSP		
2 51	GK*						
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	652	Fc-loop-EMP1 (Cys>A la variant w/4Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVSVLTVL	HQDWLNGKEY		
1 01	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GGGTYSAHFG</u>		
1 51	<u>PLTWVAKPQG</u>	GGGTKNQVSL	TCLVKGFYPS	DIAVEWESNG	QPENNYKTPP		

201	PVLDSGDSFF	LYSKLTVDKS	RWQQGNVFSC	SVMHEALHNNH	YTQKSLSLSP		
251	GK*						
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	653	Fc-loop-TMP20 (2Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVVSVLTVL	HQDWLNGKEY		
101	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GQGYCDEGPT</u>		
151	<u>LKQWLVLGL</u>	<u>QHSGG</u> TKNQV	SLTCLVKGFY	PSDIAVEWES	NGQPENNYKT		
201	TPPVLDSDGS	FFLYSKLTVD	KSRWQQGNVF	SCSVMHEALH	NHYTQKSLSL		
251	SPGK*						
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	654	Fc-loop-TMP20 (Cys>A la variant, w/2Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVVSVLTVL	HQDWLNGKEY		
101	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GQGYADEGPT</u>		
151	<u>LKQWLVALGL</u>	<u>QHSGG</u> TKNQV	SLTCLVKGFY	PSDIAVEWES	NGQPENNYKT		
201	TPPVLDSDGS	FFLYSKLTVD	KSRWQQGNVF	SCSVMHEALH	NHYTQKSLSL		
251	SPGK*						
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	655	Fc-loop-GLP1 (2Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVVSVLTVL	HQDWLNGKEY		
101	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GHAEGTFTSD</u>		
151	<u>VSSYLEGOAA</u>	<u>KEFIAWLKVG</u>	<u>RGGG</u> TKNQVS	LTCLVKGFYP	SDIAVEWESN		
201	GQPENNYKTT	PPVLDSDGSF	FLYSKLTVDK	SRWQQGNVFS	CSVMHEALHN		
251	HYTQKSLSL	PGK*					
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	656	Fc-loop-GLP1 (4Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVVSVLTVL	HQDWLNGKEY		
101	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GGGHAEGTFT</u>		
151	<u>SDVSSYLEGO</u>	<u>AAKEFIAWL</u> V	<u>KGRGGGGG</u> TK	NQVSLTCLVK	GFYPDIAVE		
201	WESNGQPENN	YKTPPVLD	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE		
251	ALHNHYTQKS	LSLSPGK*					
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	657	Fc-loop-ANG2 (2Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVVSVLTVL	HQDWLNGKEY		
101	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GQEECEWDPW</u>		
151	<u>TCEHMG</u> GTKN	QVSLTCLVKG	FYPDIAVEW	ESNGQPENNY	KTPPVLDSD		
201	GSFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGK*		
1	MDKTHTCPPC	PAPELLGGPS	VFLFPPKPKD	TLMISRTPEV	TCVVVDVSHE	612	Fc-loop-Myo7 (2Gly linkers)
51	DPEVKFNWYV	DGVEVHNAKT	KPREEQYNST	YRVVSVLTVL	HQDWLNGKEY		
101	KCKVSNKALP	APIEKTISKA	KGQPREPQVY	TLPPSRDELG	<u>GLADHGQCIR</u>		
151	<u>WPMCPPEGW</u>	<u>EGG</u> TKNQVSL	TCLVKGFYPS	DIAVEWESNG	QPENNYKTTT		
201	PVLDSGDSFF	LYSKLTVDKS	RWQQGNVFSC	SVMHEALHNNH	YTQKSLSLSP		
251	GK*						

1	MDKTHTCPPC PAPELGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE	658	Fc-loop-ANG1 (4Gly linkers)
51	DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY		
101	KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELG <u>GGGGDWTGDM</u>		
151	<u>QVKFDAMMFG PRKEGGGGT</u> KNQVSLTCLV KGFYPSDIAV EWESNGQPEN		
201	NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK		
251	SLSLSPGK		
1	MDKTHTCPPC PAPELGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE	659	Fc-loop-ANG1 (2x peptide w/4Gly linkers)
51	DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY		
101	KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELG <u>GGGGDWTGDM</u>		
151	<u>QVKFDAMMFG PRKEGGDWT</u> <u>GDMQVKFDAM MFGPRKEGGG</u> GGTKNQVSLT		
201	CLVKGFPYPSD IAVEWESNGQ PENNYKTTTP VLDSDGSFFL YSKLTVDKSR		
251	WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K		

Working examples

The compounds described above may be prepared as described below. These examples comprise preferred embodiments of the invention and are illustrative rather than limiting.

Example 1

Preparation of Fc-loop-ang2

In this example of the invention, the disulphide-constrained peptide TN8-Con4 was inserted into the human IgG1 Fc-loop domain, defined as the sequence D₁₃₇E₁₃₈L₁₃₉T₁₄₀K₁₄₁ (Fig 2A.).

TN8-Con4 QEECEWDPWTCEHM (SEQ ID NO: 147)

The peptide insertion is between Fc residues Leu₁₃₉ and Thr₁₄₀ and includes 2 Gly residues as linkers flanking either side of the inserted peptide (Fig. 10A). The Fc-loop TN8-Con4 construct is labeled with Amgen clone #6888. The carboxy-terminal TN8-Con4 fusion peptibody (Fig. 10B) includes a 5 Gly linker and is labeled with Amgen clone #5564.

Both clones #6888 and #5564 were transformed into E. coli by conventional methods known to those familiar in the art. Both clones were found to express at high levels and almost exclusively in the insoluble inclusion body fraction (Fig. 11). The isolated inclusion body fraction (1 g) was solubilized in 6 M guanidine-HCl, 50 mM Tris, 8 mM

DTT, pH 9 (10 ml) at room temperature with mixing, for 1 hour. The denatured and reduced peptibodies were refolded from the solubilized inclusion bodies by a 1:25 (v/v) dilution into a refold buffer consisting of 2 M urea, 50 mM Tris, 4 mM cysteine, 1 mM cystamine, pH 8.5. The solubilized peptibodies were added drop wise to the refold buffer at 4 °C with stirring. The refold reactions were allowed to stir for 48 hours, and then aliquots were evaluated by SDS-PAGE and reverse-phase HPLC. The Fc-loop TN8-Con4 (#6888) is considerably more homogeneous in the refold reaction than the carboxy-terminal Fc TN8-Con4 peptibody (#5564) as shown by RP-HPLC (Fig. 12).

Purification of the refolded Fc-loop TN8-Con4 and carboxy-terminal Fc TN8-Con4 was achieved using a 2-column process. First a recombinant Protein-A column was equilibrated in 2 M urea, 50 mM Tris, pH 8.5 and loaded with the filtered peptibody refold reaction. The column was then washed with 2 column volumes of equilibration buffer, followed by 2 column volumes of PBS. The peptibody fraction was eluted with 50mM NaOAc, pH3 and quickly neutralized by a 1:4 dilution into 10 mM NaOAc, 50 mM NaCl, pH 5. The diluted Protein-A eluate was again filtered and loaded to an SP Sepharose HP cation exchange column (Pharmacia) equilibrated in 10 mM NaOAc, 50 mM NaCl, pH 5. The peptibody fractions were then eluted with a linear 50-500 mM NaCl gradient, pooled and concentrated to about 2 mg/ml. The final pools of Fc-loop TN8-Con4 (#6888) and the carboxy-terminal Fc TN8-Con4 (#5564) were evaluated by RP-HPLC (Fig. 13) and SDS-PAGE (Fig. 14). Both RP-HPLC and SDS-PAGE demonstrate that improved product homogeneity is achieved with the Fc-loop TN8-Con4 (#6888) relative to the comparable carboxy-terminal fused peptibody (#5564).

Both the Fc-loop TN8-Con4 and carboxy-terminal fused TN8-Con4 peptibodies were further evaluated in an in vitro ELISA for competitive inhibition of the angiopoietin 2 receptor. In this format the peptibody competes with an angiopoietin 2 receptor-Fc fusion for binding to

immobilized angiopoietin 2. Binding of the angiopoietin 2 receptor-Fc fusion is monitored by fluorescence using an enzyme-linked immunodetection method and reported as an inhibition constant at 50% inhibition (IC₅₀). This experiment shows that the Fc-loop TN8-Con4 is
5 fully active relative to the carboxy-terminal Fc TN8-Con4 (Fig. 15).

Stability in vivo of the Fc-loop TN8-Con4 peptibody was compared to the carboxy-terminal TN8-Con4 peptibody in mice. In this study groups of 15 mice were dosed subcutaneously with either peptibody construct at 5 mg/kg. At 4 hours after injection, 5 mice were sacrificed
10 and serum collected. At 24 hours, another 5 mice were harvested and likewise at 48 hours. Each individual serum sample was evaluated by western blot for detectable human IgG-Fc peptibody. Since all the serum within each 5-mouse group was very similar, the groups were pooled to allow representative samples to be run together on a single gel/blot. The
15 result of that analysis (Fig. 16) clearly shows that both the Fc-loop TN8-Con4 peptibody and the carboxy-terminal TN8-Con4 peptibody persists in the pooled mouse sera throughout the 48-hour time course with no apparent loss. This result demonstrates that the Fc-loop designed peptibodies are not destabilized in vivo by the peptide insertion.

20

Example 2

Preparation of Fc-loop-myo7

In another embodiment of this invention, a novel, disulphide-constrained peptide TN8-19-7 (U.S. Pat App 2004-0181033-A1, which is incorporated by reference) of the sequence:

25 **TN8-19-07** **LADHGQCIRWPWMC_PPEGWE** (SEQ ID NO: 365)
was engineered between Leu139 and Thr140 as an internal fusion in the putative Fc-loop sequence DELTK of an IgG1 Fc sequence (Fig 2A). An additional two Gly residues were also added at each end of the TN8-19-07 peptide as flanking linkers. The final Fc-loop TN8-19-07 sequence is given
30 in Figure 3A and is labeled clone # 6951. Alternatively, a carboxy terminal fusion of TN8-19-07 with the same IgG1 Fc sequence was prepared to

serve as a control (Fig 3B) and labeled clone #6826. The carboxy-terminal fusion included five Gly residues between the Fc and TN8-19-07 to serve as a linker.

Both clones #6951 and #6826 were transformed into E. coli by conventional methods used by those familiar in the art, and were found to express at high levels and almost exclusively in the insoluble inclusion body fraction (Fig. 4A and 4B). The isolated inclusion body fraction (1 g) was solubilized in 6 M guanidine-HCl, 50 mM Tris, 8 mM DTT, pH 9 (10 ml) at room temperature with mixing for 1 hour. The denatured and reduced peptibodies were refolded from the solubilized inclusion body fraction by a 1:25 (v/v) dilution into 2 M urea, 50 mM Tris, 4 mM cysteine, 1 mM cystamine, pH 8.5. The solubilized peptibodies were added dropwise to the refold buffer at 4 °C with stirring. The refold reactions were allowed to stir for 48 hours, and then aliquots were evaluated by SDS-PAGE and reverse-phase HPLC. The Fc-loop TN8-19-07 (#6951) was found to be considerably more homogeneous by RP-HPLC (Fig. 5) in the refold reaction than the carboxy-terminal Fc-TN8-19-07 peptibody (#6826).

Purification was achieved by a 2-column process. First a recombinant Protein-A column was equilibrated in 2 M urea, 50 mM Tris, pH 8.5 and loaded with the filtered peptibody refold reaction. The column was then washed with 2 column volumes of equilibration buffer, followed by 2 column volumes of PBS. The peptibody fraction was eluted with 50 mM NaOAc, pH 3 and quickly neutralized by a 1:4 dilution into 10 mM NaOAc, 50 mM NaCl, pH 5. The diluted Protein-A eluate was again filtered and loaded to an SP Sepharose HP cation exchange column (Pharmacia) equilibrated in 10 mM NaOAc, 50 mM NaCl, pH 5. The peptibody fractions were then eluted with a linear 50-500 mM NaCl gradient, pooled and concentrated to about 2 mg/ml. The final pools of Fc-loop TN8-19-07 (#6951) and the carboxy-terminal Fc TN8-19-07 (#6826) were evaluated by RP-HPLC (Fig. 6) and SDS-PAGE (Fig. 7). Both RP-HPLC and SDS-PAGE demonstrate that improved homogeneity in the

final product is achieved with the Fc-loop TN8-19-07 (#6951) relative to the comparable carboxy-terminal fused peptibody (#6826).

An in vitro cell-based assay, which measures the inhibition of myostatin signaling activity, was used to determine the bioactivity of the Fc-loop TN8-19-07 (#6951) compared to the carboxy-terminal fusion (#6826). In this assay, both constructs were titrated against 4 nM myostatin and evaluated for their ability to inhibit the myostatin signaling activity as measured by a luciferase reporter system. The relative peptibody activities are reported as the effective concentration for 50% inhibition (EC₅₀). This experiment shows that the Fc-loop TN8-19-07 peptibody (#6951) retains full in vitro bioactivity (Fig. 8).

Stability in vivo of the Fc-loop TN8-19-07 peptibody was compared to the carboxy-terminal TN8-19-07 peptibody in mice. In this study, groups of 15 mice were dosed subcutaneously with either peptibody construct at 5 mg/kg. At 4 hours post injection 5 mice were sacrificed and serum collected. At 24 hours another 5 mice were harvested and likewise at 48 hours. Each individual serum was evaluated by western blot for detectable human IgG-Fc peptibody. Since all the serum within each 5-mouse group was very similar, the groups were pooled to allow representative samples to be run together on a single gel/blot. The result of that analysis (Fig. 9) clearly shows that the Fc-loop TN8-19-07 peptibody persists in the pooled mouse sera throughout the 48-hour time course with no apparent loss. In contrast, the concentration of the carboxy-terminal TN8-19-07 peptibody diminishes steadily through the course of the study until it is nearly undetectable at the 48-hour time point. This result suggests that the Fc-loop design approach may confer additional in vivo stability to the TN8-19-07 peptibody.

Example 3

Preparation of TN8-Con4

This molecule was prepared as described above in Example 1 and in U.S. Pat. App. No. 2003/0236192 (also PCT/US04/10989), which is hereby incorporated by reference.

Example 4

5

Preparation of Fc-ang2-tandem

This molecule was prepared as described in U.S. 2003/0236193, published Dec. 25, 2003 (also PCT/US04/10989, filed April 8, 2004), which is hereby incorporated by reference.

Example 5

10

Preparation of TN8-19-7

This molecule was prepared as described above in example 2 and in U.S. Serial No. 10/742,379, filed Dec. 19, 2003 (also PCT/US03/40781, filed Dec. 19, 2003), which is hereby incorporated by reference.

Example 6

15

Preparation of Fc-loop-EMP

This molecule was prepared as previously described in example 1.

Example 7

Preparation of Fc-loop-Amp2

20 In another embodiment of this invention a linear, non-constrained peptide, AMP 2 was inserted into the human IgG1 Fc -loop domain, defined as the sequence D₁₃₇E₁₃₈L₁₃₉T₁₄₀K₁₄₁ (Fig. 2A).

AMP-2: IEGPTLRQWLAARA (SEQ ID NO: 28)

The Fc insertion is between Leu₁₃₉ and Thr₁₄₀ and includes 2 Gly residues as linkers flanking either side of the inserted peptide (Fig. 3D).

25 The Fc-loop AMP 2 construct is labeled as Amgen clone #6875.

The Fc-loop AMP 2 clone (#6875) was transformed into E. coli by conventional methods known to those in the art and was found to express at high levels and almost exclusively in the insoluble inclusion body fraction (Fig. 17). The isolated inclusion body fraction (1g) was solubilized
30 in 6 M guanidine-HCl, 50 mM Tris, 8 mM DTT, pH 9 (10 ml) at room temperature with mixing, for 1 hour. The denatured and reduced

peptibody was refolded from the solubilized inclusion body fraction by a 1:25 (v/v) dilution into 2 M urea, 50 mM Tris, 4 mM cysteine, 1 mM cystamine, pH 8.5. The solubilized peptibody was added drop wise to the refold buffer at 4 °C with stirring. The refold reactions were allowed to stir for 48 hours, and then aliquots were evaluated by SDS-PAGE and reversed-phase HPLC.

Purification was achieved using a 2-column process. First a recombinant Protein-A column was equilibrated in 2 M urea, 50 mM Tris, pH 8.5 and loaded with the filtered peptibody refold reaction. The column was then washed with 2 column volumes of equilibration buffer, followed by 2 column volumes of PBS. The peptibody fraction was eluted with 50 mM NaOAc, pH 3 and quickly neutralized by a 1:4 dilution into 10 mM NaOAc, 50 mM NaCl, pH 5. The diluted Protein-A eluate was again filtered and loaded to an SP Sepharose HP cation exchange column (Pharmacia) equilibrated in 10 mM NaOAc, 50 mM NaCl, pH 5. The peptibody fractions were then eluted with a linear 50-500 mM NaCl gradient, pooled and concentrated to about 2 mg/ml. The final pools of Fc-loop AMP 2 (#6875) were evaluated by SDS-PAGE (Fig. 19) and RP-HPLC (Fig. 20).

The final preparation of Fc-loop AMP 2 was tested in an in vivo mouse bioassay against a carboxy-terminal peptibody fusion of two AMP 2 sequences linked in tandem (Fc tandem AMP2). In this comparison, the Fc-tandem-AMP2 has a total valence of four AMP 2 peptides compared to the Fc-loop AMP 2 with only two peptides. The mice received a single subcutaneous injection of 50 µg/kg of either peptibody while their platelet levels were monitored over 15 days (Fig. 21). While the Fc-tandem-AMP2 induced a significant initial platelet increase, the total response was complete by day 9. In contrast, the Fc-loop AMP 2 elicited a much smaller response that peaked at day 8 and persisted for 15 days. These results suggest that the efficacious half-life of the Fc-loop AMP 2 peptibody may be much greater than the conventional carboxy-terminal fused peptibody.

The difference in overall amplitude of the response may be a consequence of the greater valence of Fc-tandem-Amp2.

Example 8

Preparation of Amp2

5 This molecule was prepared as described above in example 7, and in U.S. Pat. No. 6,660,843.

Example 9

10 **In Vitro cell-based assay and the measurement of myostatin-signaling activity (Figure 8)**

 To quantitate myostatin activity and its blockade, a luciferase reporter system was developed, referred to as pMARE-Luc, which senses Myostatin/ Activin signaling strength. The pMARE-luc vector was constructed by subcloning a Smad-responsive CAGA tandem repeat
15 sequence into a basic reporter plasmid pLuc-MCS containing a minimal promoter element (TATA box). The pMARE-luc vector was stably transfected into a skeletal muscle-derived C2C12 cell line (murine).

 Characterization of myostatin responses of the stable clones led to the identification of C2C12-based clonal reporter cell lines that were
20 capable of detecting both myostatin and Activin signaling activities in 96-well format in a highly sensitive and reproducible manner.

Example 10

25 **In Vitro HTRF (homogeneous time-resolved fluorescence) Ang-2 binding assay (Figure 15).**

 Starting from a concentration of 100 nM, Fc-loop peptibody and proper controls were serially diluted in HTRF buffer 3-fold, 9-times across a 96-well plate. Dilutions were then mixed with the following reagents on
30 a 96-well black, round-bottomed assay plate: Streptavidin-Europium (1.6 nM), Biotinylated human angiopoietin-2 (8.0 nM), human Tie2-Fc-APC (10 nM). Assay plate was then incubated at room temperature with shaking

for 2 hours. Plate next read on a Rubystar microplate reader (BMG Labtechnologies Inc.). Results were converted to %inhibition, and IC50s were then calculated by analyzing the %inhibition values in the program GRAFIT 5.0 (IC50, 0-100% parameter).

5

Example 11

In Vivo AMP-2 efficacy assay (Figure 21)

Female BDF1 mice are injected subcutaneously with either carrier fluid (1 x PBS with 0.1% BSA), 50 mcg/kg of Fc-tandem-AMP2, or 50 mcg/kg of Fc-loop-AMP2. The injection volume is 0.2 mL. Blood is collected from each mouse via a puncture of the retro orbital sinus into a heparinized capillary tube, and then transferred to microtainers containing EDTA. Complete blood counts (CBC) including differential white blood cell counts are obtained using an ADVIA120 blood analyzer calibrated for mouse blood (Bayer Corp., Tarrytown, NY). Standard bleed days are 0, 3, 5, 7 and 10. Platelet counts are plotted as a function of time post-injection.

Example 12

UT-7 EPO Proliferation Assay for EMP Activity (Figure 18)

The UT-7Epo proliferation assay uses human megakaryoblastic leukemia cell line that responds to murine EPO (mEPO) and human EPO (huEPO) or other EPO like molecules for growth and survival.

Growth factors are serially diluted from 1000 ng/ml to 0.488 ng/ml in triplicate, in 100 µl of 10% FBS- Iscoves Modified Dulbelcco's medium (IMDM) across the 96 well plate. 15000 cells/well are added to the 96 well plate in 100 µl of 10% FBS IMDM. The total volume per well is 200 µl of media with 15000 cells per well. Cells and media alone are the zero control. Cells are incubated in a humidified chamber at 37 °C.

After incubation for 72 hours with the growth factor to be examined, viable cells are determined by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium, inner salt) incorporation (5+/-1 hr at 37 °C) and growth is measured by O.D.

(490 nm absorbance), limits not > 4.0 O.D. Reference: Yasusada Miura, Keita Kirito, and Norio Komatsu (1998), "Regulation of Both Erythroid and Megakaryocytic Differentiation of a Human Leukemia Cell Line, UT-7," *Acta Haematologica*, 99:180-184.

5

Example 13 Alternate Fc-Loop Insertion Sites

Having proven the feasibility of Fc-Loop insertion-style peptibodies with the L139/T140 insertion site using several different peptides, additional loops were surveyed in the Fc crystal structure. Using Fc-domain homology modeling, twelve different potential insertion sites were selected based on solvent accessible surface exposure, steric constraints within the loop, proximity to the Fc dimer interface and juxtaposition to sites of known effector function, such as the FcRn binding interface. The Fc-Loop sites that were identified as potential insertion sites are detailed and ranked. See Figure 2A and Table 12 below.

15

Table 12

Specific insertion sites for the human IgG1 Fc sequence

Domain	Loop	Insertion	Comments
CH2	P ₂₅ -P ₂₆	Not preferred	Tight turn
CH2	D ₄₆ -E ₅₃	H ₄₉ /E ₅₀ - 1 st E ₅₀ / D ₅₁ - 2 nd	No homology H/E site
CH2	V ₆₅ -A ₆₈	Not preferred	FcRn interactive
CH2	E ₇₄ -T ₈₀	Y ₇₇ /N ₇₈ - 1 st N ₇₈ /S ₇₉ - 2 nd	Low homology Y/N site
CH2	V ₈₉ -E ₉₉	Not preferred	FcRn interactive
CH2-CH3 linker	N ₁₀₆ -P ₁₂₇	K ₁₀₇ /A ₁₀₈ - 1 st N ₁₀₆ /K ₁₀₇ - 2 nd	Exposed turn
CH3	D ₁₃₇ -K ₁₄₁	L ₁₃₉ /T ₁₄₀ - 1 st E ₁₃₈ /L ₁₃₉ - 2 nd	Successfully tested L ₁₃₉ /T ₁₄₀
CH3	N ₁₆₅ -N ₁₇₇	E ₁₆₉ /N ₁₇₀ - 1 st N ₁₇₀ /N ₁₇₁ - 2 nd	Avoid tight turn N ₁₆₅ -P ₁₆₈ . No homology E/N site
CH3	T ₁₇₅ -S ₁₈₄	S ₁₈₁ /D ₁₈₂ - 1 st V ₁₇₈ /L ₁₇₉ - 2 nd	No homology V/L site. S/D site poss. better exposed
CH3	K ₁₉₅ -V ₂₀₃	G ₂₀₁ /N ₂₀₂ - 1 st N ₂₀₂ /V ₂₀₃ - 2 nd	α/β content. G/N site exposed. N/V site low

			homology
CH3	NA	Q ₁₆₇ /P ₁₆₈	IgA, IgM insertion site
CH3	NA	G ₁₈₃ /S ₁₈₄	IgA, IgM insertion site

Of these potential insertion sites, six were expressed using the TN8-19-7 peptide insert (Example 2) and evaluated for refolding efficiency and in vitro activity. An additional construct was added which contained an asymmetric linker system Gly4/Gly6 engineered into the original loop insertion site (L139/T140) previously described. In all, seven new Fc Loop Myostatin constructs were refolded, purified, and tested for activity.

The seven new Fc-Loop TN8-19-7 constructs that were tested included insertions in both CH2 and CH3 domains of human IgG1 Fc. Specifically, these insertions were: G201/N202 (CH3), E169/N170 (CH3), S181/D182 (CH3), H49/E50 (CH2), L139/T140 (G4-6) (CH3), Y77/N78 (CH2), and K107/A108 (CH2-CH3 linker domain). These constructs were transformed into E. coli by conventional methods known in the art, and were found to express almost exclusively in the insoluble inclusion body fraction. Interestingly, the H49/E50, L139/T140 (G4-6) and Y77/N78 constructs appeared to have the highest levels of expression. The E169/N170, S181/D182, K107/108 showed moderate expression, and the G201/202 construct showed some expression, but very little.

Those Fc-Loop TN8-19-7 constructs which expressed well in E. coli were purified by first solubilizing the isolated inclusion body fractions in 6 M Guanidine-HCl, 50 mM Tris, 8 mM DTT pH 9.0 (10 mL per 1g inclusion body) at room temperature with mixing for 1 hour. Then, a variety of refolding conditions were evaluated for each of the denatured and reduced Fc-Loop TN8-19-7 constructs to identify optimal refolding conditions. The three G201/N202, E169/N170, and S181/D182 constructs did not refold well under any of the conditions tested. Of the remaining four Fc-Loop TN8-19-7 constructs, L139/T140 (G4-6) refolded the best, while the remaining three H49/E50, Y77/N78 and K107/A108 refolded with sufficient yield to pursue further purification.

Using optimized refold conditions, the denatured and reduced Fc-Loop TN8-19-7 constructs were refolded from the solubilized inclusion body fractions by a 1:25 (v/v) dilution into 4 M Urea, 50 mM Tris-HCl, 0.16 M Arg-HCl, 20% glycerol, 3 M Cystine, 5 mM Cystamine pH 8.5. The solubilized peptibodies were added drop-wise to the refold buffer at 4°C with stirring. The refold reactions were allowed to stir for 72 hours, and subsequently purified chromatographically. Final purification was achieved by a 2-column chromatographic process, as described in Example 2.

The final pools of L139/T140 (G4-6), H49/E50, Y77/N78, and K107/108 were evaluated by RP-HPLC and SDS-PAGE, as illustrated in Figures 23 and 24. The yields from these four constructs are tabulated in Table 13.

Table 13
Expression and purification yields
of recoverable Fc-loop constructs

Insertion Site	Grams IB per Grams Paste	mg product per gram of IB
H49/E50 (CH2 domain)	0.182	2.08
L139/T140 (G4-6) (CH3 domain)	0.156	14.58
Y77/N78 (CH2 domain)	0.162	10.26
K107/A108	0.140	0.22

Among the four analogs purified the L139/T140 (G4-6) insertion site analog was produced with the best purity and in the highest yield.

The purified Fc-loop insertion analogs were further analyzed for functional myostatin receptor binding activity using an in vitro cell based inhibition assay, as described in Example 9. The results are shown in Table 14.

Table 14

***In vitro* cell based myostatin inhibition assay results**

Fc-Loop insertion analogs	IC ₅₀ (nM)
H49/E50	13.94
L139/T140 (G4-6)	0.8727
Y77/N78	17.06
Fc-Loop #6951 (139/140)	0.8335

The purified Fc-loop insertion analogs were further analyzed for FcRn binding using a Biacore assay system. Sample K107/ A108 was not tested due to insufficient sample remaining after analysis. The IC₅₀ values determined using the *in vitro* cell based Myostatin inhibition assay, were similar for the L139/ T140 (G4-6) insertion and the original Fc-Loop #6951, whereas the Fc-loop insertions at H49/ E50 and Y77/ N78 showed a reduced ability to inhibit myostatin (Figure 30). The Biacore FcRn binding experiments showed that H49/ E50 and Y77/ N78 bound the Fc receptor comparably to the control (Fc-Loop-1xTN8-19-7, #6951) with an EC₅₀ of about 680 nM, but L139/ T140 (G4-6) had a lower and more favorable EC₅₀ at around 220 nM.

In summary, of the six new insertion sites evaluated, three failed to refold efficiently. Among the three new insertion site analogs recovered, K107/ A108 folded poorly, H49/ E50 (CH2 domain) refolded marginally well, and the two remaining insertions at Y77/ N78 (CH2 domain) and the original insertion site of L139/ T140 (CH3 domain) with an extended, asymmetric linker folded with a higher efficiency. Interestingly, all of these novel insertion site analogs refolded with significantly lower yield than the original Fc-loop construct (#6951) with TN8-19-7 in position L139/ T140 using symmetric Gly2 linkers.

When tested for retention of FcRn binding capacity, all the Fc-loop molecules appeared similar in affinity with the possible exception of the extended, asymmetric linker construct, which seemed slightly better. This was consistent with the design paradigm to minimize steric interactions between the inserted peptide and the FcRn binding interface.

While all the purified Fc-loop constructs were active by the in vitro, cell-based functional assay (Table 14), the original insertion site (L139/T140) and the extended, asymmetric linker insertion at the same site appeared to be the most potent.

5 This work demonstrates that multiple loop domains within the human IgG1 Fc, as identified in Figure 23, will tolerate insertion of bioactive peptides while preserving the activity of both the peptide and Fc effector functions such as FcRn binding. Peptide insertion analogs utilizing these Fc-loop domains can vary significantly in refolding
10 efficiency and peptide activity. Each peptide/insertion combination can be individually optimized to maximize recovery and potency.

More preferable would be peptide insertions targeting the underlined sub-domains in Figure 23. Most preferable are the insertion site (L139/T140) and two additional loops in the CH2 domain (H49/E50
15 and Y77/N78).

Abbreviations

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

Ac	acetyl (used to refer to acetylated residues)
AcBpa	acetylated p-benzoyl-L-phenylalanine
ACN	acetonitrile
ADCC	antibody-dependent cellular cytotoxicity
25 Aib	aminoisobutyric acid
bA	beta-alanine
Bpa	p-benzoyl-L-phenylalanine
BrAc	bromoacetyl (BrCH ₂ C(O))
BSA	Bovine serum albumin
30 Bzl	Benzyl
Cap	Caproic acid

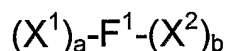
	CTL	Cytotoxic T lymphocytes
	CTLA4	Cytotoxic T lymphocyte antigen 4
	DARC	Duffy blood group antigen receptor
	DCC	Dicyclohexylcarbodiimide
5	Dde	1-(4,4-dimethyl-2,6-dioxo-cyclohexylidene)ethyl
	EDTA	ethylene diamine tetraacetic acid
	EMP	Erythropoietin-mimetic peptide
	ESI-MS	Electron spray ionization mass spectrometry
	EPO	Erythropoietin
10	Fmoc	fluorenylmethoxycarbonyl
	G-CSF	Granulocyte colony stimulating factor
	GH	Growth hormone
	HCT	hematocrit
	HGB	hemoglobin
15	hGH	Human growth hormone
	HOBt	1-Hydroxybenzotriazole
	HPLC	high performance liquid chromatography
	IL	interleukin
	IL-R	interleukin receptor
20	IL-1R	interleukin-1 receptor
	IL-1ra	interleukin-1 receptor antagonist
	Lau	Lauric acid
	LPS	lipopolysaccharide
	LYMPH	lymphocytes
25	MALDI-MS	Matrix-assisted laser desorption ionization mass spectrometry
	Me	methyl
	MeO	methoxy
	MES	(2-[N-Morpholino]ethanesulfonic acid)
30	MHC	major histocompatibility complex
	MMP	matrix metalloproteinase

	MMPI	matrix metalloproteinase inhibitor
	NaOAc	sodium acetate
	1-Nap	1-naphthylalanine
	NEUT	neutrophils
5	NGF	nerve growth factor
	Nle	norleucine
	NMP	N-methyl-2-pyrrolidinone
	PAGE	polyacrylamide gel electrophoresis
	PBS	Phosphate-buffered saline
10	Pbf	2,2,4,6,7-pendamethyldihydrobenzofuran-5-sulfonyl
	PCR	polymerase chain reaction
	Pec	pipecolic acid
	PEG	Poly(ethylene glycol)
	pGlu	pyroglutamic acid
15	Pic	picolinic acid
	PLT	platelets
	pY	phosphotyrosine
	PTFE	polytetrafluoroethylene
	RBC	red blood cells
20	RBS	ribosome binding site
	RP-HPLC	reversed phase HPLC
	RT	room temperature (25 °C)
	Sar	sarcosine
	SDS	sodium dodecyl sulfate
25	STK	serine-threonine kinases
	t-Boc	tert-Butoxycarbonyl
	tBu	tert-Butyl
	TGF	tissue growth factor
	THF	thymic humoral factor
30	TK	tyrosine kinase
	TMP	Thrombopoietin-mimetic peptide

	TNF	Tissue necrosis factor
	TPO	Thrombopoietin
	TRAIL	TNF-related apoptosis-inducing ligand
	Trt	trityl
5	UK	urokinase
	UKR	urokinase receptor
	VEGF	vascular endothelial cell growth factor
	VIP	vasoactive intestinal peptide
	WBC	white blood cells
10		

What is claimed is:

1. A composition of matter of the formula



and multimers thereof, wherein:

- 5 F^1 is an Fc domain modified so that it comprises at least one X^3 in a loop region;
 X^1 and X^2 are each independently selected from $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;
 X^3 is independently selected from $-(L^5)_c-P^5$, $-(L^5)_c-P^5-(L^6)_d-P^6$, $-(L^5)_c-P^5-(L^6)_d-P^6-(L^7)_e-P^7$, and $-(L^5)_c-P^5-(L^6)_d-P^6-(L^7)_e-P^7-(L^8)_f-P^8$;
 P^1 , P^2 , P^3 , and P^4 are each independently sequences of pharmacologically active polypeptides or pharmacologically active peptides;
 P^5 , P^6 , P^7 , and P^8 are each independently sequences of pharmacologically active peptides;
 L^1 , L^2 , L^3 , L^4 , L^5 , L^6 , L^7 , and L^8 are each independently linkers; and
 a , b , c , d , e , and f are each independently 0 or 1.
2. The composition of matter of Claim 1 wherein a and b are each 0.
3. The composition of matter of Claim 1 wherein the Fc domain
 20 comprises an IgG Fc domain.
4. The composition of matter of Claim 3 wherein the Fc domain comprises a sequence selected from SEQ ID NOS: 599 and 603 to 607.
5. The composition of matter of Claim 1 wherein the Fc domain comprises an IgG1 Fc domain.
- 25 6. The composition of matter of Claim 5 wherein the IgG1 Fc domain comprises SEQ ID NO: 599 and X^3 is inserted into or replaces all or part of a sequence selected from SEQ ID NOS: 621, 622, 624, 625, 627, 628, 630, 632, 634, and 636.
7. The composition of matter of Claim 6 wherein X^3 is inserted into or
 30 replaces all or part of a sequence selected from SEQ ID NOS: 623, 626, 629, 631, 633, 635, and 637.

8. The composition of matter of Claim 7 wherein X³ is inserted at Leu₁₃₉/Thr₁₄₀.
9. The composition of matter of Claim 5 wherein the IgG1 Fc domain comprises SEQ ID NO: 603 and X³ is inserted into or replaces all or part
5 of a sequence selected from SEQ ID NOS: 621, 622, 624, 625, 627, 628, 630, 632, 634, and 636.
10. The composition of matter of Claim 9 wherein X³ is inserted at H₅₃/E₅₄, Y₈₁/N₈₂, N₁₁₀/K₁₁₁, L₁₄₃/T₁₄₄, Q₁₇₁/P₁₇₂, E₁₇₃/N₁₇₄, S₁₈₆/D₁₈₇, G₁₈₈/S₁₈₉, or G₂₀₅/N₂₀₆.
- 10 11. The composition of matter of Claim 5 wherein the IgG1 Fc domain comprises SEQ ID NO: 604 and X³ is inserted into or replaces all or part of a sequence selected from SEQ ID NOS: 621, 622, 624, 625, 627, 628, 632, 634, 636, and 644.
12. The composition of matter of Claim 11 wherein X³ is inserted at
15 H₅₃/E₅₄, Y₈₁/N₈₂, N₁₁₀/K₁₁₁, L₁₄₃/T₁₄₄, Q₁₇₁/P₁₇₂, E₁₇₃/N₁₇₄, S₁₈₆/D₁₈₇, G₁₈₈/S₁₈₉, or G₂₀₅/N₂₀₆.
13. The composition of matter of Claim 1 wherein the Fc domain comprises an IgG3 Fc domain.
14. The composition of matter of Claim 13 wherein the IgG3 Fc domain
20 comprises SEQ ID NO: 605 and X³ is inserted into or replaces all or part of a sequence selected from SEQ ID NOS: 614, 621, 622, 624, 627, 639, 641, 644, 645, and 646.
15. The composition of matter of Claim 14 wherein X³ is inserted at
25 H₁₀₀/E₁₀₁, F₁₂₈/N₁₂₉, N₁₅₇/K₁₅₈, M₁₉₀/T₁₉₁, Q₂₁₈/P₂₁₉, E₂₂₀/N₂₂₁, S₂₃₂/D₂₃₃, G₂₃₄/S₂₃₅, or G₂₅₂/N₂₅₃.
16. The composition of matter of Claim 1 wherein the Fc domain comprises an IgG2 Fc domain.
17. The composition of matter of Claim 16 wherein the Fc domain
30 comprises SEQ ID NO: 606 and X³ is inserted into or replaces all or part of a sequence selected from SEQ ID NOS: 621, 622, 624, 632, 636, 639, 640, 642, 644, and 646.

18. The composition of matter of Claim 17 wherein X³ is inserted at
H₄₉/E₅₀, F₇₇/N₇₈, N₁₀₆/K₁₀₇, M₁₃₉/T₁₄₀, Q₁₆₇/P₁₆₈, E₁₆₉/N₁₇₀, S₁₈₁/D₁₈₂,
G₁₈₃/S₁₈₄, or G₂₀₁/N₂₀₂.
19. The composition of matter of Claim 1 wherein the Fc domain
5 comprises an IgG4 Fc domain.
20. The composition of matter of Claim 19 wherein the Fc domain
comprises SEQ ID NO: 607 and X³ is inserted into or replaces all or part
of a sequence selected from SEQ ID NOS: 620, 621, 624, 627, 632, 634,
638, 639, 643, and 644.
- 10 21. The composition of matter of Claim 20 wherein X³ is inserted at
Q₅₀/E₅₁, F₇₈/N₇₉, N₁₀₇/K₁₀₈, M₁₄₀/T₁₄₁, Q₁₆₈/P₁₆₉, E₁₇₀/N₁₇₁, S₁₈₂/D₁₈₃,
G₁₈₄/S₁₈₅, or G₂₀₂/N₂₀₃.
22. The composition of matter of Claim 1 wherein the Fc domain
comprises SEQ ID NO: 608 and X³ is inserted into or replaces all or part
15 of a sequence selected from SEQ ID NOS: 621, 622, 628, 624, 627, 632,
636, 639, 644, and 646.
23. The composition of matter of Claim 22 wherein X³ is inserted at
H₁₁₂/E₁₁₃, F₁₄₀/N₁₄₁, N₁₆₉/K₁₇₀, M₂₀₄/T₂₀₅, Q₂₃₂/P₂₃₃, E₂₃₄/N₂₃₅,
S₂₄₆/D₂₄₇, G₂₄₈/S₂₄₉, or G₂₆₈/N₂₆₉.
- 20 24. The composition of matter of Claim 1 wherein X³ comprises an
angiotensin-2 (ang-2) binding peptide sequence.
25. The composition of matter of Claim 24 wherein the ang-2 binding
peptide sequence is selected from SEQ ID NOS: 100 to 189.
26. The composition of matter of Claim 25 wherein the ang-2 binding
25 peptide sequence is SEQ ID NO: 147.
27. The composition of matter of Claim 26 wherein F¹ comprises an IgG1
Fc domain.
28. The composition of matter of Claim 27 having the sequence of SEQ ID
NO: 618.
- 30 29. The composition of matter of Claim 1 wherein X³ comprises a
myostatin binding peptide sequence.

30. The composition of matter of Claim 29 wherein the myostatin binding peptide sequence is selected from SEQ ID NOS: 218 to 509.
31. The composition of matter of Claim 30 wherein the myostatin binding peptide sequence is SEQ ID NO: 365.
- 5 32. The composition of matter of Claim 31 wherein F¹ comprises an IgG1 Fc domain.
33. The composition of matter of Claim 32 having the sequence SEQ ID NO: 612.
34. The composition of matter of Claim 1 wherein X³ comprises an
10 erythropoietin-mimetic (EPO-mimetic) peptide sequence.
35. The composition of matter of Claim 34 wherein the EPO-mimetic peptide sequence is selected from SEQ ID NOS: 1 to 27.
36. The composition of matter of Claim 35 wherein the EPO-mimetic peptide sequence is SEQ ID NO: 2.
- 15 37. The composition of matter of Claim 36 wherein F¹ comprises an IgG1 Fc domain
38. The composition of matter of Claim 37 having the sequence of SEQ ID NO: 615.
39. The composition of matter of Claim 1 wherein X³ comprises a
20 thrombopoietin-mimetic (TPO-mimetic) peptide sequence.
40. The composition of matter of Claim 39 wherein the TPO-mimetic peptide sequence is selected from SEQ ID NOS: 28 to 99.
41. The composition of matter of Claim 40 wherein the TPO-mimetic peptide sequence is SEQ ID NO: 28.
- 25 42. The composition of matter of Claim 41 wherein F¹ comprises an IgG1 Fc domain
43. The composition of matter of Claim 42 having the sequence SEQ ID NO: 616.
44. The composition of matter of Claim 1 wherein X³ comprises a nerve
30 growth factor (NGF) binding peptide sequence.

45. The composition of matter of Claim 44 wherein the NGF binding peptide sequence is selected from SEQ ID NOS: 190 to 218.
46. The composition of matter of Claim 1 wherein X³ comprises a B cell activating factor (BAFF) binding peptide sequence.
- 5 47. The composition of matter of Claim 46 wherein the BAFF binding peptide sequence is selected from SEQ ID NOS: 510 to 594.
48. A DNA encoding a composition of matter of Claim 1.
49. An expression vector comprising the DNA of Claim 46.
50. A host cell comprising the expression vector of Claim 47.
- 10 51. The cell of Claim 48, wherein the cell is an E. coli cell.
52. A process for preparing a pharmacologically active compound, which comprises:
- a. selecting at least one randomized peptide that modulates the activity of a protein of interest; and
- 15 b. preparing a pharmacologic agent comprising an amino acid sequence of the selected peptide as an internal sequence of an Fc domain..
53. The process of Claim 50, wherein the internal region of the Fc domain is a loop region.
- 20 54. The process of Claim 50, wherein the peptide is selected in a process comprising one or more techniques selected from yeast-based screening, rational design, protein structural analysis, or screening of a phage display library, an E. coli display library, a ribosomal library, or a chemical peptide library.
- 25 55. The process of Claim 50, wherein the preparation of the pharmacologic agent is carried out by:
- a. preparing a gene construct comprising a nucleic acid sequence encoding an Fc domain wherein a sequence the selected peptide is inserted into or replaces one or more amino acids within the Fc
- 30 domain; and
- b. expressing the gene construct.

56. The process of Claim 53, wherein the gene construct is expressed in an E. coli cell.
57. The process of Claim 50, wherein the protein of interest is a cell surface receptor.
- 5 58. The process of Claim 50, wherein the protein of interest has a linear epitope.
59. The process of Claim 50, wherein the protein of interest is a cytokine receptor.
60. The process of Claim 50 wherein the Fc domain is an IgG Fc domain.
- 10 61. A modified antibody, comprising an Fc domain modified so that it comprises at least one X³ in a loop region, wherein:
- X³ is independently selected from -(L⁵)_c-P⁵, -(L⁵)_c-P⁵-(L⁶)_d-P⁶, -(L⁵)_c-P⁵-(L⁶)_d-P⁶-(L⁷)_e-P⁷, and -(L⁵)_c-P⁵-(L⁶)_d-P⁶-(L⁷)_e-P⁷-(L⁸)_f-P⁸;
- P⁵, P⁶, P⁷, and P⁸ are each independently sequences of
- 15 pharmacologically active peptides;
- L⁵, L⁶, L⁷, and L⁸ are each independently linkers; and
- c, d, e, and f are each independently 0 or 1.
62. A process for preparing a modified antibody, which comprises:
- a) selecting at least one peptide that modulates the activity of a
- 20 protein of interest; and
- b) preparing an antibody comprising an amino acid sequence of the selected peptide in a loop region of an Fc domain of the antibody.

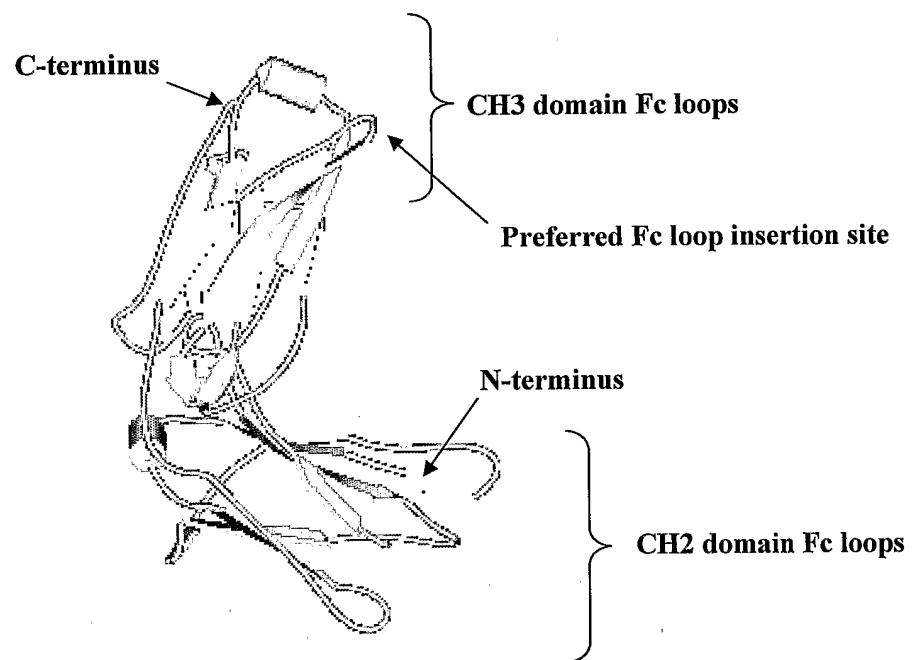


Figure 1A

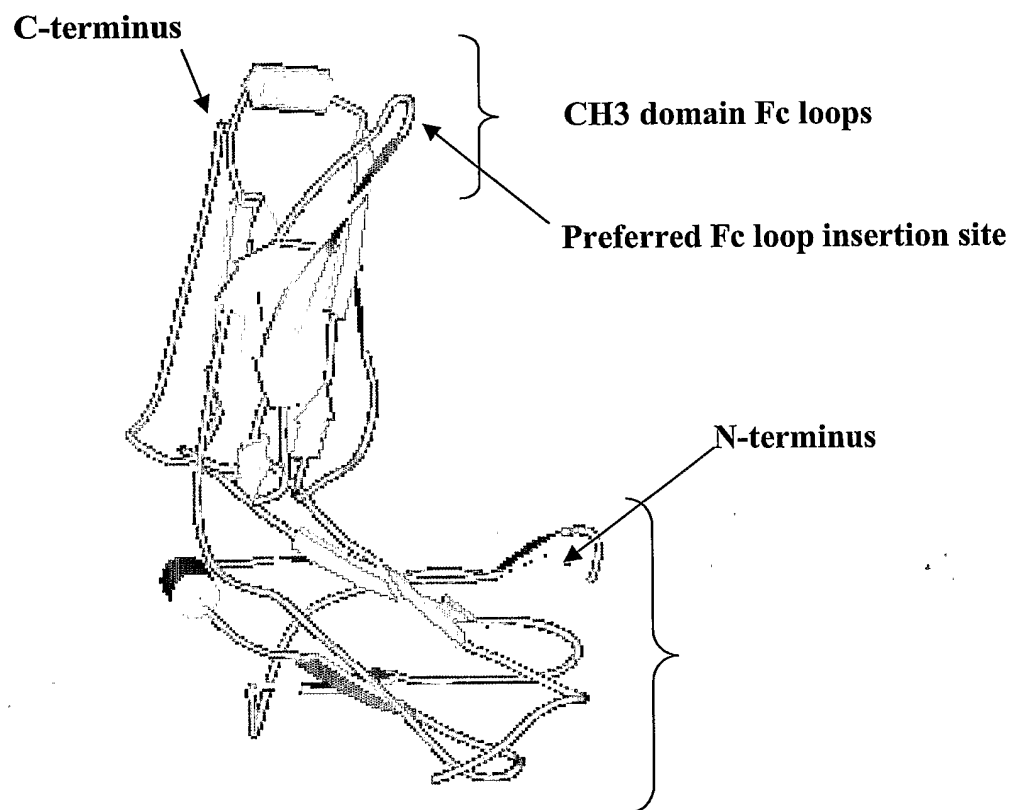


Figure 1B

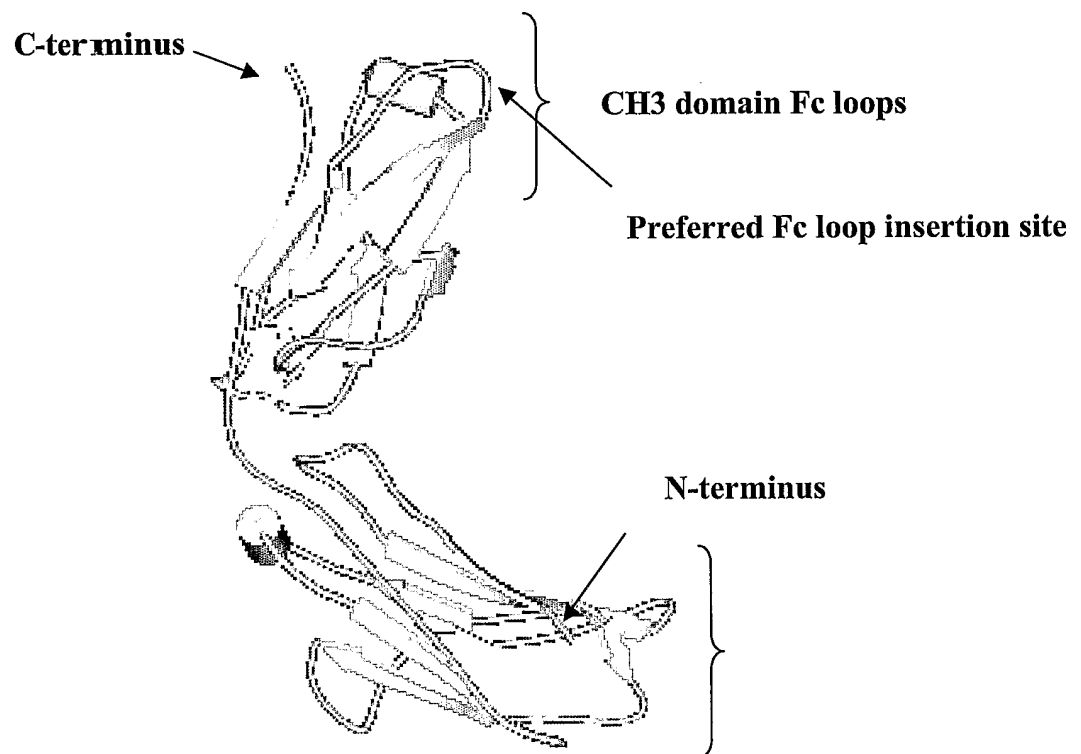


Figure 1C

1 MDKTHTCPPC PAPELLGGPS VFLF**PPKPKD** TLMISRTPEV TCVVVD**VSHE**
51 **DPEVKFNWYV** DGVEVHNAKT KPREE**QYNST** YRVVSVLTVL **HQDWLNGKEY**
101 KCKV**SNKALP** **APIEKTISKA** KGQPREPQVY TLPPSR**DELT** KNQVSLTCLV
151 KGFYPSDIAV EWESNG**OPEN** **NYKTTPPVLD** **SDGSFFLYSK** LTVDKSRW**QQ**
201 **GNVF**SCSVMH EALHNHYTQK SLSLSPGK*

Figure 2A

		1		50
huFc-IgA1	(1)	-----AGKSVTCHVKHYTNP		
huFc-IgA2	(1)	-----DGKSVTCHVKHYTNP		
huFc-IgM	(1)	-----EGK		
huFc-IgG1	(1)	-----EPK		
huFc-nIgG1	(1)	-----EPK		
huFc-IgG3	(1)	ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPK		
huFc-IgG2	(1)	-----		
huFc-IgG4	(1)	-----		
Consensus	(1)		E K	
		51		100
huFc-IgA1	(16)	SQDVTVPVPCVPSTPTPTSPSTPTPTSPSCCHPRISLHRP-ALEDLLIGSE		
huFc-IgA2	(16)	SQDVTVPVPCVP-PPPP-----CCHPRISLHRP-ALEDLLIGSE		
huFc-IgM	(4)	QVGSGVTTDQVQAEAKESG-----PTTYKVTSTLTIKEDHRGLT		
huFc-IgG1	(4)	SCDKTHTCPPCPAPELLGG-----PSVFLFPPKPKDTLMISRT		
huFc-nIgG1	(4)	SCDKTHTCPPCPAPELLGG-----PSVFLFPPKPKDTLMISRT		
huFc-IgG3	(51)	SCDTPPPCPRCPAPELLGG-----PSVFLFPPKPKDTLMISRT		
huFc-IgG2	(1)	ERKCCVECPPCPAPPVAG-----PSVFLFPPKPKDTLMISRT		
huFc-IgG4	(1)	ESKYGPCCPSCPAPEFLGG-----PSVFLFPPKPKDTLMISRT		
Consensus	(51)	S D TVPCP CPAPELLGG	PSVFLFPPKPKDTLMISRT	
		101		150
huFc-IgA1	(65)	ANITCTLTGLRDAS-GVTFTWTIPS--SGKSAVQGPPERDLGCGYSVSSVL		
huFc-IgA2	(52)	ANITCTLTGLRDAS-GATFTWTIPS--SGKSAVQGPPERDLGCGYSVSSVL		
huFc-IgM	(43)	FQONASSMCPDQDTATRVFAIEP---SFASIFLTKSTKLTCVLDTLTTY		
huFc-IgG1	(42)	PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL		
huFc-nIgG1	(42)	PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL		
huFc-IgG3	(89)	PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVL		
huFc-IgG2	(38)	PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVL		
huFc-IgG4	(39)	PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVL		
Consensus	(101)	PEVTCVVVDVSHEDPEV FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVL		
		151		200
huFc-IgA1	(112)	PGCAEPWNHGKTETCTAAYPESKTPLTATLSKS--GNTFRPEVHLLPFP		
huFc-IgA2	(99)	PGCAEPWNHGKTETCTAAPHPELKTPLTANITKS--GNTFRPEVHLLPFP		
huFc-IgM	(90)	DSVTISWNSGERETCTVHTDLESPLIKQTI SRPKGVALHRPDVYLLPFP		
huFc-IgG1	(92)	TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK-GQPREPOVYTLPP-S		
huFc-nIgG1	(92)	TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK-GQPREPOVYTLPP-S		
huFc-IgG3	(139)	TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTK-GQPREPOVYTLPP-S		
huFc-IgG2	(88)	TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTK-GQPREPOVYTLPP-S		
huFc-IgG4	(89)	TVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK-GQPREPOVYTLPP-S		
Consensus	(151)	TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPOVYTLPP S		
		201		250
huFc-IgA1	(160)	EELALNELVTLTCLARGSEPKDVLVRWLQGSQELP REKYL TWASRQEPS Q		
huFc-IgA2	(147)	EELALNELVTLTCLARGSEPKDVLVRWLQGSQELP REKYL TWASRQEPS Q		
huFc-IgM	(140)	EQLNLRESATITCLVTGFSPADVFEVQMQRGQPLS PEKYVTSAPMPEPQ A		
huFc-IgG1	(140)	RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ--P ENNYKTTTPVLDS G		
huFc-nIgG1	(140)	REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ--P ENNYKTTTPVLDS G		
huFc-IgG3	(187)	REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ--P ENNYNTTPPMLDS G		
huFc-IgG2	(136)	REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ--P ENNYKTTTPPMLDS G		
huFc-IgG4	(137)	QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ--P ENNYKTTTPVLDS G		
Consensus	(201)	REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ P ENNYKTTTPPMLDS G		

Figure 2B

		251		300
huFc-IgA1	(210)	GTTTFAVTSILRVAEDWKKGDTFSCMVGHEALPLAFTQKLT	IDRLAGKPT	
huFc-IgA2	(197)	GTTTFAVTSILRVAEDWKKGDTFSCMVGHEALPLAFTQKLT	IDRLACKPT	
huFc-IgM	(190)	PG-RYFAHSILTVSEEEWNTGETYTCTVAHDALPNRVIERITVDKSTGKPT		
huFc-IgG1	(188)	---SFFLYSKLTVDKSRWQQCNVFSCSVMHEALHNHYTQKSLSLSPGK---		
huFc-nIgG1	(188)	---SFFLYSKLTVDKSRWQQCNVFSCSVMHEALHNHYTQKSLSLSPGK---		
huFc-IgG3	(235)	---SFFLYSKLTVDKSRWQQCNVFSCSVMHEALHNHYTQKSLSLSPGK---		
huFc-IgG2	(184)	---SFFLYSKLTVDKSRWQQCNVFSCSVMHEALHNHYTQKSLSLSPGK---		
huFc-IgG4	(185)	---SFFLYSKLTVDKSRWQQCNVFSCSVMHEALHNHYTQKSLSLSLGK---		
Consensus	(251)	SFFLYSKLTVDKSRWQQCNVFSCSVMHEALHNHYTQKSLSLSPGK		

		301		316
huFc-IgA1	(260)	HVNVSVVMAEVDGTCY		
huFc-IgA2	(247)	HVNVSVVMAEVDGTCY		
huFc-IgM	(238)	LYNVSLVMSDTAGTCY		
huFc-IgG1	(233)	-----		
huFc-nIgG1	(233)	-----		
huFc-IgG3	(280)	-----		
huFc-IgG2	(229)	-----		
huFc-IgG4	(230)	-----		
Consensus	(301)			

Figure 2C

			1		50
1I1A.pdb	Angen Fc	(1)	EGGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPADITLMISRTPEVTCVVV		
	Fc chain C:	(1)	-----SVFIFPPKTDVLTITITLTKVTCVVV		
	Consensus	(1)	SVFIFPPK KD L IS TP VTCVVV		
			51		100
1I1A.pdb	Angen Fc	(51)	DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLDHQL		
	Fc chain C:	(27)	DISQNDPEVRFESWFIDDEVHTAQTHAPEKQSNSTLRVSSELPVHRDWL		
	Consensus	(51)	DIS DPEVKF WFID VEVH A T E Q NST R VS L ILH DWL		
			101		150
1I1A.pdb	Angen Fc	(101)	NGREYKCKVSNKALPAPIEKTIISKAKGQPREPQVYITLPFSRDELTKNQV		
	Fc chain C:	(77)	NGKTFCKVNSGAFAPAPIEKSSINPECTPRGPQVYTMAPPKEEMTQSQV		
	Consensus	(101)	NGK FKCKV A PAPIEKSISK G PR PQVYTL P KDEL T QVS		
			151		200
1I1A.pdb	Angen Fc	(151)	ITCLVKGFYPSDIAVEWESNGQPENNYNTPPVLDSDGSFFLYSKLTVDK		
	Fc chain C:	(127)	ITCMVKGFYPPDIYTEWKMNQGPQENYKNTTPPTMDTDCSYFLYSKLNVDK		
	Consensus	(151)	ITCLVKGFYP DI EW NGQP NYK TPP LDSDGSFFLYSKL V K		
			201		233
1I1A.pdb	Angen Fc	(201)	SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		
	Fc chain C:	(177)	ETWQQGNFTFCSVLHEGLHNHHTKSLSH----		
	Consensus	(201)	WQQGN FSCSVLHEALHNHHT KSLS		

Figure 2D

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELG ~~GLADHQCIR~~
151 ~~WFWACFPEGW~~ EGGTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTP
201 PVLDSGGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP
251 GK*

Figure 3A

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGKGG GGAQLADHG QCIRWPMCP
251 **PEGWE***

Figure 3B

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDEL **GGGGTYSCHFGPL**
151 **TWVCKPQGGGG** TKNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
201 SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK*

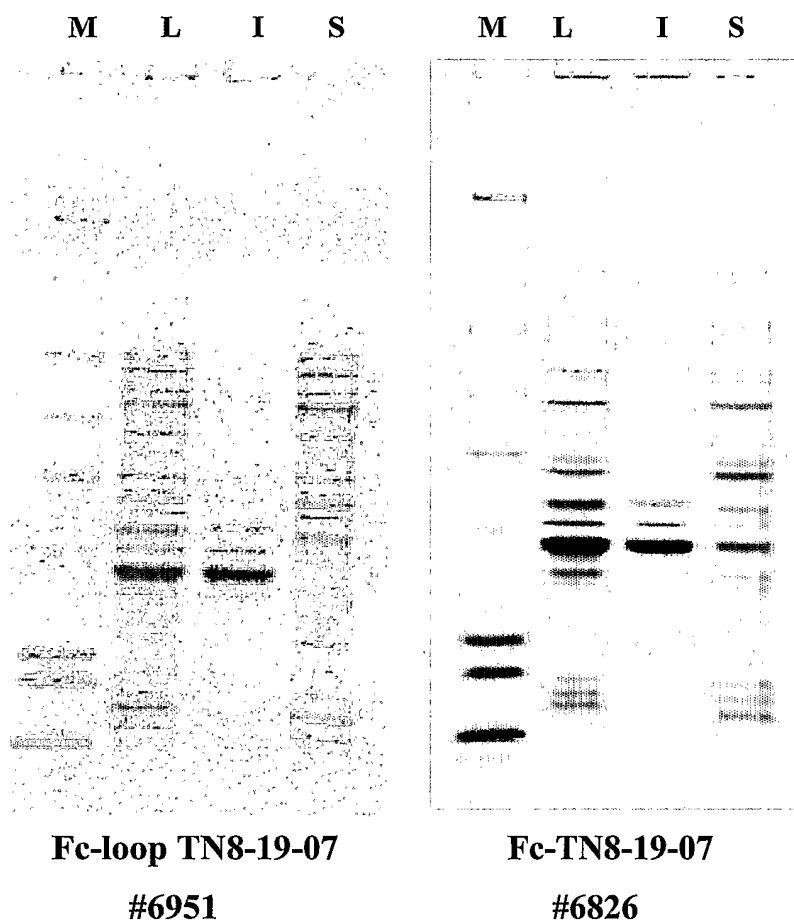
Figure 3C

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELG ~~GIEGPTLRQW~~
151 ~~LAARAGG~~TKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSD
201 GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK*

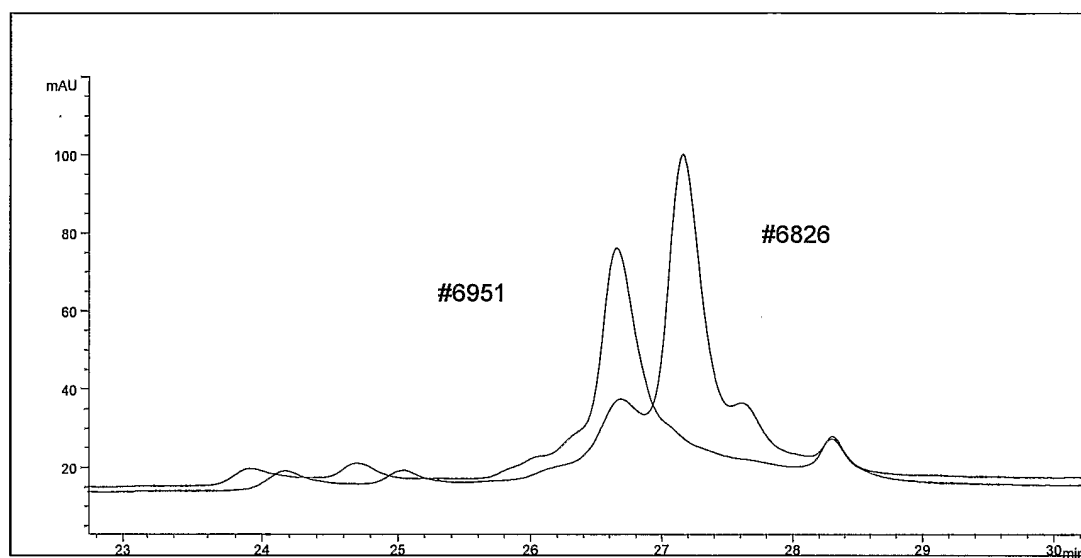
Figure 3D

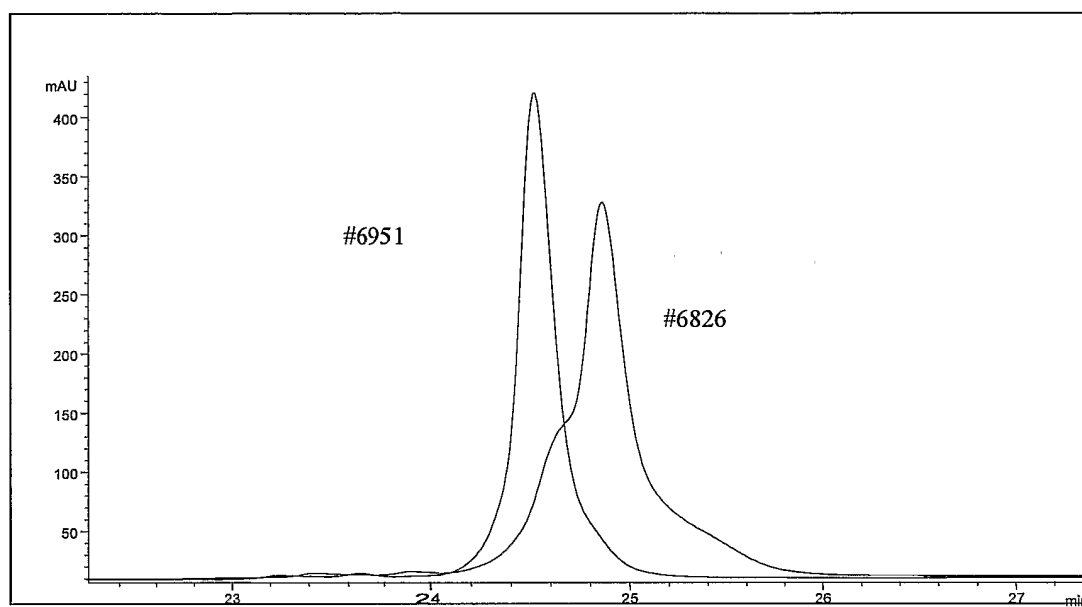
1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGKGG ~~GGGIEGPTLE~~ ~~QWLAAARAGGG~~
251 ~~GGGGIEGPT~~ ~~LRQWLAAAR~~

Figure 3E



Figures 4A and 4B

**Figure 5**

**Figure 6**

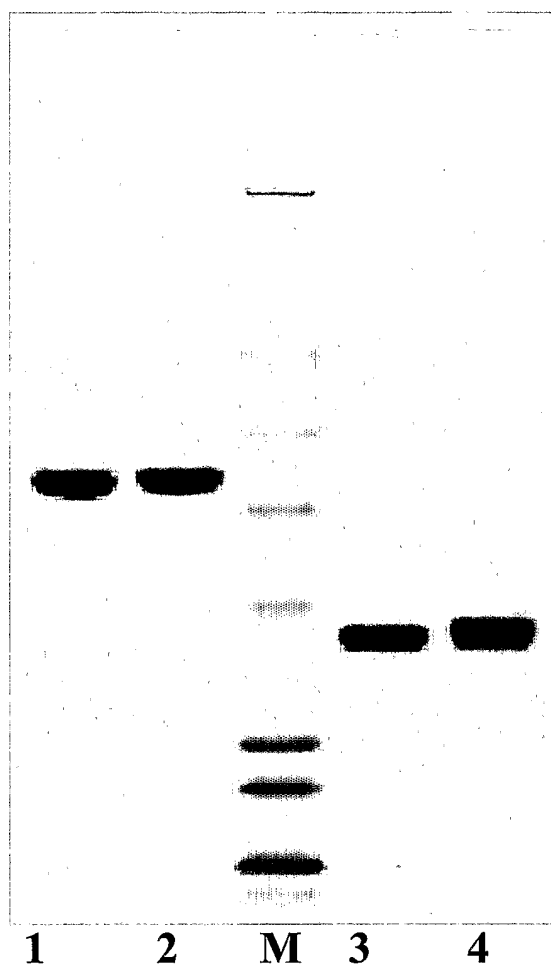


Figure 7

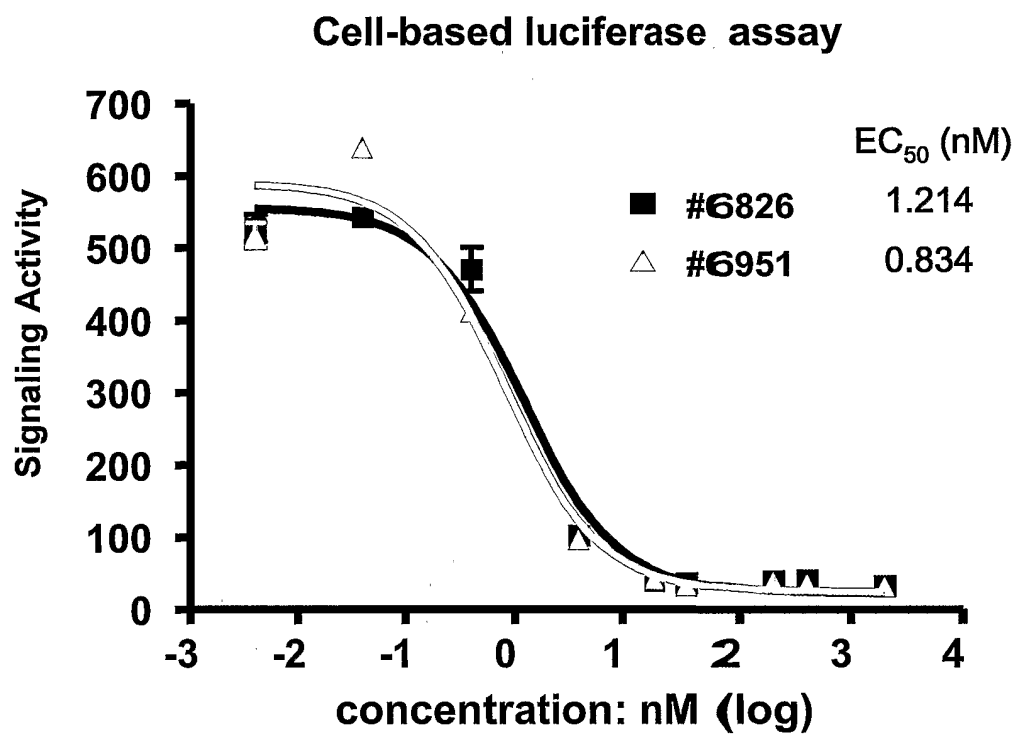
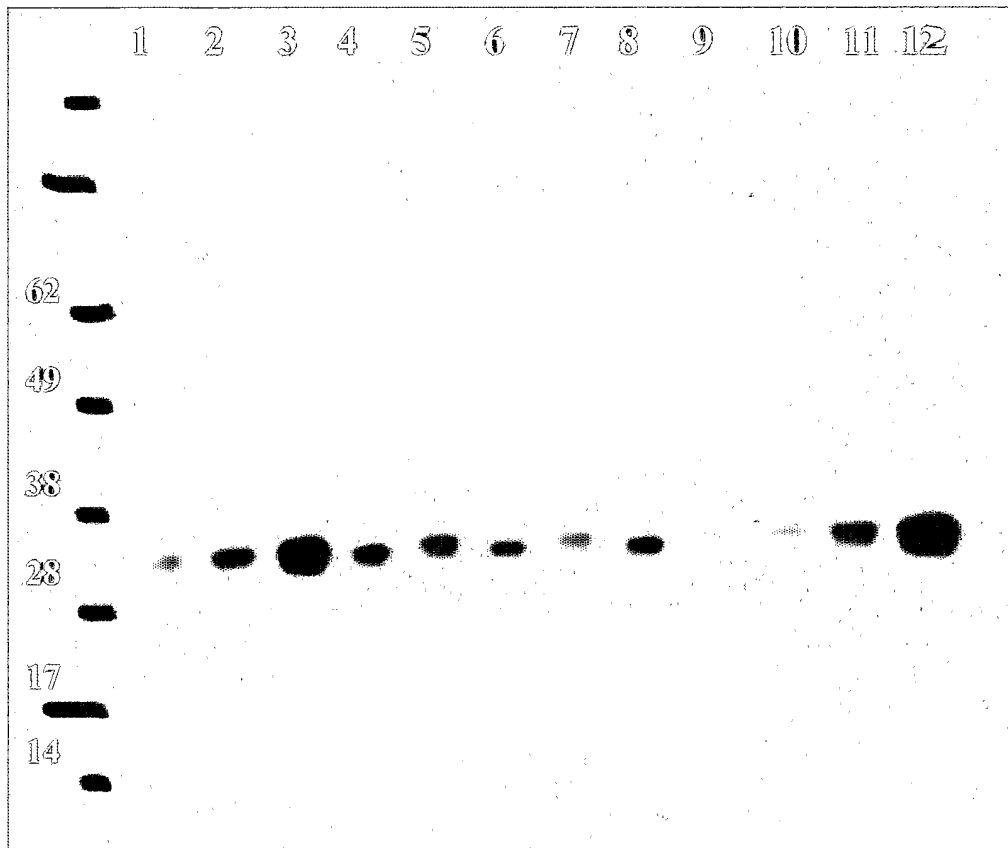


Figure 8

**Figure 9**

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101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPFSRDELG GQEECEWDPW
151 TCEHMGGTKN QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTFPVLDSID
201 GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK*

Figure 10A

1 MDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
51 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
101 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
151 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
201 GNVFSCSVMH EALHNHYTQK SLSLSPGKGG **GGGAQQEECE WDPWTCEHML**
251 **E***

Figure 10B

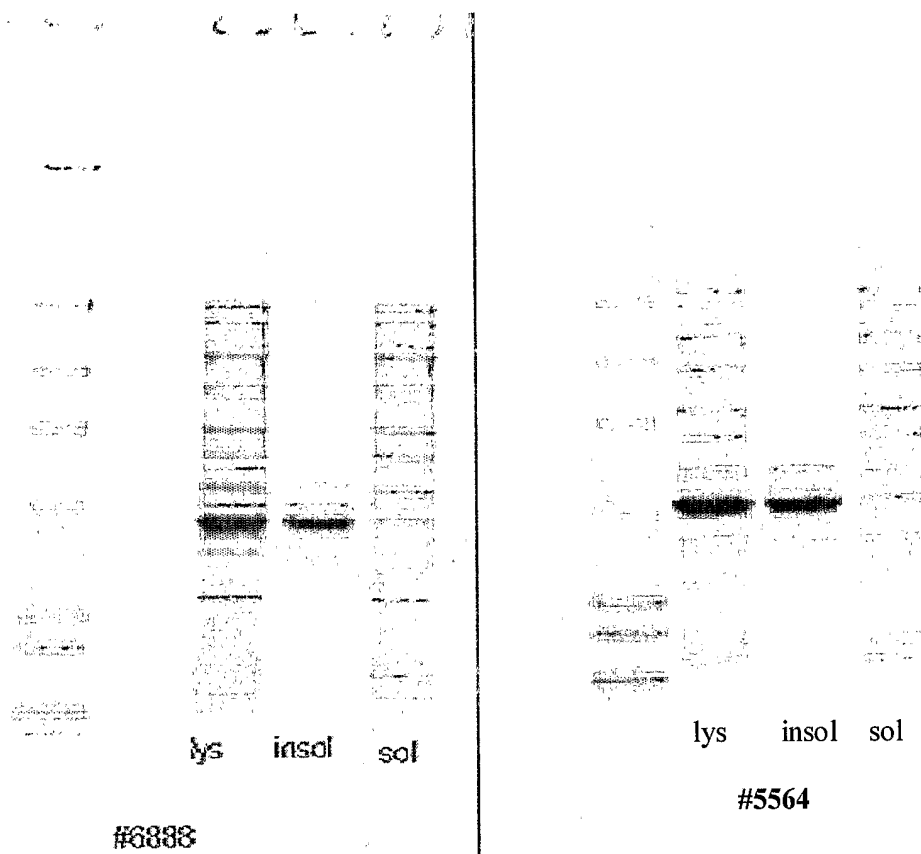
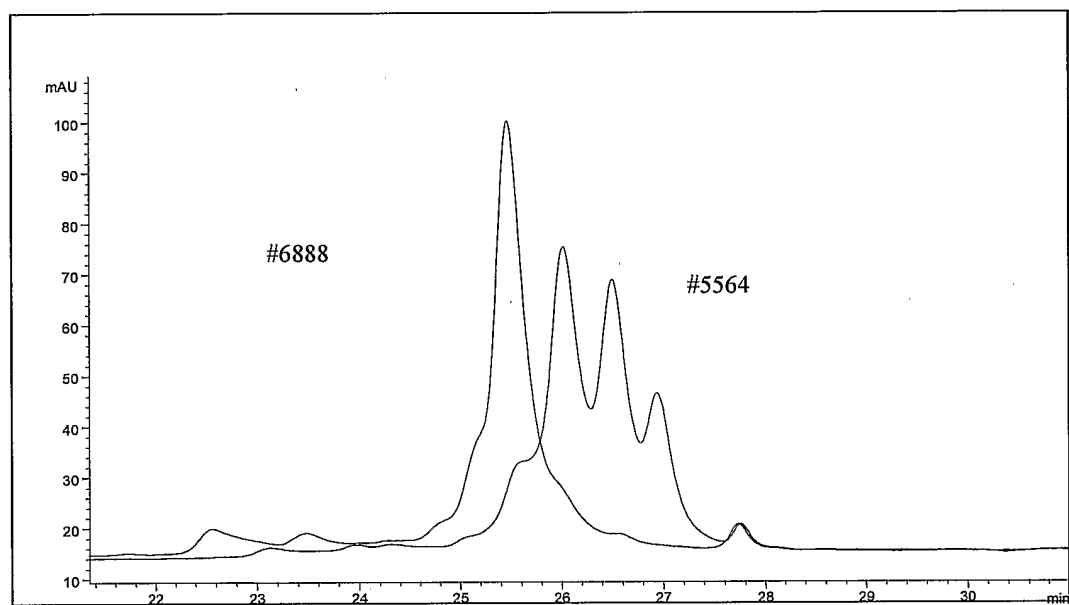
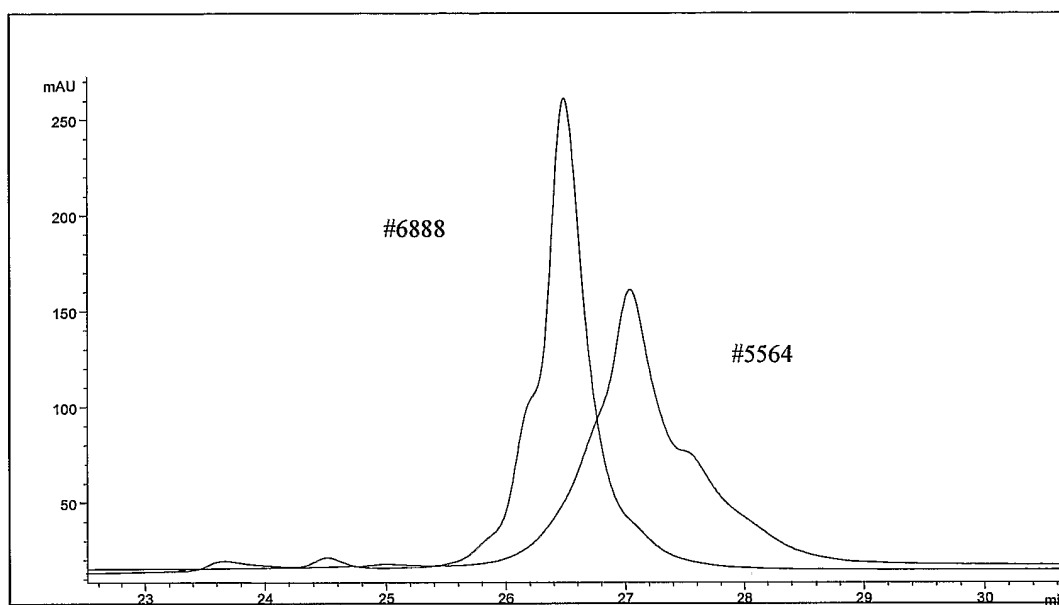
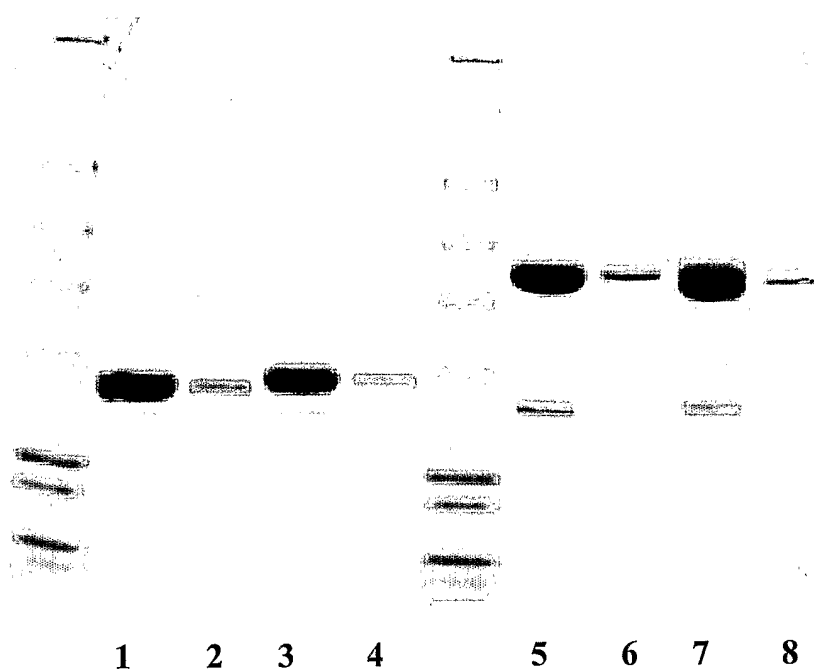
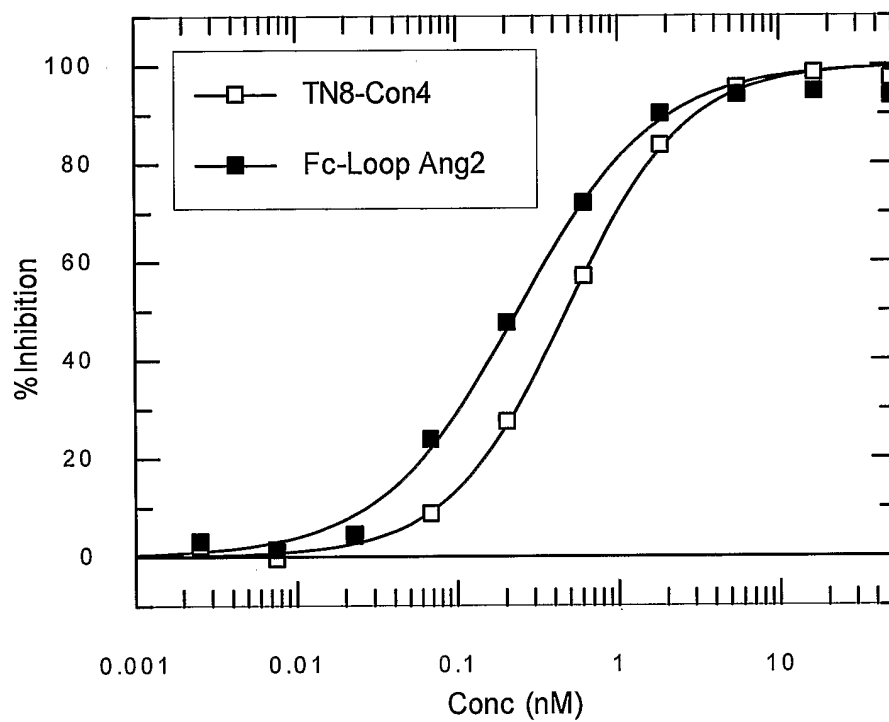


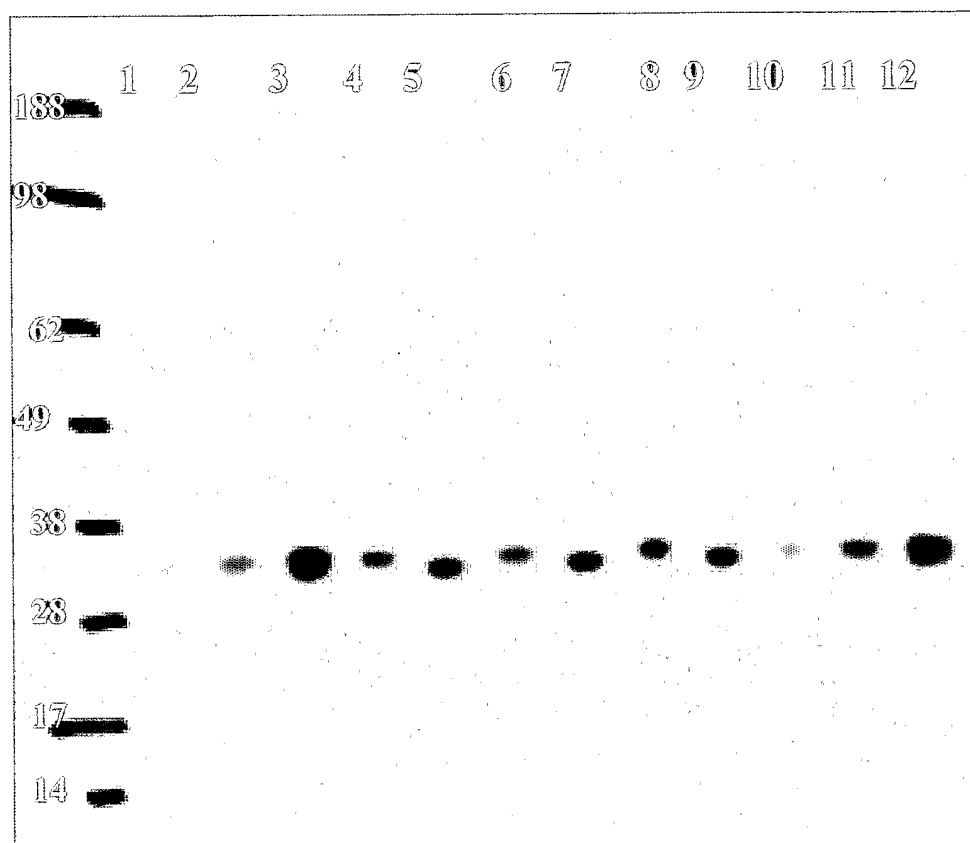
Figure 11

**Figure 12**

**Figure 13**

**Figure 14**

**Figure 15**

**Figure 16**

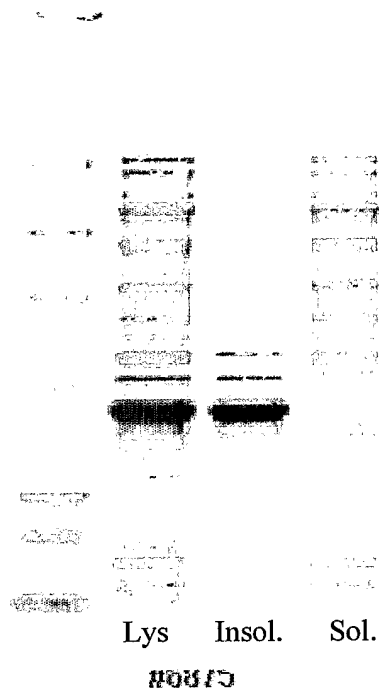


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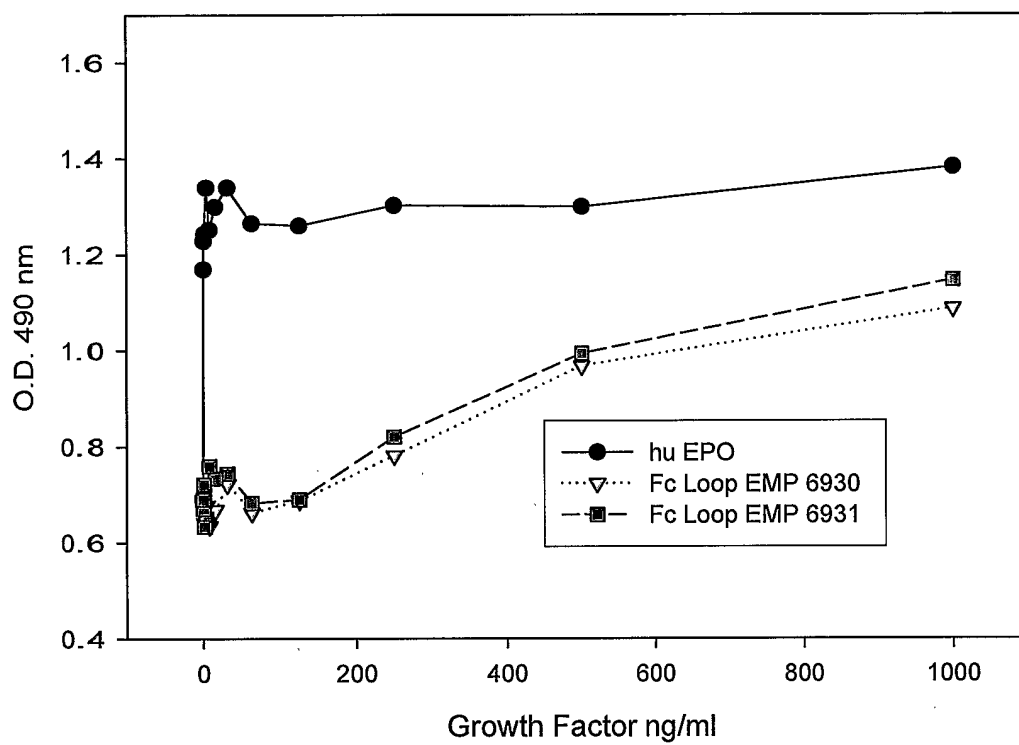
UT7 Proliferation Assay
10/27/03

Figure 18

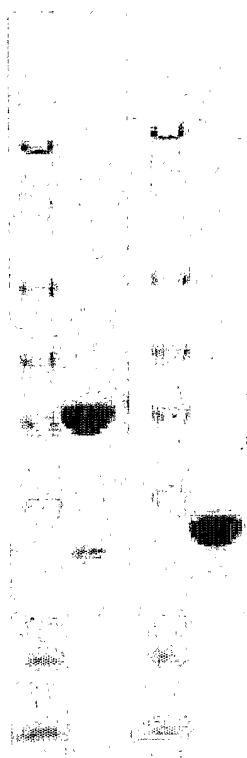
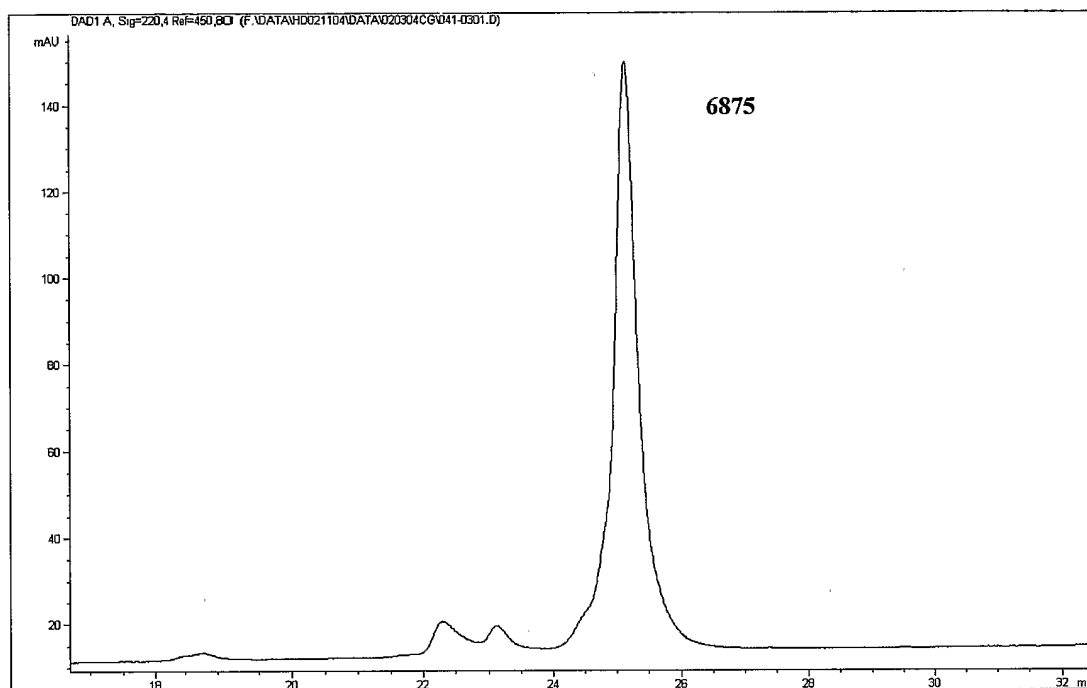


Figure 19

**Figure 20**

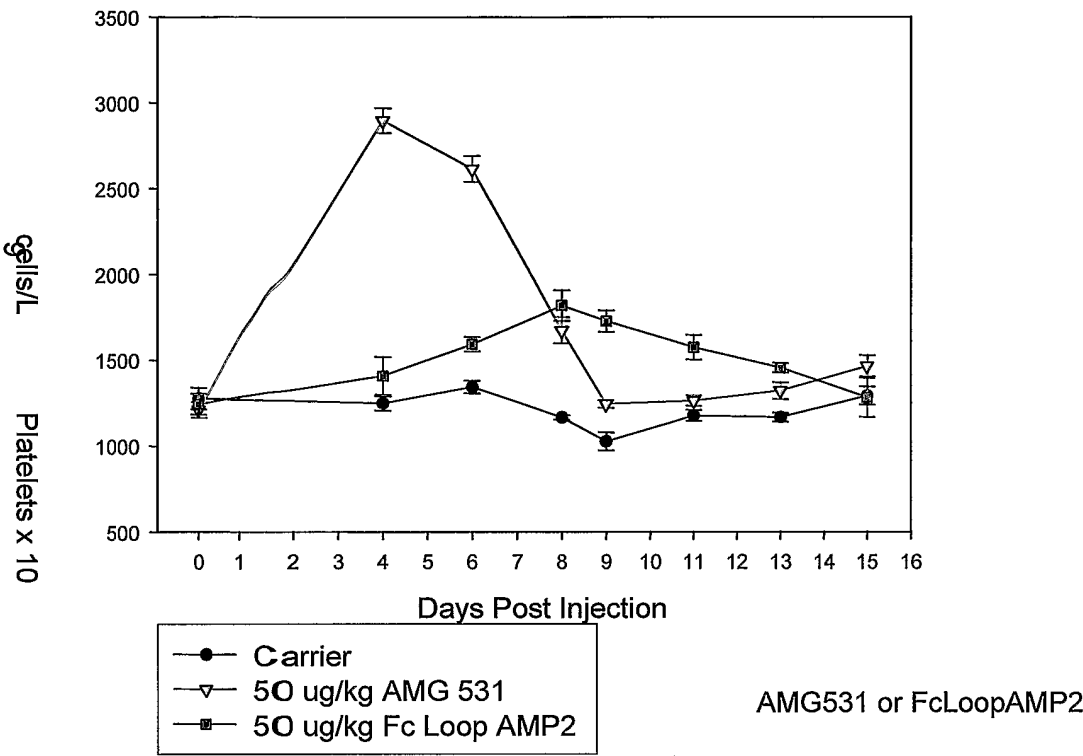


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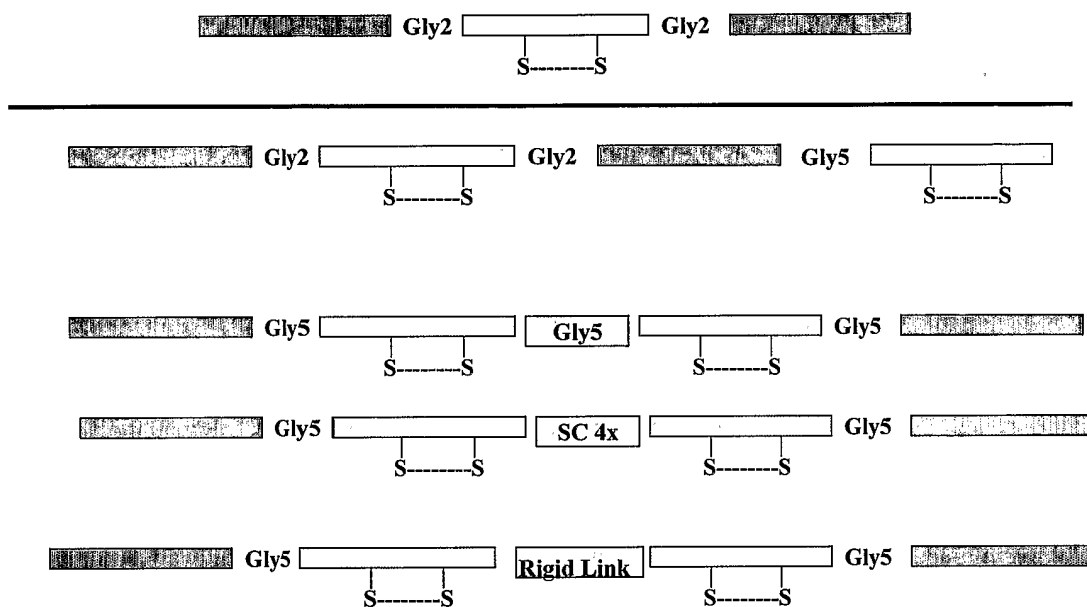


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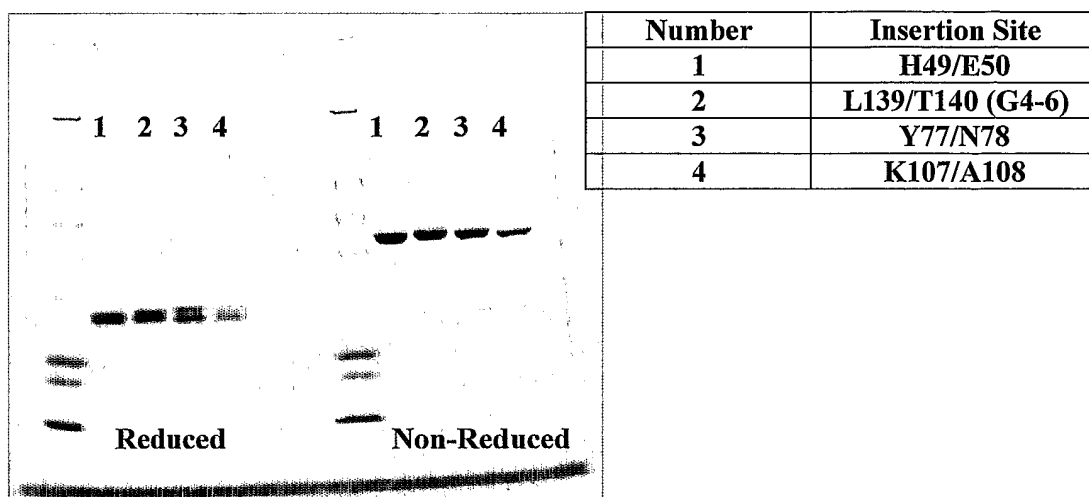


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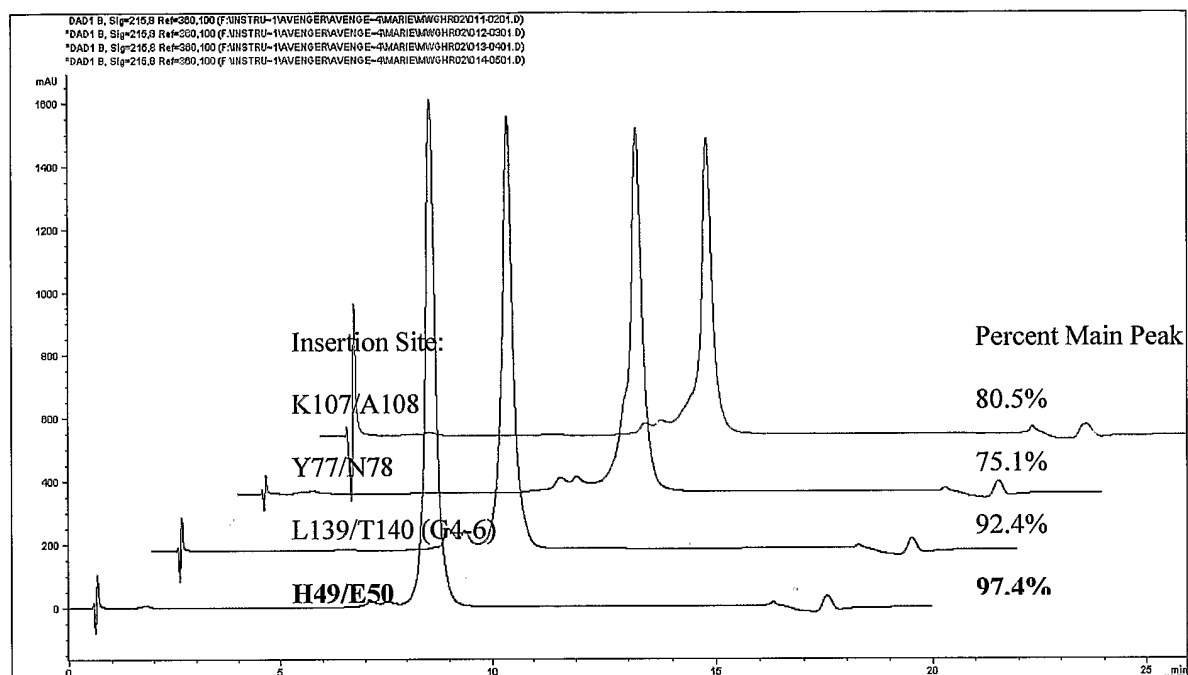


Figure 24

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<212> PRT
<213> Artificial Sequence

<220>
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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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> Synthesized 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> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide capable of binding to Ang-2

<400> 99

Trp Asp Pro Trp Thr
1 5

<210> 100
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide capable of binding to Ang-2

<400> 100

Trp Asp Pro Trp Thr Cys
1 5

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

<220>
<223> Polypeptide capable of binding to Ang-2

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

<400> 101

Trp Asp Pro Trp Thr Cys
1 5

<210> 102

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

<220>
<223> Polypeptide capable of binding to Ang-2

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa 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> Polypeptide capable of binding to Ang-2

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa can be any naturally occurring amino acid

<400> 103

Cys Xaa Trp Asp Pro Trp Thr Cys
1 5

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

<220>
<223> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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 Polypeptide

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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>
<223> Ang-2 binding Polypeptide

<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> Polypeptide capable of binding to Ang-2

<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>
<223> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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>
<223> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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
20

<210> 177
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide capable of binding to Ang-2

<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 Polypeptide

<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>
<223> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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>

<223> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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> Polypeptide capable of binding to Ang-2

<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

<213> Artificial Sequence

<220>

<223> Polypeptide capable of binding to Ang-2

<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>

<223> Ang-2 binding Polypeptide

<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> Therapeutically active peptide of randomly generated,

non-naturally occurring 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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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>

<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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>

<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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
			20

<210> 193

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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>

<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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>
<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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>
<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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>
<223> Therapeutically active peptide of randomly generated,
non-naturally occurring sequence.

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 229

Ile Asp Lys Cys Ala Ile Trp Gly Trp Met Cys Pro Pro Leu
1 5 10

<210> 230
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 230

Trp Tyr Pro Cys Gly Glu Phe Gly Met Trp Cys Leu Asn Val
1 5 10

<210> 231
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 231

Trp Phe Thr Cys Leu Trp Asn Cys Asp Asn Glu
1 5 10

<210> 232
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 232

His Thr Pro Cys Pro Trp Phe Ala Pro Leu Cys Val Glu Trp
1 5 10

<210> 233
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 233

Lys Glu Trp Cys Trp Arg Trp Lys Trp Met Cys Lys Pro Glu
1 5 10

<210> 234
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 234

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

<210> 235
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 235

Ala Tyr Lys Cys Glu Ala Asn Asp Trp Gly Cys Trp Trp Leu
1 5 10

<210> 236
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 236

Asn Ser Trp Cys Glu Asp Gln Trp His Arg Cys Trp Trp Leu
1 5 10

<210> 237
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 237

Trp Ser Ala Cys Tyr Ala Gly His Phe Trp Cys Tyr Asp Leu
1 5 10

<210> 238
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 238

Ala Asn Trp Cys Val Ser Pro Asn Trp Phe Cys Met Val Met
1 5 10

<210> 239
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 239

Trp Thr Glu Cys Tyr Gln Gln Glu Phe Trp Cys Trp Asn Leu
1 5 10

<210> 240
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 240

Glu Asn Thr Cys Glu Arg Trp Lys Trp Met Cys Pro Pro Lys
1 5 10

<210> 241
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 241

Trp	Leu	Pro	Cys	His	Gln	Glu	Gly	Phe	Trp	Cys	Met	Asn	Phe
1				5					10				

<210> 242
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 242

Ser	Thr	Met	Cys	Ser	Gln	Trp	His	Trp	Met	Cys	Asn	Pro	Phe
1				5					10				

<210> 243
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 243

Ile	Phe	Gly	Cys	His	Trp	Trp	Asp	Val	Asp	Cys	Tyr	Gln	Phe
1				5					10				

<210> 244
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 244

Ile	Tyr	Gly	Cys	Lys	Trp	Trp	Asp	Ile	Gln	Cys	Tyr	Asp	Ile
1				5					10				

<210> 245
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 245

Pro	Asp	Trp	Cys	Ile	Asp	Pro	Asp	Trp	Trp	Cys	Lys	Phe	Trp
1				5					10				

<210> 246
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 246

Gln	Gly	His	Cys	Thr	Arg	Trp	Pro	Trp	Met	Cys	Pro	Pro	Tyr
1				5					10				

<210> 247
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 247

Trp	Gln	Glu	Cys	Tyr	Arg	Glu	Gly	Phe	Trp	Cys	Leu	Gln	Thr
1				5					10				

<210> 248
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 248

Trp	Phe	Asp	Cys	Tyr	Gly	Pro	Gly	Phe	Lys	Cys	Trp	Ser	Pro
1				5					10				

<210> 249
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 251

Gly Pro Ala Cys His Ser Pro Trp Trp Trp Cys Val Phe Gly
1 5 10

<210> 252
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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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<220>
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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
 <212> PRT
 <213> Artificial Sequence

<220>
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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
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
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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
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Myostatin Binding Peptide

<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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<212> PRT
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<220>
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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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<400> 259

Ser Trp Met Cys Gly Phe Phe Lys Glu Val Cys Met Trp Val
1 5 10

<210> 260
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 260

Glu Met Leu Cys Met Ile His Pro Val Phe Cys Asn Pro His
1 5 10

<210> 261
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 261

Leu Lys Thr Cys Asn Leu Trp Pro Trp Met Cys Pro Pro Leu
1 5 10

<210> 262
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 262

Val Val Gly Cys Lys Trp Tyr Glu Ala Trp Cys Tyr Asn Lys
1 5 10

<210> 263
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 263

Pro Ile His Cys Thr Gln Trp Ala Trp Met Cys Pro Pro Thr
1 5 10

<210> 264
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 264

Asp Ser Asn Cys Pro Trp Tyr Phe Leu Ser Cys Val Ile Phe
1 5 10

<210> 265
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 265

His Ile Trp Cys Asn Leu Ala Met Met Lys Cys Val Glu Met
1 5 10

<210> 266
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 266

Asn Leu Gln Cys Ile Tyr Phe Leu Gly Lys Cys Ile Tyr Phe
1 5 10

<210> 267
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 267

Ala Trp Arg Cys Met Trp Phe Ser Asp Val Cys Thr Pro Gly
1 5 10

<210> 268
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 268

Trp Phe Arg Cys Phe Leu Asp Ala Asp Trp Cys Thr Ser Val
1 5 10

<210> 269
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 269

Glu Lys Ile Cys Gln Met Trp Ser Trp Met Cys Ala Pro Pro
1 5 10

<210> 270
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 270

Trp Phe Tyr Cys His Leu Asn Lys Ser Glu Cys Thr Glu Pro
1 5 10

<210> 271
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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
 <213> Artificial Sequence
 <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
 <213> Artificial Sequence
 <220>
 <223> Myostatin Binding Peptide
 <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>
 <223> Myostatin Binding Peptide
 <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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 290

Phe	Leu	Ala	Cys	Phe	Val	Glu	Phe	Glu	Leu	Cys	Phe	Asp	Ser
1				5					10				

<210> 291
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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

<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

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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

<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

<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

<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>
 <223> Myostatin Binding Peptide

<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

<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>
 <223> Myostatin Binding Peptide

<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>
 <223> Myostatin Binding Peptide

<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>
 <223> Myostatin Binding Peptide

<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

<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

<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
 <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

<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

<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

<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

<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

<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

<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
 <213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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
20

<210> 421

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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
20

<210> 422

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Myostatin Binding Peptid

<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
 <213> Artificial Sequence

<220>
 <223> Myostatin Binding Peptid

<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>
 <223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptid

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptid

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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

<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
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<210> 439
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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

<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
20

<210> 441
<211> 22

<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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

<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
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<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
<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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>

<223> Myostatin Binding Peptide

<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

<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

<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

<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
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<210> 452

<211> 22

<212> PRT

<213> Artificial Sequenc

<220>

<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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>
<223> Myostatin Binding Peptide

<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

<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

<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>

<223> Myostatin Binding Peptide

<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

<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

<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

<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

<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

<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

<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>

<223> Myostatin Binding Peptide

<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
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<210> 480

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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
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<210> 481

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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>
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<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

<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

<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

<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

<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>
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<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

<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

<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

<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

<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

<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

<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

<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

<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

<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>
<223> Myostatin Binding Peptide

<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

<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

<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
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<210> 500
<211> 20
<212> PRT
<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<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

<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

<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>

<223> Myostatin Binding Peptide

<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

<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

<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>

<223> Myostatin Binding Peptide

<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

<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

<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>

<223> Myostatin Binding Peptide

<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
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<210> 510
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 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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>
 <223> Preferred TALL-1 Modulating Domains

<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>

<223> Preferred TALL-1 Modulating Domains

<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>

<223> Preferred TALL-1 Modulating Domains

<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>

<223> Preferred TALL-1 Modulating Domains

<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>

<223> Preferred TALL-1 Modulating Domains

<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>

<223> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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>
 <223> Preferred TALL-1 Modulating Domains

<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>
 <223> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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>
<223> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains
<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> Preferred TALL-1 Modulating Domains
<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> Preferred TALL-1 Modulating Domains
<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred TALL-1 Modulating Domains

<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> Preferred linker

<400> 595

Gly Gly Gly Lys Gly Gly Gly Gly
1 5

<210> 596

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred linker

<400> 596

Gly Gly Gly Asn Gly Ser Gly Gly
1 5

<210> 597

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred linker

<400> 597

Gly Gly Gly Cys Gly Gly Gly Gly
1 5

<210> 598
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred 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> 275

<212> PRT

<213> Homo sapiens

<400> 600

Ala Gly Lys Ser Val Thr Cys His Val Lys His Tyr Thr Asn Pro Ser
1 5 10 15

Gln Asp Val Thr Val Pro Cys Pro Val Pro Ser Thr Pro Pro Thr Pro
20 25 30

Ser Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Cys Cys His Pro Arg
35 40 45

Leu Ser Leu His Arg Pro Ala Leu Glu Asp Leu Leu Leu Gly Ser Glu
50 55 60

Ala Asn Leu Thr Cys Thr Leu Thr Gly Leu Arg Asp Ala Ser Gly Val
65 70 75 80

Thr Phe Thr Trp Thr Pro Ser Ser Gly Lys Ser Ala Val Gln Gly Pro
85 90 95

Pro Glu Arg Asp Leu Cys Gly Cys Tyr Ser Val Ser Ser Val Leu Pro
 100 105 110

Gly Cys Ala Glu Pro Trp Asn His Gly Lys Thr Phe Thr Cys Thr Ala
 115 120 125

Ala Tyr Pro Glu Ser Lys Thr Pro Leu Thr Ala Thr Leu Ser Lys Ser
 130 135 140

Gly Asn Thr Phe Arg Pro Glu Val His Leu Leu Pro Pro Pro Ser Glu
 145 150 155 160

Glu Leu Ala Leu Asn Glu Leu Val Thr Leu Thr Cys Leu Ala Arg Gly
 165 170 175

Phe Ser Pro Lys Asp Val Leu Val Arg Trp Leu Gln Gly Ser Gln Glu
 180 185 190

Leu Pro Arg Glu Lys Tyr Leu Thr Trp Ala Ser Arg Gln Glu Pro Ser
 195 200 205

Gln Gly Thr Thr Thr Phe Ala Val Thr Ser Ile Leu Arg Val Ala Ala
 210 215 220

Glu Asp Trp Lys Lys Gly Asp Thr Phe Ser Cys Met Val Gly His Glu
 225 230 235 240

Ala Leu Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp Arg Leu Ala Gly
 245 250 255

Lys Pro Thr His Val Asn Val Ser Val Val Met Ala Glu Val Asp Gly
 260 265 270

Thr Cys Tyr
 275

<210> 601

<211> 262

<212> PRT

<213> Homo sapiens

<400> 601

Asp Gly Lys Ser Val Thr Cys His Val Lys His Tyr Thr Asn Pro Ser

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

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Asp Val Phe Val Gln Trp Met Gln Arg Gly Gln Pro Leu Ser Pro Glu
 165 170 175

Lys Tyr Val Thr Ser Ala Pro Met Pro Glu Pro Gln Ala Pro Gly Arg
 180 185 190

Tyr Phe Ala His Ser Ile Leu Thr Val Ser Glu Glu Glu Trp Asn Thr
 195 200 205

Gly Glu Thr Tyr Thr Cys Val Ala His Asp Ala Leu Pro Asn Arg Val
 210 215 220

Thr Glu Arg Thr Val Asp Lys Ser Thr Gly Lys Pro Thr Leu Tyr Asn
 225 230 235 240

Val Ser Leu Val Met Ser Asp Thr Ala Gly Thr Cys Tyr
 245 250

<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> 232
 <212> PRT
 <213> Homo sapiens

<400> 604

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 Glu Glu Met 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> 605

<211> 279

<212> PRT

<213> Homo sapiens

<400> 605

Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys

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

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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 Met 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> 607
<211> 229
<212> PRT
<213> Homo sapiens

<400> 607

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
 100 105 110

 Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 115 120 125

 Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
 130 135 140

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

 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 165 170 175

 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
 180 185 190

 Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
 195 200 205

 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 210 215 220

 Leu Ser Leu Gly Lys
 225

<210> 608
 <211> 253
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Consensus sequence.

<220>
 <221> misc_feature
 <222> (2, 5, 7, 13, 23-34, 71, 138, 152, 186-187, 204-206, and)..(252-253)
 <223> At positions 2, 5, 7, 13, 23-34, 71, 138, 152, 186-187, 204-206, and 252-253, Xaa is any amino acid or is absent.

<220>
 <221> misc_feature
 <222> (253)..(253)

<223> Xaa can be any naturally occurring amino acid

<400> 608

Glu	Xaa	Lys	Ser	Xaa	Asp	Xaa	Thr	Val	Pro	Cys	Pro	Xaa	Cys	Pro	Ala
1				5					10					15	

Pro	Glu	Leu	Leu	Gly	Gly	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
		20						25					30		

Xaa	Xaa	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
		35					40					45			

Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
	50					55					60				

His	Glu	Asp	Pro	Glu	Val	Xaa	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
65					70					75					80

Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr
				85					90					95	

Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
		100						105					110		

Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro
		115					120					125			

Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Xaa	Gly	Gln	Pro	Arg	Glu	Pro
130						135					140				

Gln	Val	Tyr	Thr	Leu	Pro	Pro	Xaa	Ser	Arg	Glu	Glu	Met	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	Xaa	Xaa	Pro	Glu	Asn	Asn	Tyr
			180					185					190		

Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Xaa	Xaa	Xaa	Ser	Phe
		195					200					205			

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 210 215 220

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 225 230 235 240

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Xaa Xaa
 245 250

<210> 609

<211> 183

<212> PRT

<213> Artificial Sequence

<220>

<223> Amgen Fc sequence

<400> 609

Glu Gly Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 1 5 10 15

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 35 40 45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 65 70 75 80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 100 105 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
 130 135 140

Thr Lys Asn Gln Val Ser Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
145 150 155 160

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
165 170 175

Leu Ser Leu Ser Pro Gly Lys
180

<210> 610

<211> 205

<212> PRT

<213> Rattus rattus

<400> 610

Ser Val Phe Ile Phe Pro Pro Lys Thr Lys Asp Val Leu Thr Ile Thr
1 5 10 15

Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Gln Asn Asp
20 25 30

Pro Glu Val Arg Phe Ser Trp Phe Ile Asp Asp Val Glu Val His Thr
35 40 45

Ala Gln Thr His Ala Pro Glu Lys Gln Ser Asn Ser Thr Leu Arg Ser
50 55 60

Val Ser Glu Leu Pro Ile Val His Arg Asp Trp Leu Asn Gly Lys Thr
65 70 75 80

Phe Lys Cys Lys Val Asn Ser Gly Ala Phe Pro Ala Pro Ile Glu Lys
85 90 95

Ser Ile Ser Lys Pro Glu Gly Thr Pro Arg Gly Pro Gln Val Tyr Thr
100 105 110

Met Ala Pro Pro Lys Glu Glu Met Thr Gln Ser Gln Val Ser Ile Thr
115 120 125

Cys Met Val Lys Gly Phe Tyr Pro Pro Asp Ile Tyr Thr Glu Trp Lys
130 135 140

Met Asn Gly Gln Pro Gln Glu Asn Tyr Lys Asn Thr Pro Pro Thr Met
 145 150 155 160

Asp Thr Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Asn Val Lys Lys
 165 170 175

Glu Thr Trp Gln Gln Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
 180 185 190

Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
 195 200 205

<210> 611
 <211> 204
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Consensus sequence.

<220>
 <221> misc_feature
 <222> (9)..(9)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (12)..(12)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (14)..(14)
 <223> Xaa can be any naturally occurring amino acid

<220>
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 <222> (17)..(17)
 <223> Xaa can be any naturally occurring amino acid

<220>
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 <222> (20)..(20)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (30)..(31)
 <223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (38)..(38)
<223> Xaa can be any naturally occurring amino acid

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<221> misc_feature
<222> (43)..(43)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (48)..(48)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (50)..(50)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (52)..(54)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (56)..(56)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (58)..(58)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (62)..(62)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (64)..(64)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (67)..(67)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (72)..(72)
<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature
<222> (79)..(79)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (85)..(87)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (89)..(89)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (100)..(101)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (103)..(103)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (106)..(106)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (113)..(113)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (115)..(115)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (121)..(122)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (136)..(136)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (139)..(140)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature

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<222> (143)..(144)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (149)..(150)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (154)..(154)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (158)..(158)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (172)..(172)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (174)..(174)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (176)..(177)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (183)..(183)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (199)..(199)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (204)..(204)
<223> Xaa can be any naturally occurring amino acid

<400> 611

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Ser Val Phe Ile Phe Pro Pro Lys Xaa Lys Asp Xaa Leu Xaa Ile Ser
1           5           10           15

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Xaa Thr Pro Xaa Val Thr Cys Val Val Val Asp Ile Ser Xaa Xaa Asp
          20           25           30

```

Pro Glu Val Lys Phe Xaa Trp Phe Ile Asp Xaa Val Glu Val His Xaa
35 40 45

Ala Xaa Thr Xaa Xaa Xaa Glu Xaa Gln Xaa Asn Ser Thr Xaa Arg Xaa
50 55 60

Val Ser Xaa Leu Ile Leu His Xaa Asp Trp Leu Asn Gly Lys Xaa Phe
65 70 75 80

Lys Cys Lys Val Xaa Xaa Xaa Ala Xaa Pro Ala Pro Ile Glu Lys Ser
85 90 95

Ile Ser Lys Xaa Xaa Gly Xaa Pro Arg Xaa Pro Gln Val Tyr Thr Leu
100 105 110

Xaa Pro Xaa Lys Asp Glu Leu Thr Xaa Xaa Gln Val Ser Ile Thr Cys
115 120 125

Leu Val Lys Gly Phe Tyr Pro Xaa Asp Ile Xaa Xaa Glu Trp Xaa Xaa
130 135 140

Asn Gly Gln Pro Xaa Xaa Asn Tyr Lys Xaa Thr Pro Pro Xaa Leu Asp
145 150 155 160

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Xaa Val Xaa Lys Xaa
165 170 175

Xaa Trp Gln Gln Gly Asn Xaa Phe Ser Cys Ser Val Leu His Glu Ala
180 185 190

Leu His Asn His His Thr Xaa Lys Ser Leu Ser Xaa
195 200

<210> 612

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin 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 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> 613
 <211> 255
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptibody fusion 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 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 Gly Gly Gly Gly Gly Ala Gln Leu Ala Asp His Gly
 225 230 235 240

Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro Glu Gly Trp Glu
 245 250 255

<210> 614

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptibody fusion sequence

<400> 614

Lys Ser Arg Trp Gln Gln Gly Asn Ile
 1 5

<210> 615

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> EPO-mimetic peptide

<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 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> 616
 <211> 246
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TPO-mimetic peptide sequences

<400> 616

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> 617

<211> 269

<212> PRT

<213> Artificial Sequence

<220>

<223> TPO-mimetic peptide sequences

<400> 617

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 Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg
 225 230 235 240

Gln Trp Leu Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Ile
 245 250 255

Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
 260 265

<210> 618

<211> 246

<212> PRT

<213> Artificial Sequence

<220>

<223> Ang-2 binding peptide sequence

<400> 618

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 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> 619
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide capable of binding to Ang-2

<400> 619

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 Gly Gly Gly Gly Gly Ala Gln Gln Glu Glu Cys Glu
 225 230 235 240

Trp Asp Pro Trp Thr Cys Glu His Met Leu Glu
 245 250

<210> 620
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 620

Lys Ser Arg Trp Gln Glu Gly Asn Val
 1 5

<210> 621
 <211> 2
 <212> PRT
 <213> Homo sapiens

<400> 621

Pro Pro
 1

<210> 622
 <211> 8
 <212> PRT
 <213> Homo sapiens

<400> 622

Asp Val Ser His Glu Asp Pro Glu
 1 5

<210> 623

<211> 3
<212> PRT
<213> Homo sapiens

<400> 623

Ser His Glu
1

<210> 624
<211> 4
<212> PRT
<213> Homo sapiens

<400> 624

Val His Asn Ala
1

<210> 625
<211> 7
<212> PRT
<213> Homo sapiens

<400> 625

Glu Glu Gln Tyr Asn Ser Thr
1 5

<210> 626
<211> 3
<212> PRT
<213> Homo sapiens

<400> 626

Tyr Asn Ser
1

<210> 627
<211> 11
<212> PRT
<213> Homo sapiens

<400> 627

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
1 5 10

<210> 628
<211> 22

<212> PRT

<213> Homo sapiens

<400> 628

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> 629

<211> 3

<212> PRT

<213> Homo sapiens

<400> 629

Asn Lys Ala
1

<210> 630

<211> 5

<212> PRT

<213> Homo sapiens

<400> 630

Asp Glu Leu Thr Lys
1 5

<210> 631

<211> 3

<212> PRT

<213> Homo sapiens

<400> 631

Leu Thr Lys
1

<210> 632

<211> 7

<212> PRT

<213> Homo sapiens

<400> 632

Asn Gly Gln Pro Glu Asn Asn
1 5

<210> 633
<211> 3
<212> PRT
<213> Homo sapiens

<400> 633

Glu Asn Asn
1

<210> 634
<211> 11
<212> PRT
<213> Homo sapiens

<400> 634

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
1 5 10

<210> 635
<211> 5
<212> PRT
<213> Homo sapiens

<400> 635

Val Leu Asp Ser Asp
1 5

<210> 636
<211> 9
<212> PRT
<213> Homo sapiens

<400> 636

Lys Ser Arg Trp Gln Gln Gly Asn Val
1 5

<210> 637
<211> 3
<212> PRT
<213> Homo sapiens

<400> 637

Gln Gly Asn
1

<210> 638
<211> 8
<212> PRT
<213> Homo sapiens

<400> 638

Asp Val Ser Gln Glu Asp Pro Glu
1 5

<210> 639
<211> 7
<212> PRT
<213> Homo sapiens

<400> 639

Glu Glu Gln Phe Asn Ser Thr
1 5

<210> 640
<211> 11
<212> PRT
<213> Homo sapiens

<400> 640

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
1 5 10

<210> 641
<211> 22
<212> PRT
<213> Homo sapiens

<400> 641

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
1 5 10 15

Gly Gln Pro Arg Glu Pro
20

<210> 642
<211> 22
<212> PRT
<213> Homo sapiens

<400> 642

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys

1 5 10 15

Gly Gln Pro Arg Glu Pro
20

<210> 643
<211> 18
<212> PRT
<213> Homo sapiens

<400> 643

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Ala Lys Gly Gln Pro Arg
1 5 10 15

Glu Pro

<210> 644
<211> 5
<212> PRT
<213> Homo sapiens

<400> 644

Glu Glu Met Thr Lys
1 5

<210> 645
<211> 7
<212> PRT
<213> Homo sapiens

<400> 645

Ser Gly Gln Pro Glu Asn Asn
1 5

<210> 646
<211> 11
<212> PRT
<213> Homo sapiens

<400> 646

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
1 5 10

<210> 647

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

<220>
 <223> Myostatin binding peptide sequence

<400> 647

Lys Asp Lys Cys Lys Met Trp His Trp Met Cys Lys Pro Pro
 1 5 10

<210> 648
 <211> 246
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred embodiments

<400> 648

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 Thr Tyr Ser Cys

130 135 140
 His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln 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> 649
 <211> 248
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred embodiments

<400> 649

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 Thr Tyr Ser
130 135 140

Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly Thr
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
245

<210> 650

<211> 250

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred embodiments

<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 Leu Gly Gly Gly Thr Tyr
 130 135 140

Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys Pro Gln Gly Gly
 145 150 155 160

Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 165 170 175

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 180 185 190

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 195 200 205

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

210						215						220					
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr		
225					230					235					240		
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys								
				245					250								
<210>	651																
<211>	252																
<212>	PRT																
<213>	Artificial Sequence																
<220>																	
<223>	Preferred embodiments																
<400>	651																
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> 652

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred embodiments

<400> 652

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 85	Val	Leu	Thr	Val	Leu 90	His	Gln	Asp	Trp	Leu 95	Asn	
Gly	Lys	Glu	Tyr 100	Lys	Cys	Lys	Val	Ser 105	Asn	Lys	Ala	Leu	Pro 110	Ala	Pro	
Ile	Glu	Lys 115	Thr	Ile	Ser	Lys	Ala 120	Lys	Gly	Gln	Pro	Arg 125	Glu	Pro	Gln	
Val	Tyr 130	Thr	Leu	Pro	Pro	Ser 135	Arg	Asp	Glu	Leu	Gly 140	Gly	Gly	Gly	Thr	
Tyr 145	Ser	Ala	His	Phe	Gly 150	Pro	Leu	Thr	Trp	Val 155	Ala	Lys	Pro	Gln	Gly 160	
Gly	Gly	Gly	Thr	Lys 165	Asn	Gln	Val	Ser	Leu 170	Thr	Cys	Leu	Val	Lys 175	Gly	
Phe	Tyr	Pro	Ser 180	Asp	Ile	Ala	Val	Glu 185	Trp	Glu	Ser	Asn	Gly 190	Gln	Pro	
Glu	Asn	Asn 195	Tyr	Lys	Thr	Thr	Pro 200	Pro	Val	Leu	Asp	Ser 205	Asp	Gly	Ser	
Phe 210	Phe	Leu	Tyr	Ser	Lys	Leu 215	Thr	Val	Asp	Lys	Ser 220	Arg	Trp	Gln	Gln	
Gly 225	Asn	Val	Phe	Ser	Cys 230	Ser	Val	Met	His	Glu 235	Ala	Leu	His	Asn	His 240	
Tyr	Thr	Gln	Lys	Ser 245	Leu	Ser	Leu	Ser	Pro	Gly	Lys					

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<210> 653
<211> 254
<212> PRT
<213> Artificial Sequence
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<220>
<223> Preferred embodiments

<400> 653

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 Gly Tyr
130 135 140

Cys Asp Glu Gly Pro Thr Leu Lys Gln Trp Leu Val Cys Leu Gly Leu
145 150 155 160

Gln His Ser Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
165 170 175

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

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
195 200 205

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
210 215 220

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 225 230 235 240

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 654
 <211> 254
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred embodiments

<400> 654

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 Gly Tyr
 130 135 140

Ala Asp Glu Gly Pro Thr Leu Lys Gln Trp Leu Val Ala Leu Gly Leu

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 His Ala Glu
130 135 140

Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala
145 150 155 160

Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly Gly Thr Lys
165 170 175

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
180 185 190

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
195 200 205

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
210 215 220

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
225 230 235 240

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
245 250 255

Leu Ser Leu Ser Pro Gly Lys
260

<210> 656

<211> 267

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred embodiments

<400> 656

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 His
 130 135 140

Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
 145 150 155 160

Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly Gly
 165 170 175

Gly Gly Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 180 185 190

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 195 200 205

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe

210 215 220
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 225 230 235 240
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 245 250 255
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 260 265

 <210> 657
 <211> 246
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Preferred embodiments

 <400> 657
 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 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> 658

<211> 258

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred embodiments

<400> 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 Gly Gly Gly Gly Gly
 130 135 140
 Asp Trp Thr Gly Asp Met Gln Val Lys Phe Asp Ala Met Met Phe Gly
 145 150 155 160
 Pro Arg Lys Glu Gly Gly Gly Gly Gly Thr Lys Asn Gln Val Ser Leu
 165 170 175
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 180 185 190
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 195 200 205
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 210 215 220
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 225 230 235 240
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 245 250 255
 Gly Lys

<210> 659

<211> 281
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred embodiments

<400> 659

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 Gly
 130 135 140

Asp Trp Thr Gly Asp Met Gln Val Lys Phe Asp Ala Met Met Phe Gly
 145 150 155 160

Pro Arg Lys Glu Gly Gly Gly Asp Trp Thr Gly Asp Met Gln Val Lys
 165 170 175

Phe Asp Ala Met Met Phe Gly Pro Arg Lys Glu Gly Gly Gly Gly Gly
 180 185 190

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

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
210 215 220

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
225 230 235 240

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
245 250 255

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
260 265 270

Lys Ser Leu Ser Leu Ser Pro Gly Lys
275 280